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in clinical practice

Experience with 55 commonly used drugs

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in der klinischen Praxis

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Iskustvo s 55 lijekova korištenih u kliničkoj praksi

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Edited by
Dragan Primorac
and
Wolfgang Höppner

St. Catherine Specialty Hospital, Zagreb, Croatia

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This book contains information obtained from authentic and highly regarded sources. Reasonable efforts have been made to publish reliable data and information, but the authors do not have intention to replace the role of a physician in process of prescribing the drugs.

Dieses Buch enthält Informationen aus authentischen und vertrauten Quellen. Es erforderte sehr große Anstrengungen um verlässliche Daten und Informationen zu veröffentlichen , aber die Autoren haben nicht die Absicht, die Rolle eines Arztes im Verfahren der Verschreibung der Medikamente zu ersetzen.

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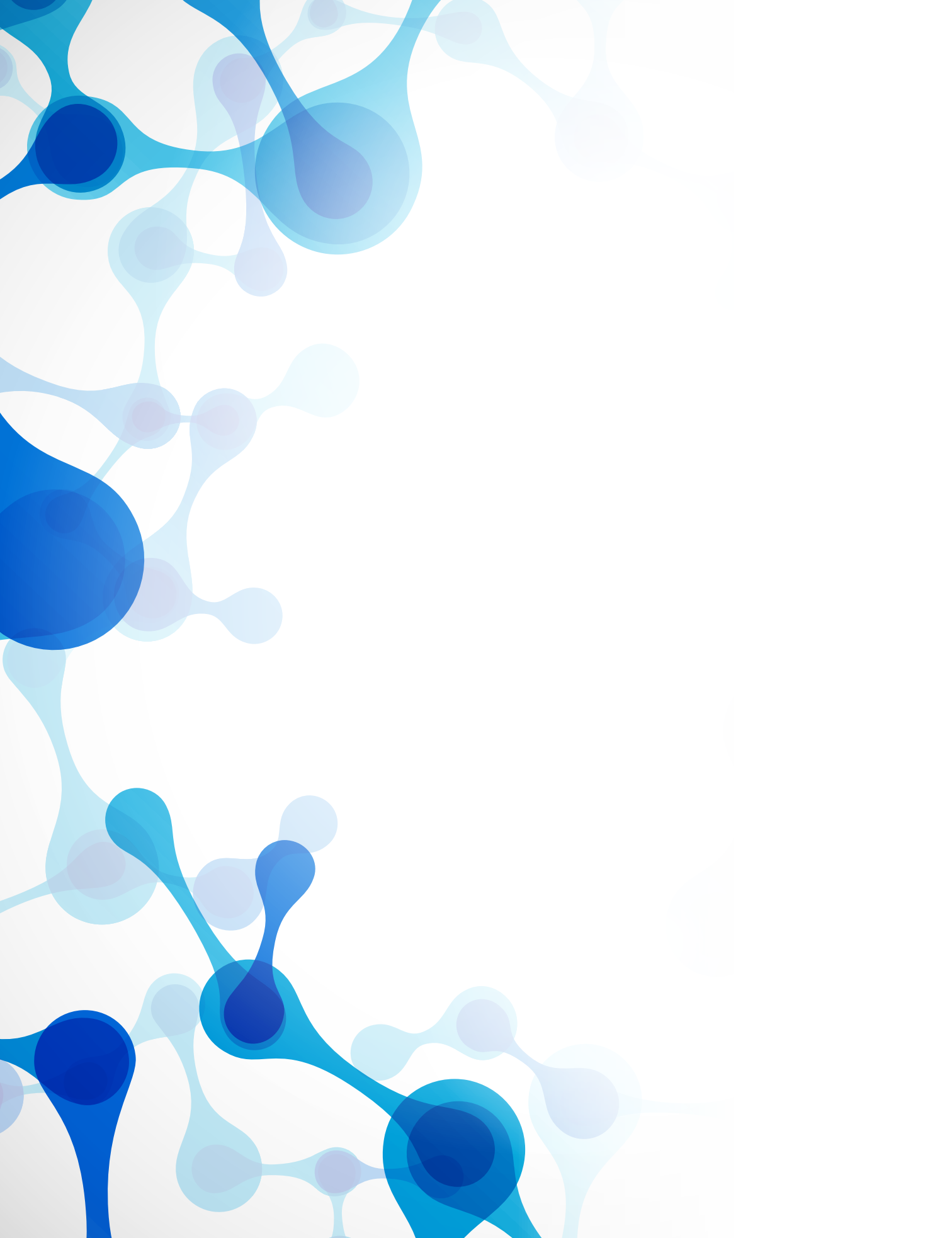

Introduction

Individualized (personalized) medicine can add tremendous value to health care. The United States Food and Drug Administration views personalized medicine as an innovative approach to disease prevention and treatment that takes into account differences in patients' genes, environments and lifestyles. Pharmacogenetics is a critical component of personalized medicine. With the advances in molecular biology and genetics, the pathogenesis of many diseases has been traced to variations in the genome. The ultimate goal of pharmacogenetics is to understand how genetic makeup determines drug action and adverse reactions. Most drugs are broken down (metabolized) by enzymes. In some cases, metabolism inactivates an active drug fully or partially. In other cases, metabolism activates an inactive (or less active) drug. Different genetic variants of a particular enzyme can metabolize a particular drug or group of drugs differently; hence, understanding the particular variant in the particular patient can directly affect the decision on the drug choice and dosage. To avoid drug-drug interactions, the decision on which drug to prescribe may also be influenced by other drugs taken. Understanding the genetic basis of a patient's metabolic differences (i.e. patient's pharmacogenetics), clinicians can select the most effective drugs while keeping the likelihood of adverse reactions to a minimum. The likelihood of drug overdose can be decreased, as the dosage is based on the genetic constitution of the patient rather than on his/her body weight and age, as in the conventional approach. Pharmacogenetics will surely become part of standard considerations in the use of pharmaceuticals.

Results of the contemporary pharmacogenetic research are finding an increasing role in clinical practice, yet the practicing physician often does not have at hand the relevant information in the appropriate form. For that reason, in this brochure we compiled the information about the pharmacogenetic considerations on some of the most often prescribed drugs according to the recommendations by the *Clinical Pharmacogenetics Implementation Consortium* and other sources.

Due to the continuous discoveries in pharmacogenomics, new medicines and clinical guidelines, and updated information on previously published medicines, we have decided to issue a second revised edition to make them available to clinicians and other users and to encourage wider application of pharmacogenomics in daily clinical practice. Fifty-five drugs are systematically overviewed (Abacavir, Acenocoumarol, Allopurinol, Amitriptyline, Atazanavir, Atomoxetine, Azathioprine, Carbamazepine, Celecoxib, Citalopram, Clomipramine, Clopidogrel, Codeine, Desflurane, Desipramine, Doxepin, Efavirenz, Enflurane, Escitalopram, 5-Fluorouracil and Capecitabine, Flurbiprofen, Fluvoxamine, Halothane, Imipramine, Isoflurane, Ibuprofen, Ivacaftor, Lornoxicam, Meloxicam, 6-Mercaptopurine, Methoxyflurane, Nortriptyline, Ondansetron, Oxcarbazepine, Paroxetine, Phenprocoumon, Phenytoin, Piroxicam, Rasburicase, Ribavirin and Peginterferon-α, Sertraline, Sevoflurane, Simvastatin, Siponimod, Succinylcholine, Tacrolimus, Tamoxifen, Tenoxicam, 6-Thioguanine, Trimipramine, Tropisetron, Voriconazole, Warfarin) from the relevant sources, and for each drug we cite the original literature that we recommend for further details.

Editors

Einführung

Eine individualisierte (personalisierte) Medizin kann der Gesundheitsfürsorge einen enormen Wert verleihen. Die US-amerikanische Food and Drug Administration (FDA) sieht in der personalisierten Medizin einen innovativen Ansatz zur Prävention und Behandlung von Krankheiten, der die Unterschiede in den Genen, Umwelt und Lebensstil der Patienten berücksichtigt. Die Pharmakogenetik ist ein kritischer Bestandteil der personalisierten Medizin. Mit den Fortschritten in der Molekularbiologie und Genetik wurde die Pathogenese vieler Krankheiten auf Veränderungen im Genom zurückgeführt. Das ultimative Ziel der Pharmakogenetik ist es zu verstehen, wie das Erbgut die Arzneimittelwirkung und Nebenwirkungen bestimmt. Die meisten Medikamente werden durch Enzyme abgebaut (metabolisiert). In einigen Fällen deaktiviert der Metabolismus einen Wirkstoff ganz oder teilweise. In anderen Fällen aktiviert der Stoffwechsel ein inaktives (oder weniger aktives) Medikament. Verschiedene genetische Varianten eines bestimmten Enzyms können ein bestimmtes Medikament oder eine bestimmte Gruppe von Medikamenten unterschiedlich metabolisieren. Daher kann das Verstehen der bestimmten Variante in dem bestimmten Patienten die Entscheidung über die Arzneimittelauswahl und -dosierung direkt beeinflussen. Um Arzneimittelwechselwirkungen zu vermeiden, kann die Entscheidung, welches Arzneimittel verschrieben werden soll, auch von anderen eingenommenen Arzneimitteln beeinflusst werden. Wenn Ärzte die genetische Grundlage der Stoffwechselunterschiede des Patienten (d. h. die Pharmakogenetik des Patienten) verstehen, können sie die wirksamsten Medikamente auswählen und gleichzeitig die Wahrscheinlichkeit von Nebenwirkungen auf ein Minimum beschränken. Die Wahrscheinlichkeit einer Überdosierung von Medikamenten kann verringert werden, da die Dosierung eher auf der genetischen Konstitution des Patienten als auf seinem Körpergewicht und Alter basiert, wie dies beim herkömmlichen Ansatz der Fall ist. Die Pharmakogenetik wird sicherlich zu einem Bestandteil der Standardüberlegungen bei der Verwendung von Arzneimitteln.

Die Ergebnisse der gegenwärtigen pharmakogenetischen Forschung finden in der klinischen Praxis eine zunehmende Rolle, doch der praktizierende Arzt verfügt häufig nicht über die relevanten Informationen in der entsprechenden Form. Aus diesem Grund haben wir in dieser Broschüre die Informationen zu den pharmakogenetischen Überlegungen für einige der am häufigsten verschriebenen Arzneimittel gemäß den Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)* und anderer Quellen zusammengestellt.

Aufgrund der ständigen Entdeckungen in der Pharmakogenomik, neuer Arzneimittel und klinischer Leitlinien sowie aktualisierter Informationen zu bereits veröffentlichten Arzneimitteln haben wir beschlossen, eine zweite überarbeitete Ausgabe herauszugeben, um sie Klinikern und anderen Anwendern zur Verfügung zu stellen und eine breitere Anwendung der Pharmakogenomik im klinischen Alltag zu fördern und zu trainieren. Fünfundfünfzig Medikamente werden systematisch überwacht: Abacavir, Acenocoumarol, Allopurinol, Amitriptylin, Atazanavir, Atomoxetin, Azathioprin, Carbamazepin, Celecoxib, Citalopram, Clomipramin, Clopidogrel, Codeine, Desfluran, Desipramin, Doxepin, Efavirenz, Enfluran, Escitalopram, 5-Fluorouracil and Capecitabin, Flurbiprofen, Fluvoxamin, Halotan, Ibuprofen, Imipramin, Isofluran, Ivacaftor, Lornoxicam, Meloxicam, 6-Mercaptopurin, Methoxyfluran, Nortriptylin, Ondansetron, Oxcarbazepin, Paroxetin, Phenprocuomon, Phenytoin, Piroxicam, Rasburicase, Ribavirin and Peginterferon-α, Sertralin, Sevofluran, Simvastatin, Siponimod, Succinylcholin, Tacrolimus, Tamoxifen, Tenoxicam, 6-Thioguanin, Trimipramin, Tropisetron, Voriconazol, Warfarin. Aus den entsprechenden Quellen, und für jedes Medikament zitieren wir die Originalliteratur, die wir für weitere Details empfehlen.

Redakteure

Uvod

Individualizirana (personalizirana) medicina predstavlja veliki iskorak u zdravstvenoj skrbi. Američka agencija za hranu i lijekove FDA (engl. Food and Drug Administration) promatra personaliziranu medicinu kao inovativan pristup prevenciji i liječenju bolesti, koji uzima u obzir razlike u genima, okruženju i načinu života pacijenata. Farmakogenetika je ključna komponenta personalizirane medicine. S napretkom u molekularnoj biologiji i genetici, patogeneza mnogih bolesti svedena je na varijacije u genomu. Krajnji cilj farmakogenetike je shvatiti kako genom determinira djelovanje tj. učinak lijeka i njegove nuspojave. Većina lijekova se razgrađuje (metabolizira) enzimima. U nekim slučajevima metabolizam deaktivira aktivni lijek u cijelosti ili djelomično. U drugim slučajevima, metabolizam aktivira neaktivni (ili manje aktivni) lijek. Različite genske varijante određenog enzima mogu različito metabolizirati određeni lijek ili skupinu lijekova; stoga razumijevanje određene varijante u određenog pacijenta može izravno utjecati na odluku o izboru i doziranju lijeka. Da bi se izbjegle interakcije između lijekova, na odluku o prepisivanju lijeka mogu utjecati i drugi lijekovi koje pacijent koristi. Razumijevajući gensku osnovu metaboličkih razlika pacijenta (tj. farmakogenetiku pacijenta), kliničari mogu odabrati najučinkovitije lijekove, a vjerojatnost nuspojava zadržati na minimumu. Vjerojatnost predoziranja lijekom može se smanjiti, jer se doziranje temelji na genskoj strukturi pacijenta, a ne samo na njegovoj tjelesnoj težini i dobi, kao u uobičajenom pristupu. Stoga, farmakogenetika će zasigurno postati dio standardnih razmatranja u korištenju lijekova. Rezultati suvremenih istraživanja pokazuju sve veću ulogu farmakogenetike u kliničkoj praksi, međutim, liječnici često nemaju pri ruci relevantne informacije u odgovarajućem obliku. Iz tog smo razloga u ovoj brošuri prikupili informacije o farmakogenetičkim razmatranjima nekih od najčešće propisanih lijekova prema preporukama CPIC-a (engl. Clinical Pharmacogenetics Implementation Consortium) i drugih izvorima.

Zbog kontinuiranih otkrića u farmakogenomici, novih lijekova i kliničkih smjernica te ažuriranih podataka o prethodno objavljenim lijekovima, odlučili smo izdati drugo izmijenjeno izdanje kako bismo ih učinili dostupnima kliničarima i drugim korisnicima te potaknuli širu primjenu farmakogenomike u svakodnevnoj kliničkoj praksi. U knjizi sustavno analiziramo principe farmakogenomskog djelovanja pedeset i pet lijekova (abakavir, acenokumarol, alopurinol, amitriptilin, atazanavir, atomoksetin, azatioprin, celekoksib, citalopram, desfluran, desipramin, doksepin, efavirenz, enfluran, escitalopram, 5-fluorouracil, fenprokumon, fenitoin, flurbiprofen, fluvoksamin, halotan, ibuprofen, imipramin, ivakaftor, izofluran, kapecitabin, karbamazepin, klomipramin, klopidogrel, kodein, lornoksikam, 6-merkaptopurin, meloksikam, metoksifluran, nortriptilin, ondansetron, okskarbazepin, paroksetin, piroksikam, rasburikaza, ribavirin, peginterferon-α, sertralin, sevofluran, simvastatin, siponimod, sukcinilkolin, takrolimus, 6-tiogvanin, tamoksifen, tenoksikam, trimipramin, tropisetron, varfarin, vorikonazol). Za svaki od gore spomenutih lijekova navodimo izvornu i svu ostalu potrebu literaturu, kako bi kliničar na jednomu mjestu dobio sve relevantne podatke.

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ABACAVIR

Genetic test to minimize the risks related to therapy with abacavir

Drug

What are the indications and mechanisms of action of abacavir?

Abacavir is an antiviral agent for the treatment of infections with the human immunodeficiency virus (HIV) in combination with other HIV medications. Abacavir is a nucleoside analog whose antiviral properties result from the inhibition of enzyme reverse transcriptase which suppresses the HIV replication. Abacavir thus prevents the integration of the viral DNA into the host cell genome as well as the replication of the HIV-virus.

Genes

What genes influence the effect of abacavir?

In individual cases, treatment with abacavir results in side effects such as pyrexia, fatigue and gastrointestinal symptoms. In 48-61 percent of the patients who carry the *HLA-B*57:01* allele (*HLA-B* gene), however, the active agent causes severe immunological hypersensitivity reactions that can be life-threatening or fatal. The *HLA-B*57:01* allele occurs in approx. 6 percent of the population.

Test

What is tested?

The genotype of patients is tested with regard to the allele *HLA-B*57:01* in the *HLA-B* gene.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with abacavir in order to change the active agent, as required, so that severe immunological hypersensitivity reactions can be avoided.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following procedure is based on the recommendations of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] and has the highest clinical level of evidence, 1A.

Table 1: Recommendations for abacavir therapy depending on the depending on the HLA-B genotype

***HLA* Genotype**	**Recommended therapy**
*HLA-B*57:01*, negative	Usage according to the Summary of Product Characteristics
*HLA-B*57:01*, heterozygous or homozygous	Therapy with abacavir not indicated, change of the active agent recommended

Costs

Costs for the determination of the *HLA-B* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Martin MA, Hoffman JM, Freimuth RR, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Abacavir Dosing: 2014 update. Clin Pharmacol Ther. 2014;95(5):499-500. doi:10.1038/clpt.2014.38

ABACAVIR

Gentest zur Risikominimierung der Therapie mit Abacavir

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Abacavir?

Abacavir ist ein antiviraler Wirkstoff zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV). Abacavir ist ein Nukleosidanalogon, dessen antivirale Eigenschaften auf Hemmung der reversen Transkriptase beruhen. Abacavir verhindert sowohl die Integration der viralen DNA in das Genom der Wirtszelle als auch die Replikation des HIV-Virus.

Gene

Welche Gene beeinflussen die Wirkung von Abacavir?

Unter der Therapie mit Abacavir treten in Einzelfällen Nebenwirkungen wie Fieber, Abgeschlagenheit und gastrointestinale Symptome auf. Der Wirkstoff löst bei 48-61 % der Patienten, die das *HLA-B*57:01*-Allel (*HLA-B*-Gen) tragen, schwere immunologische Überempfindlichkeitsreaktionen, die lebensbedrohlich oder tödlich sein können. Das *HLA-B*57: 01*-Allel kommt bei etwa 6 Prozent der Bevölkerung vor.

Prüfung

Was wird getestet?

Das Erbgut der Patienten wird auf das Allel *HLA-B*57: 01* (*HLA-B*-Gen) getestet.

Indikation

Wann sollte getestet werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Abacavir durchgeführt werden, um eventuell einen anderen Wirkstoff auszuwählen und schwere immunologische Überempfindlichkeitsreaktionen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Abacavir-Therapie in Abhängigkeit vom HLA-B-Genotyp

***HLA* Genotyp**	**Therapieempfehlung**
*HLA-B*57:01*, negativ	Anwendung gemäß Fachinformation
*HLA-B*57:01*, heterozygot oder homozygot	Abacavir kontraindiziert, Wirkstoffwechsel empfohlen

Kosten

Die Kosten für die Bestimmung des *HLA-B*-Genotyps werden für gesetzlich oder privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Martin MA, Hoffman JM, Freimuth RR, et al. *Clinical Pharmacogenetics Implementation Consortium* Guidelines for HLA-B Genotype and Abacavir Dosing: 2014 update. Clin Pharmacol Ther. 2014;95(5):499-500. doi:10.1038/clpt.2014.38

ABAKAVIR

Genetički test za smanjenje rizika pri primjeni abakavira

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja abakavira?

Abakavir je antivirusni lijek, primjenjuje se u liječenju infekcija izazvanih virusom humane imunodeficijencije (HIV). Nukleozidni je analog, inhibitor reverzne transkriptaze (NRTI). Abakavir sprječava integraciju virusne DNA u stanični genom domaćina i replikaciju HIV-a.

Geni

Koji geni utječu na djelovanje abakavira?

Uslijed liječenja abakavirom u pojedinačnim slučajevima javljaju se nuspojave poput povišene tjelesne temperature, iznemoglosti i gastrointestinalnih simptoma. Nasuprot tome, abakavir kod 48-61 % pacijenata, koji su nositelji alela *HLA-B*57:01* (gen *HLA-B*), izaziva tešku imunološku reakciju preosjetljivosti koja može završiti i smrtnim ishodom. Učestalost alela *HLA-B*57:01* (*HLA-B*5701*) u populaciji iznosi oko 6 %.

Analiza

Što se analizira?

Analizira se genotip pacijenta, odnosno alel *HLA-B*57:01*, gena *HLA-B*.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije abakavirom, kako bi se po potrebi ordinirala zamjenska terapija u svrhu sprječavanja teške imunološke reakcije preosjetljivosti.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Postupak je utemeljen je na preporukama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te ima najvišu kliničku razinu dokaza, 1A.

Tablica 1: Preporuke za liječenje abakavirom ovisno o HLA-B genotipu

***HLA* genotip**	**Preporučena terapija**
*HLA-B*57:01*, negativan	Primjena sukladno uputama o lijeku
*HLA-B*57:01*, heterozigot ili homozigot	Terapija abakavirom nije indicirana; preporučuje se primjena zamjenskog lijeka

Troškovi

Priznavanje i povrat troškova za navedenu analizu varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *HLA-B* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Martin MA, Hoffman JM, Freimuth RR, et al. *Clinical Pharmacogenetics Implementation Consortium* Guidelines for HLA-B Genotype and Abacavir Dosing: 2014 update. Clin Pharmacol Ther. 2014;95(5):499-500. doi:10.1038/clpt.2014.38

ACENOCOUMAROL

Genetic test to minimize the risks related to therapy with acenocoumarol

Drug

What are the indications and mechanisms of action of acenocoumarol?

Acenocoumarol is a widely used anticoagulant with a narrow therapeutic index prescribed for prophylaxis and treatment of venous thromboembolism (DVT), in the prevention of systematic embolism associated with atrial fibrillation and cardiac valve replacement, stroke, reinfarction or sudden cardiac death in patients with acute myocardial infarction. Large interpatient variability in the acenocoumarol concentrations implicates either lack of anticoagulant effect or serious drug adverse events and complications (bleeding). As a vitamin K antagonist, acenocoumarol suppresses the activation of the coagulation factors II, VII, IX and X as well as the synthesis of the anticoagulant proteins C and S. In comparison to the related coumarins phenprocoumon and warfarin, acenocoumarol exhibits a shorter half-life.

Genes

Which genes influence the effect of acenocoumarol?

VKORC1 and *CYP2C9* genes have the most significant impact on acenocoumarol dosage. *VKORC1* encodes the vitamin K-epoxide reductase complex, the target enzyme of acenocoumarol. A common variant upstream of *VKORC1* on position *1639 G>A* is significantly associated with acenocoumarol sensitivity and patients carrying such polymorphism (*1639 A/A* and *A/G*) require progressively lower acenocoumarol doses than homozygotes (*1639 G/G*). *CYP2C9* encodes for hepatic drug-metabolizing enzyme important for dose variability. Two common gene variants in *CYP2C9*2* and **3* influence the metabolism rate among individuals of European and East Asian ancestry. Additionally, identified gene variants in genes *CYP4F2*3* and *CYP2C cluster* (rs12777823) have minor contribution to dose requirements.

Test

What will be tested?

To determine the optimal acenocoumarol dose, the most common risk variants of the *VKORC1 1639G>A* are tested.

Indication

When should a test be performed?

The genetic test should be performed before a planned therapy with acenocoumarol in order to quickly achieve stable INR (international normalized ratio) values through dose adjustment if necessary and to avoid bleeding, specifically in individuals who are carriers of multiple allelic variants. The risk of developing complications is the greatest for acenocoumarol starting dosing.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following procedure takes place in accordance with *Royal Dutch Pharmacists Association - Pharmacogenetics Working Group* (DPWG) guidelines[1,2] for acenocoumarol and have the clinical level of evidence 1B to VKORC1.

Table 1: Recommendations for acenocoumarol dosing based on genotype for adult patients

Genotype	Recommended therapy
VKORC1 (1639G>A) AA	50 % of the standard initial dose of acenocoumarol more frequent INR monitoring
VKORC1 (1639G>A) AG	No recommendation
*CYP2C9 *2, *3*	No recommendation
*CYP2C9 *5, *6, *8, *11*	No recommendation
*CYP4F2*3*	No recommendation
CYP2C cluster (rs 12777823)	No recommendation

Costs

Costs for the *VKORC1* genetic analysis will be reimbursed for statutory and privately insured patients if the physician prescribes the testing, although most insurance plans do not currently pay for acenocoumarol pharmacogenetic testing.

[1] https://www.knmp.nl/producten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics

[2] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf

ACENOCOUMAROL

Gentest zur Optimierung der Arzneimitteltherapie mit Acenocoumarol

Wirkstoff

Was sind Indikationen und Wirkmechanismen von Acenocoumarol?

Acenocoumarol ist ein weit verbreitetes Antikoagulans mit einem engen therapeutischen Index, das zur Prophylaxe und Behandlung von venösen Thromboembolien (DVT) verschrieben wird, um systematische Embolien im Zusammenhang mit Vorhofflimmern und Herzklappenersatz, Schlaganfall, Reinfarkt oder plötzlichem Herztod bei Patienten mit akutem Myokardinfarkt zu verhindern. Eine große Variabilität der Acenocoumarol Konzentrationen impliziert entweder einen Mangel an gerinnungshemmender Wirkung oder in den Patienten schwerwiegende unerwünschte Ereignisse und Komplikationen (Blutungen). Als Vitamin-K-Antagonist unterdrückt Acenocoumarol die Aktivierung der Gerinnungsfaktoren II, VII, IX und X sowie die Synthese der Antikoagulansproteine C und S. Im Vergleich zu den verwandten Cumarinen Phenprocoumon und Warfarin besitzt Acenocoumarol eine kürzere Halbwertszeit.

Gene

Welche Gene beeinflussen die Wirkung von Acenocoumarol?

Die *VKORC1*- und *CYP2C9*-Gene beeinflussen maßgeblich die Acenocoumarol-Metabolisierung. VKORC1 codiert den Vitamin K-Epoxid-Reduktase-Komplex, das Zielenzym von Acenocoumarol. Eine häufige Variante stromaufwärts von *VKORC1* an Position *1639 G> A* ist signifikant mit der Acenocoumarolsensitivität assoziiert, und Patienten mit einem solchen Polymorphismus (*1639A/A*) benötigen zunehmend niedrigere Acenocoumarol Dosen als Homozygote (*1639 G/G*). *CYP2C9* kodiert für ein für die Dosisvariabilität wichtiges hepatisches Arzneimittel metabolisierendes Enzym. Zwei häufige Genvarianten in *CYP2C9*2*,**3* beeinflussen die Stoffwechselrate bei Personen europäischer und ostasiatischer Abstammung. Zusätzlich leisten identifizierte Genvarianten in den Genen *CYP4F2*3* und im *CYP2C-Cluster* (rs12777823) einen geringen Beitrag zum Dosisbedarf.

Test

Was wird getestet?

Um die am besten geeignete Acenocoumarol-Dosis zu bestimmen, wird die häufigste Risikovariante von *VKORC1 1639G>A* im Erbgut der Patienten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor einer geplanten Therapie mit Acenocoumarol durchgeführt werden, um bei Bedarf durch Dosisanpassung schnell konstante INR-Werte (*International Normalized Ratio*) zu erreichen und Nebenwirkungen (Blutungen) zu vermeiden. Das Risiko, Komplikationen zu entwickeln, ist bei Beginn der Acenocoumarol-Dosierung am größten. Beachtet werden sollte eine Einführung von Acenocoumarol in die Therapie und eine Titration seiner stabilen Dosis sowie einige individuelle Faktoren: Alter, Geschlecht, Körpergewicht, Rasse, interagierende Medikamente (insbesondere Amiodaron), Vitamin-K-Aufnahme (Lebensmittel, insbesondere Zitrusfrüchte (Grapefruit), grünes Gemüse), Rauchen und Komorbiditäten.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] für Acenocoumarol und zeigt das höchste klinische Evidenzlevel 1B für VKOCR1.

Tabelle 1: Empfehlungen für die Acenocoumarol-Dosierung mit VKORC1-CYP2C9-CYP4F2-CYP2C cluster-Genotyp für erwachsene Patienten

Genotyp	Therapieempfehlung
VKORC1 (1639G>A) AA	50 % der Standard-Anfangsdosis von Acenocoumarol häufigere INR-Überwachung
VKORC1 (1639G>A) AG	Keine Empfehlung
*CYP2C9 *2, *3*	Keine Empfehlung
*CYP2C9 *5,*6, *8, *11*	Keine Empfehlung
*CYP4F2*3*	Keine Empfehlung
CYP2C cluster (rs 12777823)	Keine Empfehlung

Kosten

Die Kosten für die genetische Analyse der *VKORC1*- und *CYP2C9*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird, obwohl die meisten Versicherungspläne derzeit nicht für pharmakogenetische Warfarin-Tests bezahlen. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] https://www.knmp.nl/producten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics

[2] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf

ACENOKUMAROL

Genetički test za smanjenje rizika pri primjeni acenokumarola

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja acenokumarola?

Acenokumarol je antikoagulans s uskom terapijskom širinom u liječenju i prevenciji duboke venske tromboze (DVT) i plućne embolije, u prevenciji sustavne embolije kod pacijenata s atrijskom fibrilacijom i umjetnim srčanim zaliscima, prevenciji moždanog udara, ponovnog infarkta ili iznenadne smrti u pacijenata s akutnim infarktom miokarda. Velika interindividualna varijabilnost u odgovoru na terapiju acenokumarolom može utjecati ili na izostanak antikoagulacijskog učinka ili često potencira niz nuspojava, kao i opasnost od krvarenja. Kao antagonist vitamina K, acenokumarol smanjuje aktivaciju faktora zgrušavanja II, VII, IX i X, ali i sintezu antikoagulacijskih proteina C i S. Za razliku od drugih kumarina varfarina i fenprokumona, acenokumarol ima kraće poluvrijeme eliminacije.

Geni

Koji geni utječu na djelovanje acenokumarola?

Na doziranje acenokumarola najznačajnije utječe gen VKORC1. Enzim vitamin K-epoksid reduktaza kompleks ciljno je mjesto djelovanja acenokumarola kojeg kodira *VKORC1*. Jednonukleotidni polimorfizam na poziciji 1639 je supstitucija aminokiseline gvanin u adenin (*1639G>A*) koji je povezan s povećanom osjetljivošću na acenokumarol pa nositelji ovog polimorfizma (*1639 A/A* i *A/G*) zahtjevaju niže doze acenokumarola u odnosu na pojedince koji su homozigoti (*1639 G/G*). *CYP2C9* kodira za jetreni enzim koji metabolizira acenokumarol. Na učinkovitost razgradnje lijeka značajno utječu polimorfizmi gena *CYP2C9* 2* i 3* koji su najčešće zastupljeni kod populacije europskog i istočno-azijskog porijekla. Utvrđene su varijante u genima *CYP4F2*3* i *CYP2C* klastera (rs12777823) koje imaju minimalan utjecaj na doziranje acenokumarola.

Analiza

Što se analizira?

Da bi se ustanovila optimalna doza lijeka, analiziraju se najučestalije rizične varijante gena *VKORC1 1639G>A*.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi se trebalo provesti prije planirane terapije acenokumarolom kako bi se prilagodilo doziranje i postigao terapijski INR (međunarodno normalizirani omjer) 2-3 te izbjegle nuspojave krvarenja, osobito kod nositelja višestrukih alelnih varijanti. Rizik razvoja komplikacija najveći je u samom početku primjene acenokumarola.

Posljedice rezultata testova

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke za doziranje acenokumarola ovisno o *VKORC1* genotipu su utemeljene na smjernicama *Royal Dutch Pharmacists Association - Pharmacogenetics Working Group* (DPWG) guidelines[1] i maju kliničku razinu dokaza 1B.

Tablica 1: Preporuke za liječenje acenokumarolom ovisno o genotipu za odrasle

Genotip	Preporučena terapija
VKORC1 (1639G>A) AA	Početi terapiju s 50 % od standardne početne doze acenokumarola; potrebno je češće praćenje INR-a
VKORC1 (1639G>A) AG	Nema preporuka
*CYP2C9 *2, *3*	Nema preporuka
*CYP2C9 *5, *6, *8, *11*	Nema preporuka
*CYP4F2*3*	Nema preporuka
CYP2C cluster (rs 12777823)	Nema preporuka

Troškovi

Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize gena bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje, iako većina osiguranja za sada ne plaća farmakogenomsko testiranje acenokumarola.

[1] https://www.knmp.nl/producten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics

[2] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf

ALLOPURINOL

Genetic test to minimize the risks related to therapy with allopurinol

Drug

What are the indications and mechanisms of action of allopurinol?

Allopurinol inhibits the breakdown of purines and is used to treat chronic gout caused by permanently elevated levels of uric acid in the blood. Further indications are connected with the treatment of uric acid concrements in the kidney and for preventing tumor lysis syndrome following chemotherapy. Due to its parasitostatic effect, allopurinol is also successfully used in combination with other drugs to treat leishmaniasis. The uricostatic properties of allopurinol are based on the inhibition of the breakdown enzyme xanthine oxidase. The enzyme blockage inhibits the breakdown of purine nucleotides to uric acid as well as de novo synthesis of uric acid, reducing the uric acid concentration in the blood and urine.

Genes

What genes influence the effect of allopurinol?

In patients who carry the *HLA-B*57:01* allele (*HLA-B* gene), allopurinol can cause severe immunological hypersensitivity reactions. The *HLA-B*57:01* allele occurs in 1-5 % of the European population.

If a patient is *HLA-B*57:01* allele positive, allopurinol should only be used if no therapeutic alternatives are available or if the benefits of the therapy outweigh the risks.

Test

What is tested?

The genotype of patients is tested with regard to the allele *HLA-B*57:01* in the *HLA-B* gene.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with allopurinol in order to change the active agent, as required, so that severe side effects can be avoided.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] and the American College of Rheumatology guidelines[3] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for allopurinol therapy depending on the HLA-B genotype

Genotype	Recommended therapy
*HLA-B*57:01*, negative	Usage according to the Summary of Product Characteristics
*HLA-B*57:01*, heterozygous or homozygous	Allopurinol contraindicated, change of the active agent recommended

Costs

Costs for the determination of the *HLA-B* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013;93(2):153-158. doi:10.1038/clpt.2012.209

[2] Saito Y, Stamp LK, Caudle KE, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther. 2016;99(1):36-37. doi:10.1002/cpt.161

[3] Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431-1446. doi:10.1002/acr.21772

ALLOPURINOL

Gentest zur Risikominimierung der Therapie mit Allopurinol

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Allopurinol?

Bei durch dauerhaft erhöhtem Harnsäurespiegel im Blut verursachter chronischer Gicht wird der Purinabbau-Hemmer Allopurinol eingesetzt. Weitere Indikationsfelder beinhalten die Therapie von Uratsteinen der Niere und die Prävention des Tumorlyse-Syndroms nach Chemotherapie. Aufgrund seiner parasitostatischen Wirkung wird Allopurinol auch erfolgreich in Kombination mit anderen Arzneimitteln zur Behandlung der Leishmaniose eingesetzt. Die urikostatischen Eigenschaften von Allopurinol beruhen auf der Inhibition des Abbauenzyms Xanthinoxidase. Diese Enzymblockade hemmt sowohl den Abbau von Purinnukleotiden zu Harnsäure als auch die Neusynthese von Harnsäure und führt zu einer Verringerung der Harnsäurekonzentration in Blut und Urin.

Gene

Welche Gene beeinflussen die Wirkung von Allopurinol?

Bei Patienten, die das *HLA-B*57:01* Allel (*HLA-B*-Gen) tragen, kann Allopurinol schwere immunologische Überempfindlichkeitsreaktionen verursachen. Die Häufigkeit des *HLA-B*57:01* Allel in der europäischen Bevölkerung liegt bei 1-5 %. Wird ein Patient positiv auf *HLA-B*57:01* getestet, sollte Allopurinol nur angewendet werden, wenn keine therapeutischen Alternativen verfügbar sind und der Therapienutzen die Risiken überwiegt.

Prüfung

Was wird getestet?

Der Genotyp von Patienten wird im Hinblick auf das Allel *HLA-B*57:01* im *HLA-B*-Gen getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Allopurinol durchgeführt werden, um gegebenfalls einen Wirkstoffwechsel vorzunehmen und schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und des *American College of Rheumatology guidelines*[3] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen bei der Allopurinol-Therapie in Abhängigkeit vom Genotyp des HLA-B-Gens

Genotyp	Therapieempfehlung
*HLA-B*57:01*, negativ	Anwendung gemäß Fachinformation
*HLA-B*57:01*, heterozygot oder homozygot	Allopurinol kontraindiziert, Wirkstoffwechsel empfohlen

Kosten

Die Kosten für die Bestimmung des *HLA-B*-Genotyps werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013;93(2):153-158. doi:10.1038/clpt.2012.209

[2] Saito Y, Stamp LK, Caudle KE, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther. 2016;99(1):36-37. doi:10.1002/cpt.161

[3] Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431-1446. doi:10.1002/acr.21772

ALOPURINOL

Genetički test za smanjenje rizika pri primjeni alopurinola

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja alopurinola?

Alopurinol inhibira razgradnju purina i primjenjuje se u liječenju kroničnog gihta koji su posljedica trajno povišene razine mokraćne kiseline u krvi. Daljnja indikacijska područja su liječenje i prevencija bolesti nastalih zbog povišene vrijednosti mokraćne kiseline poput bubrežnih kamenaca, te sindroma lize tumora. Urikostatička obilježja alopurinola temelje se na inhibiciji enzima ksantin oksidaze. Blokadom enzima zaustavlja se kako razgradnja purinskih nukleotida u mokraćnu kiselinu tako i nova sinteza mokraćne kiseline pri čemu dolazi do pada njene koncentracije u krvi i u urinu. Na temelju njegovog parazitostatičkog djelovanja alopurinol se u kombinaciji s drugim lijekovima uspješno primjenjuje i kod liječenja lišmanijaze.

Geni

Koji geni utječu na učinkovitost alopurinola?

Kod pacijenata koji su nositelji alela *HLA-B*58:01* (gen *HLA-B*) alopurinol može izazivati tešku imunološku reakciju preosjetljivosti. Učestalost alela *HLA-B*58:01* u Europskoj populaciji iznosi 1-5 %. Ukoliko pacijent ima alel *HLA-B*58:01*, alopurinol se primjenjuje samo u slučajevima kada ne postoji niti jedan alternativni oblik liječenja te kad korist od terapije premašuje same rizike.

Analiza

Što se analizira?

Analizira se genotip bolesnika, posebice prisutnost alela *HLA-B*58:01* (gen *HLA-B*).

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka planirane terapije alopurinolom, kako bi se po potrebi ordinirala zamjenska terapija u svrhu sprečavanja teških nuspojava.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su utemeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] i American College of Rheumatology guidelines[3] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje alopurinolom ovisno o HLA-B genotipu

Genotip	Preporučena terapija
*HLA-B*57:01*, negativan	Terapija sukladno uputama o lijeku
*HLA-B*57:01*, heterozigot ili homozigot	Alopurinol je kontraindiciran, preporučuje se primjena zamjenskog lijeka

Troškovi

Priznavanje i povrat troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa *HLA-B* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013;93(2):153-158. doi:10.1038/clpt.2012.209

[2] Saito Y, Stamp LK, Caudle KE, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther. 2016;99(1):36-37. doi:10.1002/cpt.161

[3] Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431-1446. doi:10.1002/acr.21772

AMITRIPTYLINE

Genetic test to minimize the risks related to therapy with amitriptyline

Drug

What are the indications and mechanism of action of amitriptyline?

Tricyclic antidepressant amitriptyline is an inhibitor of both serotonin and norepinephrine reuptake in the presynaptic neurons. Additionally, it blocks the α1-adrenergic receptor, the histamine H1, the serotonin and the muscarinic acetylcholine receptors. Amitriptyline is indicated for the treatment of depression, anxiety disorder, nocturnal enuresis, as well as neuropathic pain and migraine prophylaxis.

Genes

Which genes influence the effect of amitriptyline?

Amitriptyline as tertiary amine is metabolized via the enzyme CYP2C19 to secondary amine nortriptyline. Both are further metabolized via the CYP2D6 enzyme to less-active metabolites. Both enzymes play a decisive role in efficiency and duration of action to all tricyclic antidepressants (TCAs). Several variants in the genes of these two enzymes are known in our population. These lead to great variability in the enzymatic efficacy of CYP2C19 and CYP2D6, and can, therefore, be of vital importance for TCAs therapy.

Test

What will be tested?

In order to determine the CYP2C19 as well as the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants in the *CYP2C19* gene (**2, *3, *17*) and in the *CYP2D6* gene (**1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41*).

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with amitriptyline in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] guideline and have the highest clinical level of evidence 1A.

Table 1: Recommendations for amitriptyline therapy according to the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-20 %)	Usage of amitriptyline is not recommended, prescribe an alternative drug not metabolized via CYP2D6. If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Therapeutic drug monitoring is strongly recommended
Normal metabolizer (77-88 %)	Usage according to the Summary of Product Characteristics
Intermediate metabolizer (1-13 %)	Reduction of starting dose of amitriptyline by 25 %
Poor metabolizer (1-10 %)	Usage of amitriptyline is not recommended, prescribe an alternative drug not metabolized via CYP2D6. If amitriptyline is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Table 2: Recommendations for amitriptyline therapy according to the phenotype of the CYP2C19 gene

CYP2C19 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (2-5 %)	Usage amitriptyline is not recommended, prescribe an alternative drug not metabolized via CYP2C19. If amitriptyline is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Rapid metabolizer (2-30 %)	Usage of amitriptyline is not recommended, prescribe an alternative drug not metabolized via CYP2C19. If amitriptyline is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Normal metabolizer (35-50 %)	Initiate therapy with the recommended starting dose
Intermediate metabolizer (18-45 %)	Reduced metabolism of amitriptyline compared to normal metabolizers, initiate therapy with the recommended starting dose
Poor metabolizer (2-15 %)	Usage of amitriptyline is not recommended, prescribe an alternative drug not metabolized via CYP2C19. If amitriptyline is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Nota bene: If a patient is treated for neuropathic pain with amitriptyline and is an intermediate or poor CYP2D6/CYP2C19 metabolizer, no dose adjustment is recommended because of a lower prescribed dose initially. Patients should be monitored for potential side effects.

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

AMITRIPTYLIN

Gentest zur Risikominimierung der Therapie mit Amitriptylin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Amitriptylin?

Das trizyklische Antidepressivum Amitriptylin hemmt die Wiederaufnahme von Serotonin und Noradrenalin im präsynaptischen Neuron. Es blockiert zusätzlich den α1-adrenergen Rezeptor, das Histamin H1, das Serotonin und die muskarinischen Acetylcholinrezeptoren. Dieser Wirkstoff wird bei der Behandlung von Depressionen und Zwangsstörungen, nächtlicher Enuresis sowie neuropathischen Schmerzen und Migräneprophylaxe eingesetzt.

Gen

Welche Gene beeinflussen die Wirkung von Amitriptylin?

Das tertiäre Amin Amitriptylin wird über das Enzym CYP2C19 zum sekundärem Amin Nortriptylin metabolisiert. Beide werden über das CYP2D6-Enzym zu weniger aktiven Metaboliten weiter metabolisiert. Beide Cytochrome spielen für alle trizyklische Antidepressiva (TCAs) eine entscheidende Rolle in ihrer Effizienz und Wirkdauer. In unserer Population sind verschiedene Varianten der Gene beider Enzyme mit einer großen Variabilität der enzymatischen Wirksamkeit bekannt. Sie können für die TCAs-Therapie von entscheidender Bedeutung sein.

Test

Was wird getestet?

Um sowohl den CYP2C19- als auch den CYP2D6-Metabolismustyp zu bestimmen, wird der Genotyp des Patienten im *CYP2C19*-Gen *(*2, *3, *17)* und im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Amitriptylin durchgeführt werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu ändern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Amitriptylin-Therapie nach Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Amitriptylin kontrainidziert, Wirkstoffwechsel empfohlen Bei Einsatz von Amitriptylin: auf höhere Zieldosis (verglichen zu normalen Metabolisierern) titrieren; therapeutisches *Drug Monitoring*
Normale Metabolisierer (77-88 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis um 25 % reduzieren
Langsame Metabolisierer (1-10 %)	Amitriptylin kontrainidziert, Wirkstoffwechsel empfohlen Bei Einsatz von Amitriptylin: Startdosis um 50 % reduzieren, bei therapeutischem *Drug Monitoring*

Tabelle 2: Empfehlungen für die Amitriptylintherapie nach Phänotyp des CYP2C19-Gens

CYP2C19 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (2-5 %)	Amitriptylin kontrainidziert, Wirkstoffwechsel empfohlen Bei Einsatz von Amitriptylin: therapeutisches *Drug Monitoring* zur Steuererung der Dosisanpassung
Schnelle Metabolisierer (2-30 %)	Amitriptylin kontrainidziert, Wirkstoffwechsel empfohlen Bei Einsatz von Amitriptylin: therapeutisches *Drug Monitoring* zur Steuererung der Dosisanpassung
Normale Metabolisierer (35-50 %)	Einleitung Therapie mit empfohlener Anfangsdosis
Intermediäre Metabolisierer (18-45 %)	Einleitung Therapie mit empfohlener Anfangsdosis
Langsame Metabolisierer (2-15 %)	Amitriptylin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz von Amitriptylin: Startdosis um 50 % reduzieren, bei therapeutischem *Drug Monitoring*

Nota bene: Wenn ein Patient wegen neuropathischer Schmerzen mit Amitriptylin behandelt wird und ein intermediärer oder langsamer CYP2D6/CYP2C19-Metabolisierer ist, wird aufgrund einer anfänglich niedrigeren verschriebenen Dosis keine Dosisanpassung empfohlen. Die Patienten sollten auf mögliche Nebenwirkungen überwacht werden.

Kosten

Die Kosten für genetische Analysen werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Untersuchung von einem Arzt verordnet wurde. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

AMITRIPTILIN

Genetički test za smanjenje rizika pri primjeni amitriptilina

Lijek

Koje su indikacije i mehanizmi djelovanja amitriptilina?

Triciklički antidepresiv amitriptilin je inhibitor ponovne pohrane serotonina i noradrenalina u presinaptičkom neuronu. Dodatno blokira α1 adrenergičke, H1 histaminske, muskarinske i serotoninske receptore. Koristi se za liječenje depresije, anksioznih poremećaja, nokturalne enureze, neuropatske boli te za profilaksu migrene.

Geni

Koji geni utječu na djelovanje amitriptilina?

Amitriptilin se kao tercijarni amin metabolizira preko enzima CYP2C19 u sekundarni amin nortriptilin. Oboje se dalje metaboliziraju putem enzima CYP2D6 u manje aktivne metabolite. Oba enzima determiniraju učinkovitost i duljinu djelovanja većine tricikličkih antidepresiva. Nekoliko genskih polimorfizama dovode do velike varijabilnosti u enzimatskoj funkciji CYP2C19 i CYP2D6, što može biti značajno za terapijsku učinkovitost amitriptilina.

Analiza

Što se analizira?

Kako bi se odredio fenotip enzima CYP2C19 i CYP2D6, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2C19 (*2,*3,*17)* te gena *CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, 9*, *10, *41)*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije amitriptilinom, kako bi se po potrebi prilagodilo doziranje lijeka ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje amitriptilinom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-20 %)	Ne preporučuje se liječenje amitriptilinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja amitriptilinom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (77-88 %)	Koristiti lijek prema sažetku opisa svojstava lijeka
Intermedijarni metabolizator (1-13 %)	Smanjenje početne doze amitriptilina za 25 %
Spori metabolizator (1-10 %)	Ne preporučuje se liječenje amitriptilinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja amitriptilinom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Tablica 2: Preporuke za liječenje amitriptilinom ovisno o fenotipu CYP2C19

CYP2C19 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (2-5 %)	Ne preporučuje se liječenje amitriptilinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja amitriptilinom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Brzi metabolizator (2-30 %)	Ne preporučuje se liječenje amitriptilinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja amitriptilinom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (35-50 %)	Započinje se terapija preporučenom početnom dozom
Intermedijarni metabolizator (18-45 %)	Započinje se terapija preporučenom početnom dozom
Spori metabolizator (2-15 %)	Ne preporučuje se liječenje amitriptilinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja amitriptilinom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Nota bene: Ukoliko se liječi neuropatska bol, a pacijent je intermedijarni ili spori *CYP2D6* / *CYP2C19* metabolizator, ne preporučuje se prilagodba doze zbog već inicijalno propisane niže doze. Pacijente treba nadzirati zbog potencijalnih nuspojava.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa CYP2C19 i CYP2D6 biti će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

ATAZANAVIR

Genetic test to minimize the risks related to therapy with atazanavir

Drug

What are the indications and mechanisms of action of atazanavir?

Atazanavir is an antiretroviral active agent for the treatment of infections with the human immunodeficiency virus (HIV). Atazanavir is a protease inhibitor that prevents HIV from multiplying, thereby reducing the amount of HIV in the body.

Genes

What genes influence the effect of atazanavir?

Atazanavir is a generally safe medication with fewer adverse effects compared to other protease inhibitors. Atazanavir inhibits hepatic uridine diphosphate glucuronosyltransferase (UGT1A1) and prevents the glucuronidation and elimination of bilirubin. For patients carrying two *UGT1A1* decreased function alleles (i.e., **28/*28, *28/*37, *37/*37* or rs887829 T/T), the risk of jaundice and bilirubin-related atazanavir discontinuation is considerable. For individuals with only one or without decreased function allele, atazanavir discontinuation and jaundice aren't likely.

Test

What is tested?

The genotype of patients is tested with regard to the *UGT1A1* alleles (i.e., **28/*28, *28/*37, *37/*37,* rs887829 T/T) of the *UGT1A1* gene.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with atazanavir in order to change the active agent, as required, so that severe adverse reactions can be avoided.

Consequences of test results

How does the therapy need to be adjusted to the test results?

The following procedure is based on the recommendations of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for atazanavir therapy (boosted with either ritonavir or cobicistat) depending on the UGT1A1 genotype

***UGT1A1* Genotype**	**Recommended therapy**
*1/*1, *1/*36, *36/*36* or rs887829 C/C	Usage according to the Summary of Product Characteristics
**1/*28, *1/*37, *36/*28, *36/*37,* rs887829 C/C or rs887829 C/T	Usage according to the Summary of Product Characteristics
**28/*28, *28/*37, *37/*37* or rs887829 T/T	The usage of atazanavir is not recommended. Change of active agent is recommended. Prescribing atazanavir, there is a high risk of developing jaundice that will result in atazanavir discontinuation with a chance of 20-60 %

Costs

Costs for the determination of the *UGT1A1* genotype are reimbursed for patients with a statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for treatment is not affected.

[1] Gammal RS, Court MH, Haidar CE, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther. 2016;99(4):363-369. doi:10.1002/cpt.269

ATAZANAVIR

Gentest zur Risikominimierung der Therapie mit Atazanavir

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Atazanavir?

Atazanavir ist ein antiretroviraler Wirkstoff zur Behandlung von Infektionen mit dem humanen Immundefizienzvirus (HIV). Atazanavir ist ein Proteasehemmer, der die Vermehrung von HIV verhindert und dadurch die Menge an HIV im Körper verringert.

Gene

Welche Gene beeinflussen die Wirkung von Atazanavir?

Atazanavir ist ein allgemein sicheres Medikament mit weniger Nebenwirkungen im Vergleich zu anderen HIV-Proteaseinhibitoren. Atazanavir hemmt die Uridindiphosphat-Glucuronosyltransferase (UGT1A1) in der Leber und verhindert die Glucuronidierung und Elimination von Bilirubin. Patienten mit *UGT1A1*-Allelen (*28/*28, *28/*37, *37/*37 oder rs887829 T/T), die eine verminderte Funktion des Enzyms aufweisen, zeigen ein erhöhtes Risiko für die Entwicklung eines Ikterus und können bei 20-60 % den Abbruch der Atazanavir-Therapie erforderlich machen. Patienten, die nur ein solches Allel tragen, sind hiervon eher nicht betroffen.

Test

Was wird getestet?

Der Genotyp von Patienten wird im Hinblick auf die *UGT1A1*-Allele (d.h. *28/*28, *28/*37, *37/*37, rs887829 T/T) des *UGT1A1*-Gens getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Atazanavir durchgeführt werden, um gegebenfalls einen Wirkstoffwechsel vorzunehmen, um schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Atazanavir-Therapie (verstärkt mit Ritonavir oder Cobicistat) in Abhängigkeit vom UGT1A1-Genotyp

UGT1A1 Genotyp	Therapieempfehlungen
**1/*1, *1/*36, *36/*36* oder rs887829 C/C	Anwendung gemäß Fachinformation
**1/*28, *1/*37, *36/*28, *36/*37,* rs887829 C/C oder rs887829 C/T	Anwendung gemäß Fachinformation
**28/*28, *28/*37, *37/*37* oder rs887829 T/T	Atazanavir kontraindiziert, Wirkstoffwechsel empfohlen Hohes Risiko für Entwicklung eines Ikterus und Absetzen von Atazanavir (20-60 %)

Kosten

Die Kosten für die Bestimmung des *UGT1A1*-Genotyps werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Untersuchung von einem Arzt verordnet wurde. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Gammal RS, Court MH, Haidar CE, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther. 2016;99(4):363-369. doi:10.1002/cpt.269

ATAZANAVIR

Genetički test za smanjenje rizika pri primjeni atazanavira

Lijek

Koje su indikacije za primjenu i mehanizam djelovanja atazanavira?

Atazanavir je antivirusni lijek koji se primjenjuje u liječenju infekcija izazvanih virusom humane imunodeficijencije (HIV). Pripada u skupinu ihibitora proteaze. Inhibirajući nastajanje funkcionalnih virusnih proteina sprječava umnožavanje virusa i time smanjuje ukupnu količinu virusa u tijelu.

Geni

Koji geni utječu na djelovanje atazanavira?

Atazanavir je uglavnom siguran lijek za primjenu s manje nuspojava u usporedbi s ostalim inhibitorima proteaza. Atazanavir ihibira jetreni enzim uridin-difosfat-glukuronoziltransferazu (UGT1A1) te sprječava glukuronidaciju i eliminaciju bilirubina. U pacijenata koji imaju dva *UGT1A1* alela snižene funkcije (npr. **28/*28, *28/*37, *37/*37* ili rs887829 T/T) povećan je rizik od razvijanja žutice što može dovesti do posljedičnog ukidanja atazanavira. U pojedinaca s jednim ili bez *UGT1A1* alela snižene funkcije razvijanje žutice i ukidanje atazanavira malo su vjerojatni.

Indikacija

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije uvođenja atazanavira u terapiju kako bi se mogao zamijeniti alternativnim lijekom, ukoliko je to potrebno, radi izbjegavanja mogućih nuspojava.

Preporuke i rezultati testiranja

Na koji način se terapija prilagođava rezultatima testa?

Postupak je utemeljen na preporukama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] i ima najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje atazanavirom (uz korištenje ritonavira ili kobicistata) ovisno o UGT1A1 genotipu

***UGT1A1* genotip**	**Preporučena terapija**
*1/*1, *1/*36, *36/*36* ili rs887829 C/C	Terapija sukladno uputama u sažetku opisa svojstava lijeka
**1/*28, *1/*37, *36/*28, *36/*37,* rs887829 C/C ili rs887829 C/T	Terapija sukladno uputama u sažetku opisa svojstava lijeka
**28/*28, *28/*37, *37/*37* ili rs887829 T/T	Upotreba atazanavira se ne preporučuje Preporučuje se uvođenje alternativnog lijeka. Pri uvođenju atazanavira postoji visok rizik od razvoja žutice što posljedično vodi k mogućem ukidanju atazanavira u 20-60 % slučajeva

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *UGT1A1* različito je ovisno o državi. Ukoliko je analiza indicirana od strane liječnika, troškovi za određivanje genotipa *UGT1A1* bit će priznati i refundirani pojedincima koji imaju obavezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Gammal RS, Court MH, Haidar CE, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther. 2016;99(4):363-369. doi:10.1002/cpt.269

ATOMOXETINE

Genetic test to minimize the risk related to therapy with atomoxetine

Drug

What are the indications and mechanisms of action of atomoxetine?

Atomoxetine is a selective norepinephrine reuptake inhibitor used for treating attention-deficit/hyperactivity-disorder (ADHD). Being a nonstimulant, atomoxetine has a delayed onset to clinical effect and typically takes 2–4 weeks for full impact on symptoms to be observed.

Genes

What genes influence the effect of atomoxetine?

Atomoxetine has known adverse effects that include increases in both heart rate and diastolic heart pressure. *CYP2D6* is the main gene that regulates the metabolism of atomoxetine. CYP2C9 enzyme is included in metabolism of atomoxetine to a lesser extent.

Test

What is tested?

In order to determine the highly polymorphic *CYP2D6* (over 100 known variant alleles) metabolism type, the patients' genotype is tested for the most common activity-varying gene variants which are classified into functional groups: normal function (e.g., **1, *2, *35*), decreased function (e.g., **9, *10, *17, *29, *41*) and no function (e.g., *. *3, *4, *5, *6*)

Indication

When should a test be performed?

The genetic test should be performed before the start of the planned therapy with atomoxetine in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted according to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] guideline and have the highest clinical level of evidence 1A.

Table 1: Recommendations for atomoxetine therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype	Recommended therapy
Ultrarapid metabolizer	Usage according to the Summary of Product Characteristics. If no clinical response is observed after 2 weeks, or the peak concentration is less than 200 ng/ml, consider increasing the dose proportionally to approach 400 ng/ml
Rapid metabolizer	Usage according to the Summary of Product Characteristics. If no clinical response is observed after 2 weeks, or the peak concentration is less than 200 ng/ml, consider increasing the dose proportionally to approach 400 ng/ml
Normal or intermediate metabolizer (no *10 allele)	Usage according to the Summary of Product Characteristics. If no clinical response is observed after 2 weeks, or the peak concentration is less than 200 ng/ml, consider increasing the dose proportionally to approach 400 ng/ml
Normal or intermediate metabolizer (*10 allele present)	Initiate atomoxetine with standard dosing. If after 2 weeks the response or plasma concentration are inadequate (<200 ng/ml), consider increasing the dose proportionally to approach concentration 400 ng/ml. If unacceptable side-effects are present, consider a reduction in dose
Intermediate metabolizer	Initiate atomoxetine with standard dosing. If after 2 weeks the response or plasma concentration are inadequate (<200 ng/ml), consider increasing the dose proportionally to approach concentration 400 ng/ml. If unacceptable side-effects are present, consider a reduction in dose
Poor metabolizer	Initiate atomoxetine with standard dosing. If after 2 weeks the response or plasma concentration are inadequate (<200 ng/ml), consider an increase in dose increasing the dose proportionally to approach concentration 400 ng/ml. If unacceptable side-effects are present, consider a reduction in dose

Cost

Costs for the determination of the *CYP2D6* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Brown JT, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther. 2019;106(1):94-102. doi:10.1002/cpt.1409

ATOMOXETIN

Gentest zur Risikominimierung der Therapie mit Atomoxetin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Atomoxetin?

Atomoxetin ist ein aktiver selektiver Noradrenalin-Wiederaufnahmehemmer zur Behandlung von Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (ADHS). Atomoxetin ist ein nicht stimulierendes Mittel, dessen klinische Wirkung verzögert einsetzt. Im allgemeinen dauert es 2 bis 4 Wochen, bis der volle Effekt auf die zu behandelnden Symptome sichtbar wird.

Gene

Welche Gene beeinflussen die Wirkung von Atomoxetin?

Atomoxetin zeigt bekannte Nebenwirkungen in Form von Anstieg der Herzfrequenz und Erhöhung des Blutdrucks. CYP2D6 reguliert hauptsächlich den Stoffwechsel von Atomoxetin. Zusätzlich ist *CYP2C9* in geringerem Maße bei der Metabolisierung beteiligt.

Test

Was wird getestet?

Um den hochpolymorphen Metabolismustyp *CYP2D6* (es sind mehr als 100 Allelvarianten bekannt) zu bestimmen, wird der Genotyp des Patienten auf die häufigsten aktivitätsvarianten Genvarianten getestet, die in funktionelle Gruppen eingeteilt sind: normale Funktion (z. B. **1, *2, *35*), verringerte Funktion (z.B. **9, *10, *17, *29, *41*) und keine Funktion (z.B. **3, *4, *5, *6*).

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Atomoxetin durchgeführt werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu ändern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Atomoxetin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp	Therapieempfehlung
Ultraschnelle Metabolisierer	Anwendung gemäß Fachinformation. Beurteilung nach 2 Wochen Therapie: unzureichendes Ansprechen oder unzureichende Plasmakonzentration (<200ng/ml) Dosiserhöhung (bis zu 400ng/ml); Auftreten inakzeptabler Nebenwirkungen Dosisreduktion
Schnelle Metabolisierer	Anwendung gemäß Fachinformation. Beurteilung nach 2 Wochen Therapie: unzureichendes Ansprechen oder unzureichende Plasmakonzentration (<200ng/ml) Dosiserhöhung (bis zu 400ng/ml); Auftreten inakzeptabler Nebenwirkungen Dosisreduktion
Normale oder intermediäre Metabolisierer (kein *10 Allel)	Anwendung gemäß Fachinformation. Beurteilung nach 2 Wochen Therapie: unzureichendes Ansprechen oder unzureichende Plasmakonzentration (<200ng/ml) Dosiserhöhung (bis zu 400ng/ml); Auftreten inakzeptabler Nebenwirkungen Dosisreduktion
Normale oder intermediäre Metabolisierer (*10 Allel präsent)	Anwendung gemäß Fachinformation. Beurteilung nach 2 Wochen Therapie: unzureichendes Ansprechen oder unzureichende Plasmakonzentration (<200ng/ml) Dosiserhöhung (bis zu 400ng/ml); Auftreten inakzeptabler Nebenwirkungen Dosisreduktion
Intermediäre Metabolisierer	Anwendung gemäß Fachinformation. Beurteilung nach 2 Wochen Therapie: unzureichendes Ansprechen oder unzureichende Plasmakonzentration (<200ng/ml) Dosiserhöhung (bis zu 400ng/ml); Auftreten inakzeptabler Nebenwirkungen Dosisreduktion
Langsame Metabolisierer	Anwendung gemäß Fachinformation. Beurteilung nach 2 Wochen Therapie: unzureichendes Ansprechen oder unzureichende Plasmakonzentration Dosiserhöhung; Auftreten inakzeptabler Nebenwirkungen Dosisreduktion

Kosten

Die Kosten für die Bestimmung des *CYP2D6*-Genotyps werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Untersuchung von einem Arzt verordnet wurde. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Brown JT, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther. 2019 106(1):94-102. (PMID: 30801677)

ATOMOKSETIN

Genetički test za smanjenje rizika pri primjeni atomoksetina

Lijek

Koje su indikacije i mehanizmi djelovanja atomoksetina?

Atomoksetin je selektivni inhibitor ponovne pohrane noradrenalina koji se koristi u liječenju poremećaja pozornosti s hiperaktivnošću (ADHD). Atomoksetin nema stimulirajuće djelovanje, a klinički učinak je odgođen, te je uglavnom potrebno 2 do 4 tjedna kako bi se primijetio potpun učinak na simptome.

Geni

Koji geni utječu na metabolizam atomoksetina?

Atomoksetin ima poznate nuspojave koje uključuju porast srčane frekvencije i dijastoličkog srčanog tlaka. CYP2D6 je glavni enzim uključen u metabolizam atomoksetina. *CYP2C9* gen ima manje značajnu ulogu u metabolizmu atomoksetina.

Analiza

Što se analizira?

Kako bi se odredio tip metabolizma visoko polimorfnog *CYP2D6* gena (preko 100 poznatih varijanti alela), genom pacijenta testira se na najčešće genske varijante koje određuju njegovu aktivnost koje se potom klasificiraju u funkcionalne skupine: normalna funkcija (npr. **1, *2, *35*), smanjena funkcija (npr. **9, *10, *17, *29, *41*) i bez funkcije (npr. **3, *4, *5*6*).

Indikacija

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka liječenja atomoksetinom kako bi se pravovremeno prilagodila doza ili ordinirala zamjenska terapija ukoliko postoji potreba za istom.

Preporuka

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su utemeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za terapiju atomoksetinom ovisno o fenotipu CYP2D6

CYP2D6 fenotip	Preporučena terapija (za djecu i odrasle)
Ultrabrzi metabolizator	Terapija sukladno uputama o lijeku. Ukoliko je nakon 2 tjedna terapijski odgovor nezadovoljavajući, a plazmatska koncentracija <200 ng/ml, razmotriti povećanje doze do koncentracije od 400 ng/ml
Normalni metabolizator	Terapija sukladno uputama o lijeku. Ukoliko je nakon 2 tjedna terapijski odgovor nezadovoljavajući, a plazmatska koncentracija <200 ng/ml, razmotriti povećanje doze do koncentracije od 400 ng/ml
Normalni metabolizator ili intermedijarni metabolizator (nema *10 alela)	Terapija sukladno uputama o lijeku. Ukoliko je nakon 2 tjedna terapijski odgovor nezadovoljavajući, a plazmatska koncentracija <200 ng/ml, razmotriti povećanje doze do koncentracije od 400 ng/ml
Normalni ili intermedijarni metabolizator (*10 alel prisutan)	Terapija sukladno uputama o lijeku. Ukoliko su nakon 2 tjedna terapijski odgovor ili plazmatska koncentracija nezadovoljavajuća (<200 ng/ml), razmotriti povećanje doze do koncentracije 400 ng/ml. Ukoliko dođe do razvoja neprihvatljivih nuspojava, razmotriti sniženje doze
Intermedijarni metabolizator	Terapija sukladno uputama o lijeku. Ukoliko je nakon 2 tjedna terapijski odgovor ili plazmatska koncentracija nezadovoljavajuća (<200 ng/ml), razmotriti povećanje doze do ciljane koncentracije (400 ng/ml). Ukoliko dođe do razvoja neprihvatljivih nuspojava, razmotriti sniženje doze
Spori metabolizator	Terapija sukladno uputama o lijeku. Ukoliko je nakon 2 tjedna terapijski odgovor ili plazmatska koncentracija nezadovoljavajuća (<200 ng/ml), razmotriti povećanje doze do ciljane koncentracije (400 ng/ml). Ukoliko dođe do razvoja neprihvatljivih nuspojava, razmotriti sniženje doze

Troškovi

Priznavanje i povrat troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje *CYP2D6* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Brown JT, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther. 2019;106(1):94-102. doi:10.1002/cpt.1409

AZATHIOPRINE

Genetic test to minimize the risk related to therapy with azathioprine

Drug

What are the indications and mechanisms of action of azathioprine?

Azathioprine is a prodrug and belongs to the group of immunosuppressive drugs mainly used to prevent rejection following allogeneic organ transplantations as well as for the treatment of autoimmune diseases (e.g., rheumatoid arthritis and chronic-inflammatory bowel diseases). Azathioprine is converted to the purine anti-metabolite 6-mercaptopurine by glutathione S-transferase, which antagonistically inhibits purine synthesis as well as DNA and RNA synthesis and thus blocks the propagation of immune cells.

Genes

What genes influence the effect of azathioprine?

Following the conversion of azathioprine into the active agent 6-mercaptopurine, it is inactivated by the enzyme thiopurine methyltransferase (TPMT). In the case of genetically caused *TPMT* deficiency, toxic by-products increasingly accumulate, which can lead to myelosuppression with life-threatening side effects due to their cytotoxic potential. There are known activity-reducing gene variants for the *TPMT* gene which require an adjustment of the dose in order to increase the tolerability with regard to azathioprine.

As a nucleoside diphosphatase, *NUDT15* catalyzes the conversion of the cytotoxic thioguanine triphosphate (TGTP) metabolites to the less toxic thioguanine monophosphate. Genetic variants in *NUDT15* have been identified that strongly influence thiopurine tolerance in patients with acute lymphoblastic leukemia (ALL) and those with inflammatory bowel disease. In the case of genetically caused *NUDT15* deficiency, toxic by-products increasingly accumulate, which can lead to myelosuppression with life-threatening side effects due to their cytotoxic potential.

Test

What is tested?

The genotype of patients is examined with regard to the most common clinically relevant *TPMT* gene variants *(*2, *3A, *3B, *3C, *4)* which in the compound heterozygous or homozygous state lead to a complete loss of the TPMT enzyme activity. The genotype of patients is also examined with regard to the most common clinically relevant *NUDT15* gene variants *(*2, *3)* which in the compound heterozygous or homozygous state lead to a partial or complete loss of the NUDT15 enzyme activity.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with azathioprine in order to reduce the risk of myelosuppression, as required, by means of an adjustment of the initial dose or by prescribing an alternative active agent. In 30-60 percent of patients with a heterozygous *TPMT* risk genotype, the standard dose involves the risk of side effects. Inherited TMPT deficiency is the primary genetic cause of thiopurine intolerance in Europeans and Africans, whereas risk alleles in *NUDT15* explain the majority of thiopurine-related myelosuppression in Asians and are also common in Hispanics.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for azathioprine therapy depending on the TPMT genotype

***TPMT* Genotype / Phenotype**	**Recommended therapy**
Wild type / Normal metabolizer	Usage according to the Summary of Product Characteristics
Risk variant, heterozygous / Intermediate metabolizer	The initial dose should correspond to 30-80 % of the normal dose, adjust doses based on degree of myelosuppression
Risk variant, compound heterozygous or homozygous / Poor metabolizer	In non-malignant conditions: substitution of an active agent with non-thiopurine imunosuppressants is recommended In malignancy: Change of the active agent or drastic reduction of the initial dose (10-fold reduction and only on 3 days/week)

Table 2: Recommendations for azathioprine therapy depending on the NUDT15 genotype

***NUDT15* Genotype / Phenotype**	**Recommended therapy**
Wild type / Normal metabolizer	Usage according to the Summary of Product Characteristics
Risk variant, heterozygous / Intermediate metabolizer	The initial dose should correspond to 30-80 % of the normal dose usage based on the degree of myelosuppression
Risk variant, compound heterozygous or homozygous / Poor metabolizer	For nonmalignant conditions: consider alternative nonthiopurine immunosuppressant therapy For malignancy: Change of the active agent or drastic reduction of the initial dose (10-fold reduction)

Costs

Costs for the *TPMT* and *NUDT15* genes analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

AZATHIOPRIN

Gentest zur Risikominimierung der Therapie mit Azathioprin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Azathioprin?

Azathioprin ist ein Prodrug und gehört zur Gruppe der Immunsuppressiva. Es wird vorrangig zur Verhinderung der Abstoßung nach allogenen Organtransplantationen sowie zur Behandlung von Autoimmunerkrankungen wie rheumatoider Arthritis und chronisch-entzündlichen Darmerkrankungen verwendet. Azathioprin wird durch die Glutathion-S-Transferase in den Purinantimetaboliten 6-Mercaptopurin umgewandelt. Dieser hemmt antagonistisch sowohl die Purinsynthese als auch die DNA- und RNA-Synthese und blockiert so die Vermehrung von Immunzellen.

Gene

Welche Gene beeinflussen die Wirkung von Azathioprin?

Nach der Umwandlung von Azathioprin in den Wirkstoff 6-Mercaptopurin wird dieser durch das Enzym Thiopurin-Methyltransferase (TPMT) inaktiviert. Bei einer genetisch bedingten *TPMT*-Defizienz kumulieren zunehmend toxische Nebenprodukte, die aufgrund ihres zytotoxischen Potenzials zu einer Myelosuppression mit lebensbedrohlichen Nebenwirkungen führen können. Für das *TPMT*-Gen sind in der Bevölkerung aktivitätsreduzierende Genvarianten bekannt, die eine Dosisanpassung erfordern, um die Verträglichkeit von Azathioprin zu erhöhen.

Die Nucleosiddiphosphatase/Nudix-Hydrolase 15 (NUDT15) katalysiert die Umwandlung der zytotoxischen Thioguanintriphosphat (TGTP)-Metaboliten in das weniger toxische Thioguaninmonophosphat (TGMP). Es gibt genetische Varianten von *NUDT15*, die Thiopurintoleranz bei Patienten mit akuter lymphoblastischer Leukämie (ALL) und bei Patienten mit entzündlichen Darmerkrankungen stark beeinflussen. Bei genetisch bedingtem funktionellem *NUDT15*-Mangel reichern sich toxische Nebenprodukte an, die zu einer Myelosuppression mit lebensbedrohlichen Nebenwirkungen führen können.

Test

Was wird getestet?

Der Genotyp von Patienten wird auf die häufigsten klinisch relevanten *TPMT*-Genvarianten *(*2, *3A, *3B, *3C, *4)* untersucht, die im compound heterozygoten oder homozygoten Zustand zu einem vollständigen Verlust der TPMT-Enzymaktivität führen. Zudem wird der Genotyp von Patienten auf die häufigsten klinisch relevanten *NUDT15*-Genvarianten *(*2, *3)* untersucht, die im compound heterozygoten oder homozygoten Zustand zu einem partiellen oder vollständigen Verlust der NUDT15-Enzymaktivität führen.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Azathioprin durchgeführt werden, um gegebenfalls durch eine Anpassung der Startdosis oder die Verordnung eines alternativen Wirkstoffs das Risiko einer Myelosuppression zu senken. Bei 30-60 % der Patienten mit einem heterozygoten *TPMT*-Risikogenotyp ist die Standarddosis mit dem Risiko von Nebenwirkungen verbunden. Der angeborene TMPT-Mangel ist die primäre genetische Ursache für die Thiopurin-Intoleranz bei Europäern und Afrikanern, während bei Asiaten und Hispanics Risiko-Allele in *NUDT15* die Mehrheit der Thiopurin-bedingten Myelosuppression erklären.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Azathioprin-Therapie in Abhängigkeit vom TPMT-Genotyp

TPMT Genotyp / Phänotyp	Therapieempfehlung
Wildtyp / Normale Metabolisierer	Anwendung gemäß der Fachinformation
Risikovariante, heterozygot / Intermediäre Metabolisierer	Startdosis um 30-80 % reduzieren Anpassung der Dosis an Grad der Myelosuppression
Risikovariante, compound heterozygot oder homozygote / Langsame Metabolisierer	Bei nicht malignen Erkrankungen: Wirkstoffwechsel mit nicht-Thiopurin-Immunspressiva empfohlen Bei malignen Erkrankungen: Startdosis drastisch reduzieren (10-fach reduziert und nur an 3 Tagen/Woche)

Tabelle 2: Empfehlungen für die Azathioprin-Therapie in Abhängigkeit vom NUDT15-Genotyp

***NUDT15* Genotyp / Phänotyp**	**Therapieempfehlung**
Wildtyp / Normale Metabolisierer	Anwendung gemäß der Fachinformation
Risikovariante, heterozygot / Intermediäre Metabolisierer	Startdosis um 30-80 % reduzieren Anpassung der Dosis an Grad der Myelosuppression
Risikovariante, compound heterozygot oder homozygote / Langsame Metabolisierer	Bei nicht malignen Erkrankungen: Wirkstoffwechsel mit nicht-Thiopurin-Immunspressiva empfohlen Bei malignen Erkrankungen: Startdosis drastisch reduzieren (10-fach reduziert)

Kosten

Die Kosten für die genetische Analyse des *TMPT*-Gens und des *NUDT15*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

AZATIOPRIN

Genetički test za smanjenje rizika pri primjeni azatioprina

Lijek

Koje su indikacije i mehanizmi djelovanja azatioprina?

Azatioprin je prolijek i pripada grupi imunosupresivnih lijekova koji se uglavnom koriste u prevenciji odbacivanja presatka nakon alogenične transplantacije organa kao i u terapiji autoimunih bolesti (reumatoidni artritis i kronične upalne bolesti crijeva). Azatioprin se konvertira u purinski anti-metabolit 6-merkaptopurin putem glutation S-transferaze, koji inhibira sintezu purina kao i sintezu DNA i RNA.

Geni

Koji geni utječu na djelovanje azatioprina?

Nakon konverzije azatioprina u aktivnu formu 6-merkaptopurin, lijek se inaktivira putem enzima tiopurin metiltransferaze (TPMT). U slučaju genski uzrokovane deficijencije TPMT dolazi do odgođene razgradnje aktivne tvari, pri čemu može doći do teške, po život opasne supresije koštane srži. Poznate su varijante *TPMT* gena koje za posljedicu imaju smanjenu aktivnost enzima koja zahtjeva prilagodbu doze azatioprina kako bi se povećala podnošljivost terapije.

NUDT15, nukleozidna difosfataza, enzim je koji katalizira konverziju citotoksičnog metabolita tiogvanin trifosfata (TGTP) u manje toksičan tiogvanin monofosfat. Genetske varijante u *NUDT15* snažno utječu na toleranciju na tiopurine kod pacijenata koji boluju od akutne limfoblastične leukemije (ALL) i upalnih bolesti crijeva. Smanjena aktivnost NUDT15 također za posljedicu ima akumulaciju toksičnih metabolita koji mogu dovesti do oštećenja funkcije koštane srži (mijelosupresija) s nuspojavama opasnim po život.

Test

Što se analizira?

Analizira se genotip pacijenta na najučestalije klinički relevantne varijante gena *TPMT (*2, *3A, *3B, *3C i *4)* koji u kombiniranih (združenih) heterozigota (eng. compound heterozygous) ili homozigota vode do potpunog gubitka aktivnosti enzima *TPMT*.

Također se analiziraju najučestalije klinički relevantne varijante gena *NUDT15 (*2, *3)* koje kombinirane (združene) u heterozigota ili homozigota za posljedicu imaju djelomični ili potpuni gubitak aktivnosti enzima NUDT15.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije azatioprinom da bi se smanjio rizik supresije koštane srži (poremećaj hematopoeze) putem prilagođavanja početne doze ili ordiniranjem alternativnog lijeka.

U 30-60 % pacijenata s heterozigotnim *TPMT* genotipom, standardna doza lijeka uključuje rizik od nuspojava. Genski uvjetovana smanjena aktivnost TMPT kao primarni uzrok nepodnošenja tiogvanina češća je u Europljana i Afrikanaca dok rizični aleli u *NUDT15* objašnjavaju većinu supresija koštane srži povezanih s terapijom tiopurinima u Azijata i Hispanoamerikanaca.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Postupak je temeljen na preporukama smjernica the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] uz najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje azatioprinom ovisno o TPMT genotipu

***TPMT* genotip / Fenotip**	**Preporučena terapija**
Divlji tip / Normalni metabolizator	Terapija sukladno uputama o lijeku
Rizična varijanta, heterozigot / Intermedijarni metabolizator	Početna doza trebala bi iznositi 30-80 % normalne doze lijeka u nemalignim stanjima. Potrebno je podešavanje doze s obzirom na stupanj mijelosupresije
Rizična varijanta, recipročni/translokacijski heterozigoti ("compound heterozygous") ili homozigot / Spori metabolizator	Za maligna stanja: drastična redukcija inicijalne doze (10-struko reducirana doza i samo 3 dana/tjedno), potrebno je podešavanje doze s obzirom na stupanj mijelosupresije Za nemaligna stanja: razmotriti alternativnu imunosupresivnu terapiju koja nije iz skupine tiopurina

Tablica 2: Preporuke za liječenje azatioprinom ovisno o NUDT15 genotipu

***NUDT15* genotip / Fenotip**	**Preporučena terapija**
Divlji tip / Normalni metabolizator	Terapija sukladno uputama o lijeku
Rizična varijanta, heterozigot / Intermedijarni metabolizator	Početna doza trebala bi iznositi 30-80 % prosječne doze lijeka, potrebno je podešavanje doze s obzirom na stupanj mijelosupresije
Rizična varijanta, recipročni/translokacijski heterozigoti ("compound heterozygous") ili homozigot / Spori metabolizator	Za malignitete: drastična redukcija početne doze (10-struko reducirana doza) Za nemaligna stanja: razmotriti alternativnu imunosupresivnu terapiju koja nije iz skupine tiopurina

Troškovi

Priznavanje i povrat troškova za navedenu analizu *TPMT* i *NUDT15* varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

CARBAMAZEPINE

Genetic test to minimize the risks related to therapy with carbamazepine

Drug

What are the indications and mechanisms of action of carbamazepine?

Carbamazepine is a frequently prescribed anticonvulsant drug, used for the treatment of different forms of epilepsy, neuropathic pain, bipolar disorders and for co-treatment during alcohol withdrawal. Carbamazepine suppresses the excitability of nerve cells by blocking the sodium channels of the cell membrane. It furthermore inhibits the release of the neurotransmitter glutamate.

Genes

What genes influence the effect of carbamazepine?

Approximately 5-10 percent of patients present with different side effects under carbamazepine therapy, such as central nervous disorders, problems with the gastrointestinal tract or hematopoietic changes. Furthermore, the drug can cause severe immunological hypersensitivity reactions in patients who carry the alleles *HLA-A*31:01* (*HLA-A* gene) or *HLA-B*15:02* (*HLA-B* gene) which manifest as DRESS (drug reaction with eosinophilia and systemic symptoms), MPE (maculopapular exanthema), SJS (Stevens-Johnson syndrome) and TEN (toxic epidermal necrolysis).

Test

What is tested?

The genotype of patients is tested with regard to the alleles *HLA-A*31:01* and *HLA-B*15:02* in the *HLA-A* and *HLA-B* genes[1,2,3].

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with carbamazepine in order to change the active agent, as required, so that severe side effects can be avoided.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on the guidelines of *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] for *HLA* Genotype and have the highest clinical level of evidence 1A.

Table 1: Recommendations for carbamazepine therapy according to HLA-gene A and B genotype

***HLA* Genotype**	**Recommended therapy**
*HLA-B*15:02* negative *HLA-A* 31:01* negative	Usage according to the Summary of Product Characteristics
*HLA-B*15:02* negative *HLA-A*31:01* positive	Change of active agent recommended
*HLA-B*15:02* positive *HLA-A*31:01* negative	Change of active agent recommended
*HLA-B*15:02* or *HLA-A*31:01* positive (heterozygote, compound heterozygote or homozygote)	Change of active agent recommended

Nota bene: Patients who have been continuously taking carbamazepine for longer than 3 months without developing cutaneous reactions are at extremely low risk of adverse events in the future, regardless of *HLA-B*15:02* status.

Costs

Costs for the determination of the *HLA-A* and *HL-B* gene are reimbursed for patients with statutory or private health insurance if testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Amstutz U, Shear NH, Rieder MJ, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55(4):496-506. doi:10.1111/epi.12564

[2] Leckband SG, Kelsoe JR, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013;94(3):324-328. doi:10.1038/clpt.2013.103

[3] Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581. doi:10.1002/cpt.1004

CARBAMAZEPIN

Gentest zur Risikominimierung der Therapie mit Carbamazepin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Carbamazepin?

Carbamazepin ist eines der am häufigsten verordneten Antikonvulsiva. Es wird zur Behandlung verschiedener Formen der Epilepsie, bei Neuralgien, der bipolaren Störung und zur Begleitung des Alkoholentzugs eingesetzt. Carbamazepin unterdrückt die Erregbarkeit von Neuronen durch eine Blockade der Natriumkanäle in der Zellmembran. Es inhibiert zudem die Freisetzung des Neurotransmitters Glutamat.

Gene

Welche Gene beeinflussen die Wirkung von Carbamazepin?

Ungefähr 5-10 % der Patienten erleiden bei einer Carbamazepin-Therapie verschiedenartige Nebenwirkungen, wie zentralnervöse Störungen, Beschwerden im Magen-Darm-Trakt, Blutbildungsveränderungen und weiteres. Demgegenüber kann das Medikament bei Patienten, die Träger der HLA-Allele *HLA-A*31:01* (*HLA-A*-Gen) oder *HLA-B*15:02* (*HLA-B*-Gen) sind, schwerste immunologische Überempfindlichkeitsreaktionen auslösen, die sich als Arzneimittelreaktion mit Eosinophilie und systemischen Symptomen (DRESS), makulopapuläres Exanthem (MPE), Stevens-Johnson-Syndrom (SJS) oder toxische epidermale Nekrolyse (TEN) manifestieren.

Test

Was wird getestet?

Das Erbgut der Patienten wird auf die Allele *HLA-A*31:01* (*HLA-A*-Gen) und *HLA-B*15:02* (*HLA-B*-Gen) getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Carbamazepin durchgeführt werden, um gegebenfalls einen Wirkstoffwechsel vorzunehmen und schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und für den HLA-Genotyp und die Verwendung von Carbamazepin und Oxcarbazepin: Update[3] 2017. Die Empfehlungen zeigen das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Carbamazepin-Therapie in Abhängigkeit vom HLA-Gen A- und B-Genotyp

***HLA* Genotyp**	**Therapieempfehlung**
*HLA-B*15:02* negativ *HLA-A*31:01* negativ	Anwendung gemäß Fachinformation
*HLA-B*15:02* negativ *HLA-A*31:01* positiv	Wirkstoffwechsel empfohlen
*HLA-B*15:02* positiv *HLA-A*31:01* negativ	Wirkstoffwechsel empfohlen
*HLA-B*15:02* oder *HLA-A*31:01* positiv (heterozygot, compound heterozygot oder homozygot)	Wirkstoffwechsel empfohlen

Nota bene: Patienten, die Carbamazepin länger als 3 Monate kontinuierlich eingenommen haben ohne Hautreaktionen zu entwickeln, weisen unabhängig vom *HLA-B * 15: 02*-Status ein äußerst geringes Risiko für zukünftige Nebenwirkungen auf.

Kosten

Die Kosten für die genetische Analyse der *HLA-A*- und *HLA-B*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Leckband SG, Kelsoe JR, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013;94(3):324-328. doi:10.1038/clpt.2013.103.

[2] Amstutz U, Shear NH, Rieder MJ, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55(4):496-506. doi:10.1111/epi.12564.

[3] Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581. doi:10.1002/cpt.1004.

KARBAMAZEPIN

Genetički test za smanjenje rizika pri primjeni karbamazepina

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja karbamazepina?

Karbamazepin je često ordiniran antikonvulzivni lijek. Primjenjuje se u liječenju različitih oblika epilepsije, zatim kod neuropatske boli, bipolarnih poremećaja te kod sindroma ustezanja od alkohola. Karbamazepin suprimira podražljivost živčanih stanica putem blokade natrijskih kanala stanične membrane, te inhibira oslobađanje neurotransmitora glutamata.

Geni

Koji geni utječu na djelovanje karbamazepina?

Tijekom liječenja karbamazepinom, 5-10 % pacijenata žali se na različite nuspojave, kao što su smetnje središnjeg živčanog sustava, problemi s probavnim sustavom ili hematopoetske promjene. Nadalje, ovaj lijek može kod pacijenata koji su nositelji alela *HLA-A*31:01* (gen *HLA-A*) ili alela *HLA-B*15:02* (gen *HLA-B*) izazvati teške imunološke reakcije preosjetljivosti koje se manifestiraju kao reakcija na lijek s eozinofilijom i sistemskim simptomima (eng. drug reaction with eosinophilia and systemic symptoms, DRESS), makulopapularni osip (eng. maculopapular exanthema, MPE), Steven-Johnsonov sindrom (eng. Stevens-Johnson syndrome, SJS) i toksična epidermalna nekroliza (eng. toxic epidermal necrolysis, TEN).

Analiza

Što se analizira?

Analizira se genotip pacijenata, prvenstveno aleli *HLA-A*31:01* (gen *HLA-A*) i *HLA-B*15:02* (gen *HLA-B*) [1,2,3].

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka liječenja karbamazepinom, kako bi se pravovremeno ordinirala zamjenska terapija i izbjegle teške nuspojave.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] za *HLA* genotip. Preporuke imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za terapiju karbamazepinom ovisno o HLA-A i HLA-B genotipovima

***HLA* genotip**	**Preporučena terapija**
*HLA-B*15:02* negativan *HLA-A* 31:01* negativan	Korištenje sukladno uputama o lijeku
*HLA-B*15:02* negativan *HLA-A*31:01* pozitivan	Preporučuje se primjena zamjenskog lijeka
*HLA-B*15:02* pozitivan *HLA-A*31:01* negativan	Preporučuje se primjena zamjenskog lijeka
*HLA-B*15:02* ili *HLA-A*31:01* pozitivan (heterozigot, kombinirani heterozigot ili homozigot)	Preporučuje se primjena zamjenskog lijeka

Nota bene: Pacijenti koji su kontinuirano uzimali karbamazepin dulje od 3 mjeseca bez razvijanja kožne reakcije imaju izuzetno niski rizik nuspojava u budućnosti, neovisno o statusu *HLA-B*15:02*.

Troškovi

Troškovi za određivanje *HLA-A* i *HLA-B* genotipova bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje ukoliko je testiranje zatraženo od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Amstutz U, Shear NH, Rieder MJ, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55(4):496-506. doi:10.1111/epi.12564

[2] Leckband SG, Kelsoe JR, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013;94(3):324-328. doi:10.1038/clpt.2013.103

[3] Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581. doi:10.1002/cpt.1004

CELECOXIB

Genetic test to minimize the risks related to therapy with celecoxib

Drug

What are the indications and mechanisms of action of celecoxib?

Celecoxib is a nonsteroidal drug with antiinflammatory and analgesic properties. Its therapeutic effects occur via inhibition of prostaglandin biosynthesis from arachidonic acid by cyclooxygenases (COX) isoforms 1 and 2. Celecoxib preferentially inhibits COX-2 isoform.

Genes

Which genes influence the effect of celecoxib?

Celecoxib is metabolized via the enzyme CYP2C9. A decrease in the CYP2C9 function decreases the metabolic clearance of celecoxib thus prolonging its plasma elimination half-life. Several variants of the *CYP2C9* gene with great variability in the enzymatic activity of CYP2C9 are known in the population.

Test

What is tested?

To determine the CYP2C9 metabolism type, the testing of *CYP2C9* gene variants *(*2, *3)* associated with significantly reduced CYP2C9 enzyme activity is recommended.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the therapy with celecoxib, in order to minimize the risk for side effects such as gastrointestinal bleeding, hypertension, myocardial infarction, heart failure, and renal damage through an adjustment of the starting dose or the prescription of an alternative treatment.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for celecoxib therapy according to the CYP2C9 genotype

***CYP2C9* Genotype / Phenotype**	**Recommended therapy**
*CYP2C9*1/*1* / Normal metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*2* / Intermediate metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*3, *2/*2* / Intermediate metabolizer	Initiate therapy with the lowest recommended starting dose and titrate upward to clinical effect or maximum recommended dose with caution, especially in individuals with other factors affecting clearance such as hepatic impairment or advanced age
*CYP2C9*2/*3, *3/*3* / Poor metabolizer	Initiate therapy with 25–50 % of the lowest recommended starting dose and titrate dose upward to clinical effect or 25–50 % of the maximum recommended dose with caution. Alternatively, consider the other drug not primarily metabolized by CYP2C9

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

CELECOXIB

Gentest zur Risikominimierung der Therapie mit Celecoxib

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Celecoxib?

Celecoxib ist ein nichtsteroidales Medikament mit entzündungshemmenden und analgetischen Eigenschaften. Seine therapeutischen Wirkungen treten über die Hemmung der Prostaglandin-Biosynthese aus Arachidonsäure durch die Cyclooxygenasen (COX)-Isoformen 1 und 2 auf. Celecoxib hemmt vorzugsweise die COX-2-Isoform.

Gene

Welche Gene beeinflussen die Wirkung von Celecobix?

Celecobix wird über das Enzym CYP2C9 metabolisiert. Eine Abnahme der CYP2C9-Funktion verringert die metabolische Clearance (Ausscheidung) von Celecoxib und verlängert so die Halbwertszeit der Plasmaelimination. In der Population sind mehrere Varianten des *CYP2C9*-Gens mit großer Variabilität der enzymatischen Aktivität von CYP2C9 bekannt.

Test

Was wird getestet?

Zur Bestimmung des *CYP2C9*-Metabolismus wird empfohlen, *CYP2C9*-Genvarianten *(*2, *3)* zu testen, die mit einer signifikant verringerten *CYP2C9*-Enzymaktivität assoziiert sind.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der Therapie mit Celecoxib durchgeführt werden, um das Risiko für Nebenwirkungen wie gastrointestinale Blutungen, Bluthochdruck, Myokardinfarkt, Herzinsuffizienz und Nierenschäden durch Anpassung der Anfangsdosis oder der Verschreibung einer alternativen Behandlung zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Celecoxib-Therapie in Abhängigkeit vom CYP2C9-Genotyp

***CYP2C9* Genotyp / Phänotyp**	**Therapieempfehlung**
*CYP2C9*1/*1* / Normale Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*2* / Intermediate metabolizer	Anwendung gemäß Fachinformation
*CYP2C9*1/*3, *2/*2* / Intermediäre Metabolisierer	Start mit der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder empfohlene maximale Dosis, insbesondere bei Vorliegen von Leberfunktionsstörung oder höherem Alter
*CYP2C9*2/*3, *3/*3* / Langsame Metabolisierer	Start mit 25-50 % der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder 25-50 % der empfohlenen maximalen Dosis Alternativ: Wechsel auf Wirkstoff ohne *CYP2C9*-Metabolismus

Kosten

Die Kosten für die genetische Analyse des *CYP2C9* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

CELEKOKSIB

Genetički test za smanjenje rizika pri primjeni celekoksiba

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja celekoksiba?

Celekoksib je nesteroidni lijek s protuupalnim i analgetskim djelovanjem. Njegov mehanizam djelovanja temelji se na inhibiciji biosinteze prostaglandina iz arahidonske kiseline djelovanjem enzima ciklooksigenaze (COX), izoformi 1 i 2. Celekoksib je selektivniji, reverzibilni inhibitor COX-2 izoforme.

Geni

Koji geni utječu na djelovanje celekoksiba?

Celekoksib se metabolizira putem enzima CYP2C9. Smanjenje funkcije CYP2C9 usporava eliminaciju celekoksiba iz organizma i produljuje poluvrijeme eliminacije. Poznato je nekoliko varijanti *CYP2C9* gena s velikom varijabilnošću u enzimskoj aktivnosti CYP2C9 u populaciji.

Analiza

Što se analizira?

Kako bi se odredio metabolizam s obzirom na CYP2C9, preporučuje se utvrđivanje prisutnosti varijanti *CYP2C9* gena *(*2, *3)* koje su povezane sa značajno reduciranim kapacitetom enzimske aktivnosti.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije celekoksibom kako bi se smanjio rizik nuspojava kao što su gastrointestinalno krvarenje, hipertenzija, infarkt miokarda, srčano zatajenje i bubrežno oštećenje tako da se prilagodi početna doza ili propiše druga terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje celekoksibom ovisno o CYP2C9 genotipu

***CYP2C9* genotip / fenotip**	**Preporučena terapija**
*CYP2C9*1/*1* / Normalni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*2* / Intermedijarni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*3, *2/*2* / Intermedijarni metabolizator	Započnite terapiju s najnižom preporučenom dozom i titrirajte do željenog kliničkog učinka ili do najveće preporučene doze s oprezom, osobito u pojedinaca koji imaju rizične faktore koji utječu na eliminaciju lijeka kao što su jetreno oštećenje i starija životna dob
*CYP2C9*2/*3, *3/*3* / Spori metabolizator	Započnite terapiju s 25–50 % najniže preporučene doze i oprezno titrirajte do željenog kliničkog učinka ili do najviše 25–50 % od maksimalne preporučene doze. Alternativno, odaberite lijek koji se primarno ne metabolizira putem CYP2C9

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *CYP2C9* varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *CYP2C9* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugss [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

CITALOPRAM

Genetic test to minimize the risks related to therapy with citalopram

Drug

What are the indications and mechanism of action of citalopram?

Citalopram belongs to the class of drugs called selective serotonin reuptake inhibitors (SSRIs). SSRIs are typically used in the treatment of major depressive disorder and anxiety disorders. SSRIs inhibit the reuptake of serotonin into the presynaptic cell, thus increasing its level in the synaptic cleft and presynaptic and postsynaptic actions. They also have a low degree of selectivity for the norepinephrine and dopamine transporters.

Genes

Which genes influence the effect of citalopram?

Citalopram is extensively metabolized by CYP2C19 enzyme to inactive metabolites. *CYP2C19* genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis.

Test

What will be tested?

Commonly reported *CYP2C19* star-alleles are categorized into functional groups (e.g., normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme. To determine the CYP2C19 metabolism type, the patient's *CYP2C19* genotype is tested for the most common activity-variant gene variants (*1, *2, *3, *17).

Indications

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with citalopram in order to change the active agent, as required, so that severe side effects can be avoided.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for therapy with citalopram depending on CYP2C19 genotype and resulting phenotype

***CYP2C19* Genotype / Phenotype (metabolizer status frequencies)**	**Recommended therapy**
**17/*17, *1/*17* / Ultrarapid metabolizer (5-30 %)	Change of active agent recommended
**1/*1* / Rapid metabolizer (35-50 %)	Usage according to the Summary of Product Characteristics
**1/*2, *1/*3, *2/*17* / Intermediate metabolizer (18-45 %)	Usage according to the Summary of Product Characteristics
**2/*2, *2/*3, *3/*3* / Poor metabolizer (2-15 %)	Change of active agent recommended If introducing citalopram: reduction of initial dose to 50 % of the normal dose, titration is needed to a higher target doses

Costs

Costs for the determination of the *CYP2C19* genotype are reimbursed for patients with statutory or private health insurance if testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

CITALOPRAM

Gentest zur Risikominimierung der Therapie mit Citalopram

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Citalopram?

Citalopram ist ein selektiver Serotonin-Wiederaufnahmehemmer (SSRIs), der als Antidepressiva bei der Behandlung von Depressionen und Angststörungen eingesetzt wird. Der genaue Wirkungsmechanismus von SSRIs ist unbekannt. Es wird angenommen, dass eine Erhöhung des extrazellulären Serotoninspiegel im synaptischen Spalt durch Limitierung der Reabsorption (Wiederaufnahme) in die präsynaptische Zelle erreicht wird. Es sind unterschiedliche Selektivitätsgrade für die anderen Monoamintransporter vorhanden, wobei reine SSRIs nur eine schwache Affinität für die Norepinephrin- und Dopamintransporter aufweisen.

Gene

Welche Gene beeinflussen die Wirkung von Citalopram?

Citalopram wird durch das CYP2C19-Enzym weitgehend zu inaktiven Metaboliten metabolisiert. Genetische Varianten von *CYP2C19* werden typischerweise als Haplotypen angegeben, die durch eine spezifische Kombination von Einzelnukleotidpolymorphismen (SNPs) und / oder anderen Sequenzvarianten definiert sind, einschließlich Insertionen und Deletionen, die während der Genotypisierungsanalyse abgefragt werden.

Test

Was wird getestet?

Häufig berichtete *CYP2C19*-Allele werden basierend auf der vorhergesagten Aktivität des kodierten Enzyms in Phänotypen (ultraschnelle-schnelle-normale-langsame) eingeteilt. Um den CYP2C19-Metabolismustyp zu bestimmen, wird der Genotyp des Patienten im *CYP2C19*-Gen *(*1, *2, *3, *17)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikationen

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Citalopram durchgeführt werden, um gegebenfalls einen Wirkstoffwechsel in Erwägung zu ziehen, um schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Citalopram-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

***CYP2C19* Genotyp / Phänotyp (Metabolisiererhäufigkeit)**	**Therapieempfehlung**
**17/*17, *1/*17* / Ultraschnelle Metabolisierer (5-30 %)	Wirkstoffwechsel empfohlen
**1/*1* / Schnelle Metabolisierer (35-50 %)	Therapie gemäß Fachinformation
**1/*2, *1/*3, *2/*17* / Intermediäre Metabolisierer (18-45 %)	Therapie gemäß Fachinformation
**2/*2, *2/*3, *3/*3* / Langsame Metabolisierer (2-15 %)	Wirkstoffwechsel empfohlen Bei Einsatz von Citalopram: Startdosis um 50 % reduzieren, auf höhere Zieldosis titrieren

Kosten

Die Kosten für die genetische Analyse des *CYP2C19*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A; Clinical Pharmacogenetics Implementation Consortium. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015 98(2):127-34. PMID: 25974703

CITALOPRAM

Genetički test za smanjenje rizika pri primjeni citaloprama

Lijek

Koje su indikacije i mehanizmi djelovanja citaloprama?

Citalopram pripada skupini lijekova koja se naziva selektivni inhibitori ponovne pohrane serotonina (eng. selective serotonin reuptake inhibitors, SSRI). Ova se skupina lijekova tipično koristi u liječenju depresivnih i anksioznih poremećaja. Citalopram inhibira ponovni povrat serotonina u presinaptički neuron čime se povećava njegova količina u sinaptičkoj pukotini, kao i presinaptičko i postsinaptičko djelovanje. Također, ima nisku razinu selektivnosti za transportere noradrenalina i dopamina.

Geni

Koji geni utječu na djelovanje citaloprama?

Citalopram se ekstenzivno metabolizira putem CYP2C19 enzima do inaktivnih metabolita. *CYP2C19* genetičke varijante tipično se opisuju kao haplotipovi, koji su definirani pomoću specifične kombinacije polimorfizma jednog nukleotida (SNP) i drugih varijacija, uključujući insercije i delecije, koje se ispituju tijekom genotipizacije.

Analiza

Što se analizira?

CYP2C19 aleli označeni zvjezdicom kategoriziraju se u funkcionalne skupine (npr. pojačana funkcija, normalna funkcija, oslabljena funkcija) prema predviđenoj aktivnosti kodiranog enzima. Za određivanje vrste CYP2C19 metabolizma, pacijentov *CYP2C19* genotip se testira za česte genske varijante (*1, *2, *3, *17).

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka terapije citalopramom kako bi se mogao primijeniti zamjenski lijek, ukoliko je potrebno, da se izbjegnu značajne nuspojave.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za terapiju citalopramom ovisno o genotipu CYP2C19 i rezultirajućim fenotipom

***CYP2C19* Genotip / Fenotip (učestalost metabolizatora)**	**Preporučena terapija**
**17/*17, *1/*17* / Ultrabrzi metabolizator (5-30 %)	Preporučuje se primjena zamjenskog lijeka
**1/*1* / Brzi metabolizator (35-50 %)	Terapija sukladno uputama o lijeku
**1/*2, *1/*3, *2/*17* / Intermedijarni metabolizator (18-45 %)	Terapija sukladno uputama o lijeku
**2/*2, *2/*3, *3/*3* / Spori metabolizator (2-15 %)	Preporučuje se primjena zamjenskog lijeka Ukoliko se uvodi citalopram: smanjiti početnu dozu na 50 % normalne doze. Titracija je potrebna za više doze

Troškovi

Troškovi za određivanje *CYP2C19* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje ukoliko je testiranje zatraženo od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

CLOMIPRAMINE

Genetic test to minimize the risks related to therapy with clomipramine

Drug

What are the indications and mechanisms of action of clomipramine?

Tricyclic antidepressant clomipramine is an inhibitor of both serotonin and norepinephrine reuptake in the presynaptic neuron. In addition, clomipramine has antiadrenergic, antihistaminic, antiserotonergic, antidopaminergic, and anticholinergic activities. It is indicated for the treatment of depression, obsessive-compulsive disorders as well as neuropathic pain and migraine prophylaxis.

Genes

Which genes influence the effect of clomipramine?

Clomipramine, as tertiary amine, is metabolized via the enzyme CYP2C19 to secondary amine. Both are further metabolized via the CYP2D6 enzyme to less-active metabolites. Both enzymes play a decisive role in its efficiency and duration of action of clomipramine. Several variants in the genes of these two enzymes are known in the population. These lead to great variability in the enzymatic efficacy of CYP2C19 and CYP2D6.

Test

What will be tested?

In order to determine the CYP2C19 as well as the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying gene variants in the *CYP2C19* gene *(*2, *3, *17)* and in the *CYP2D6* gene *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)*.

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with clomipramine in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1,2] and have the highest clinical level of evidence 1A for *CYP2D6* and medium clinical evidence level 2A for *CYP2C19*.

Table 1: Recommendations for clomipramine therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-20 %)	Usage of clomipramine is not recommended, prescription of an alternative agent should be considered. If clomipramine is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Therapeutic drug monitoring is strongly recommended
Normal metabolizer (72-88 %)	Usage according to the Summary of Product Characteristics
Intermediate metabolizer (1-13 %)	Reduction of starting dose of clomipramine by 25 %
Poor metabolizer (1-10 %)	Usage of clomipramine is not recommended, prescription of an alternative agent recommended. If clomipramine is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Table 2: Recommendations for clomipramine therapy depending on the phenotype of the CYP2C19 gene

CYP2C19 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (2-5 %)	Usage of clomipramine not recommended, prescription of an alternative agent recommended. If clomipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Rapid metabolizer (2-30 %)	Usage of clomipramine not recommended, prescription of an alternative agent is recommended. If clomipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Normal metabolizer (35-50 %)	Initiate therapy with recommended starting dose
Intermediate metabolizer (18-45 %)	Initiate therapy with recommended starting dose
Poor metabolizer (2-15 %)	Usage of clomipramine not recommended, prescription of an alternative agent should be considered. If clomipramine is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Nota bene: If used for neuropathic pain, no dose adjustment in intermediate or poor CYP2D6/CYP2C19 metabolizer is recommended because of a lower prescribed dose initially. Patients should be monitored for potential side effects.

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

CLOMIPRAMIN

Gentest zur Risikominimierung der Therapie mit Clomipramin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Clomipramin?

Clomipramin hemmt die Wiederaufnahme von Serotonin und Noradrenalin im präsynaptische Neuron. Darüber hinaus hat Clomipramin antiadrenerge, antihistaminische, antiserotonerge, antidopaminerge und anticholinerge Wirkungen. Dieser Wirkstoff wird bei der Behandlung von Depressionen und Zwangsstörungen sowie neuropathischen Schmerzen und Migräneprophylaxe eingesetzt.

Gene

Welche Gene beeinflussen die Wirkung von Clomipramin?

Clomipramin als tertiäres Amin wird über das Enzym CYP2C19 zu sekundärem Amin metabolisiert. Beide werden über das CYP2D6-Enzym zu weniger aktiven Metaboliten weiter metabolisiert. Beide Enzyme spielen für Clomipramin eine entscheidende Rolle in ihrer Effizienz und Wirkdauer. Es sind verschiedene Varianten der Gene dieser beiden Enzyme bekannt, welche zu einer großen Variabilität der enzymatischen Wirksamkeit führen.

Test

Was wird getestet?

Um sowohl den *CYP2C19*- als auch den *CYP2D6*-Metabolismustyp zu bestimmen, wird das Erbgut des Patienten im *CYP2C19*-Gen *(*2, *3, *17)* und im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Clomipramin durchgeführt werden, um eine Dosisanpassung vorzunehmen und gegebenfalls einen Wirkstoffwechsel in Erwägung zu ziehen, um schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt für *CYP2D6* das höchste klinische Evidenzlevel 1A, für *CYP2C19* ein mittleres klinisches Evidenzlevel 2A.

Tabelle 1: Empfehlungen für die Clomipramin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Clomipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Clomipramin: Titration auf höhere Zieldosis (verglichen zu normalen Metabolisierern) durch therapeutisches *Drug Monitoring*
Normale Metabolisierer (72-88 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis um 25 % reduzieren bei therapeutischem *Drug Monitoring*
Langsame Metabolisierer (1-10 %)	Clomipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Clomipramin: Startdosis um 50 % reduzieren bei therapeutischem *Drug Monitoring*

Tabelle 2: Empfehlungen für die Clomipramin-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

CYP2C19 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (2-5 %)	Clomipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Clomipramin: therapeutisches *Drug Monitoring*
Schnelle Metabolisierer (2-30 %)	Clomipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Clomipramin: therapeutisches *Drug Monitoring*
Normale Metabolisierer (35-50 %)	Beginn mit Startdosis
Intermediäre Metabolisierer (18-45 %)	Beginn mit Startdosis
Langsame Metabolisierer (2-15 %)	Clomipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Clomipramin: Reduktion Startdosis um 50 % bei therapeutischem *Drug Monitoring*

Nota bene: Wenn ein Patient wegen neuropathischer Schmerzen mit Clomipramin behandelt wird und ein intermediärer oder schlechter CYP2D6 / CYP2C19-Metabolisierer ist, wird aufgrund einer anfänglich niedrigeren verschriebenen Dosis keine Dosisanpassung empfohlen. Die Patienten sollten auf mögliche Nebenwirkungen überwacht werden.

Kosten

Die Kosten für die genetische Analyse der *CYP2D6*- und *CAP2C19*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

KLOMIPRAMIN

Genetički test za smanjenje rizika pri primjeni klomipramina

Lijek

Koje su indikacije i mehanizmi djelovanja klomipramina?

Triciklički antidepresiv klomipramin je inhibitor ponovne pohrane serotonina i noradrenalina u presinaptičkom neuronu. Dodatno blokira α1 adrenergičke, H1 histaminske, serotoninske i muskarinske receptore. Koristi se za liječenje depresije, opsesivno-kompulzivnog poremećaja, neuropatske boli te za profilaksu migrene.

Geni

Koji geni utječu na djelovanje klomipramina?

Klomipramin se kao tercijarni amin metabolizira preko enzima CYP2C19 u sekundarni amin. Oboje se dalje metaboliziraju putem enzima CYP2D6 u manje aktivne metabolite. Oba enzima determiniraju učinkovitost i duljinu djelovanja klomipramina. Nekoliko genskih polimorfizama ovih enzima dovode do velike varijabilnosti u enzimatskoj funkciji CYP2C19 i CYP2D6.

Analiza

Što se analizira?

Kako bi se odredio fenotip enzima CYP2C19 i CYP2D6, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2C19 (*2,*3,*17)* te gena *CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, 9*, *10, *41)*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije klomipraminom, kako bi se po potrebi prilagodilo doziranje lijeka ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] te imaju najvišu kliničku razinu dokaza 1A za *CYP2D6* te srednju kliničku razinu dokaza 2A za *CYP2C19*.

Tablica 1: Preporuke za liječenje klomipraminom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-20 %)	Ne preporučuje se liječenje klomipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja klomipraminom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (77-88 %)	Koristiti lijek prema sažetku opisa svojstava lijeka
Intermedijarni metabolizator (1-13 %)	Smanjenje početne doze klomipramina za 25 %
Spori metabolizatori (1-10 %)	Ne preporučuje se liječenje klomipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja klomipraminom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Tablica 2: Preporuke za liječenje klomipraminom ovisno o fenotipu CYP2C19

CYP2C19 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (2-5 %)	Ne preporučuje se liječenje klomipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja klomipraminom te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Brzi metabolizator (2-30 %)	Ne preporučuje se liječenje klomipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja klomipraminom te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (35-50 %)	Započeti terapiju preporučenom početnom dozom
Intermedijarni metabolizator (18-45 %)	Započeti terapiju preporučenom početnom dozom
Spori metabolizatori (2-15 %)	Ne preporučuje se liječenje klomipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja klomipraminom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Nota bene: Ukoliko se liječi neuropatska bol, a pacijent je intermedijarni ili spori CYP2D6 / CYP2C19 metabolizator, ne preporučuje se prilagodba doze zbog već inicijalno propisane niže doze. Pacijente treba nadzirati zbog potencijalnih nuspojava.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa *CYP2C19* i *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

CLOPIDOGREL

Genetic test to minimize the risks related to therapy with clopidogrel

Drug

What are the indications and mechanisms of action of clopidogrel?

Clopidogrel is a platelet function inhibitor that is used for therapy after atherothrombotic events as well as for ischemia with peripheral artery disease, acute coronary syndrome and after stent implantation. As a prodrug, clopidogrel is converted in the liver into a pharmacologically active thiol derivative which irreversibly binds to the platelet receptor ($P2Y_{12}$) and inhibits adenosine diphosphate (ADP) - dependent platelet aggregation. Blood platelets blocked by clopidogrel remain incapable of clotting throughout their entire lifespan (7-10 days).

Genes

Which genes influence the effect of clopidogrel?

Clopidogrel is converted in the liver by the CYP enzymes, including CYP2C19, into the active ingredient. Whether the targeted level of the active ingredient in the blood is achieved is particularly dependent on the activity of the CYP2C19 enzyme. Based on which influence the *CYP2C19* gene variants have on the enzyme activity, a distinction is made between poor, intermediate, extensive and ultra-rapid metabolizers for clopidogrel.

Test

What will be tested?

In order to determine the CYP2C19 metabolism type, the patient's *CYP2C19* genotype is tested for the two most common activity - reducing gene variants *(*2, *3)* as well as the activity-increasing variant *(*17)*.

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with clopidogrel in order to consider a change of active ingredient if necessary and in order to avoid serious adverse effects. Individuals with moderate or high clinical risk for poor outcomes in the setting of sub-optimal antiplatelet therapy are recommended for *CYP2C19* genotype derived therapy, which includes patients undergoing high-risk multivessel PCI procedures, patients who already had an adverse outcome (e.g., stent thrombosis) and/or those with other high clinical risk (e.g., acute coronary syndrome, diabetes mellitus, chronic kidney failure) or angiographic features.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1,2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for clopidogrel therapy depending on the phenotype of the CYP2C19 gene

CYP2C19 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (5-30 %)	Usage according to Summary of Product Characteristics
Extensive metabolizer (35-50 %)	Usage according to Summary of Product Characteristics
Intermediate metabolizer (18-45 %)	Change of active agent recommended (prasugrel, ticagrelor)
Poor metabolizer (2-15 %)	Change of active agent recommended (prasugrel, ticagrelor)

Costs

Costs for the genetic analysis of the *CYP2C19* will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Scott SA, Sangkuhl K, Gardner EE, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther. 2011;90(2):328-332. doi:10.1038/clpt.2011.132

[2] Scott SA, Sangkuhl K, Stein CM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94(3):317-323. doi:10.1038/clpt.2013.105

CLOPIDOGREL

Gentest zur Risikominimierung der Therapie mit Clopidogrel

Wirkstoff

Was sind die Indikationen und der Wirkmechanismus von Clopidogrel?

Clopidogrel ist ein Thrombozytenfunktionshemmer, der sowohl zur Therapie nach atherothrombotischen Ereignissen (u. a. Herzinfarkt, Schlaganfall) als auch zur Prävention einer Ischämie bei peripherer arterieller Verschlusskrankheit, akutem Koronarsyndrom und nach einer Stentimplantation eingesetzt wird. Als Prodrug wird Clopidogrel in der Leber in ein pharmakologisch wirksames Thiolderivat umgewandelt, das die Bindung von Adenosindiphosphat (ADP) an den Thrombozytenrezeptor ($P2Y_{12}$) irreversibel hemmt, dadurch die ADP-abhängige Thrombozytenaggregation unterbindet und so die Blutgerinnung hemmt. Durch Clopidogrel blockierte Thromobzyten bleiben während ihrer gesamten Lebensdauer (7-10 Tage) gerinnungsunfähig.

Gene

Welche Gene beeinflussen die Wirkung von Clopidogrel?

Clopidogrel wird in der Leber durch das Enzym CYP2C19 in den aktiven Wirkstoff umgewandelt. Ob der angestrebte Wirkstoffgehalt im Blut erreicht wird, hängt insbesondere von der Aktivität des CYP2C19-Enzyms ab. Ausgehend davon, welchen Einfluss die CYP2C19-Genvarianten auf die Enzymaktivität besitzen, unterscheidet man ultraschnelle, schnelle, intermediäre und langsame Metabolisierer für Clopidogrel.

Test

Was wird getestet?

Um den CYP2C19-Metabolisierungstyp zu ermitteln, wird das Erbgut der Patienten sowohl auf die beiden häufigsten aktivitätsreduzierenden Genvarianten *(*2, *3)* als auch die aktivitätssteigernde Variante *(* 17)* untersucht.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Clopidogrel durchgeführt werden, um gegebenenfalls einen Wirkstoffwechsel in Erwägung zu ziehen, um schwere Nebenwirkungen zu vermeiden. Personen mit einem mittleren oder hohen klinischen Risiko für die Festlegung einer suboptimalen Thrombozytenaggregationshemmung wird die *CYP2C19*-Genotypisierung empfohlen. Dies schließt die Patienten mit ein, die sich einem Multi-Gefäß-PCI-Verfahren mit hohem Risiko unterziehen, und Patienten, die bereits einen unerwünschten Ausgang hatten (z. B. Stentthrombose) und/oder solche mit einem anderen hohen klinischen Risiko (z.B. ACS, Diabetes mellitus, chronisches Nierenversagen) oder angiografischen Merkmalen.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Clopidogrel-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

CYP2C19 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (5-30 %)	Therapie gemäß Fachinformation
Schnelle Metabolisierer (35-50 %)	Therapie gemäß Fachinformation
Intermediäre Metabolisierer (18-45 %)	Wirkstoffwechsel empfohlen (Prasugrel, Ticagrelor)
Langsame Metabolisierer (2-15 %)	Wirkstoffwechsel empfohlen (Prasugrel, Ticagrelor)

Kosten

Die Kosten für die genetische Analyse des *CYP2C19*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Scott SA, Sangkuhl K, Gardner EE, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther. 2011;90(2):328-332. doi:10.1038/clpt.2011.132.

[2] Scott SA, Sangkuhl K, Stein CM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94(3):317-323. doi:10.1038/clpt.2013.105.

KLOPIDOGREL

Genetički test za smanjenje rizika pri primjeni klopidogrela

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja klopidogrela?

Klopidogrel je lijek iz skupine inhibitora agregacije trombocita. Primjenjuje se za sekundarnu prevenciju aterotrombotičkih događaja, posebice u odraslih bolesnika koji su pretrpjeli infarkt miokarda, ishemijski moždani udar ili imaju utvrđenu bolest perifernih arterija. Isto tako primjenjuje se i u odraslih osoba s akutnim koronarnim sindromom bez elevacije ST segmenta te u bolesnika podvrgnutih postavljanju stenta. Kao prolijek, klopidogrel se u jetri pretvara u farmakološki djelotvorni tiolni derivat koji ireverzibilno inhibira vezivanje adenozin difosfata (ADP) za $P2Y_{12}$ receptor na trombocitima te njegovo pro-agregacijsko djelovanje. Trombociti koji su blokirani klopidogrelom, trajno su oštećeni i za vrijeme svojeg životnog vijeka (7-10 dana) nemaju sposobnost zgrušanja krvi.

Geni

Koji geni utječu na djelovanje klopidogrela?

Klopidogrel se pretvara u jetri putem CYP enzima, prvenstveno CYP2C19 u aktivni oblik, čija razina u krvi posebice ovisi o aktivnosti tog enzima. Ovisno koja varijanta gena *CYP2C19* direktno utječe na aktivnost enzima razlikuju se spori, intermedijarni, brzi i ultra brzi metabolizatori klopidogrela.

Analiza

Što se analizira?

Da bi se ustanovio fenotip vezan uz sposobnost metaboliziranja lijeka putem enzima CYP2C19, analiziraju se dvije najučestalije varijante gena *(*2 i *3)* koje dovode do smanjene aktivnosti enzima te varijanta *(*17)* koja dovodi do pojačane aktivnosti enzima.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo provesti prije početka terapije s klopidogrelom kako bi se po potrebi ordinirala zamjenska terapija u svrhu sprječavanja ozbiljnih nuspojava. Preporuka je učiniti testiranje pojedincima s umjerenim i visokim kliničkim rizikom kod kojih je dokazana neučinkovitost terapije (tromboza unutar stenta) i/ili kod visoko rizičnih pacijenata (akutni koronarni sindrom, šećerna bolest i kronično bubrežno popuštanje) i osobama izloženim angiografskoj proceduri.

Posljedice rezultata testova

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] i imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje klopidogrelom ovisno o fenotipu CYP2C19 gena

CYP2C19 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (5-30 %)	Terapija sukladno uputama o lijeku
Brzi metabolizator (35-50 %)	Terapija sukladno uputama o lijeku
Intermedijarni metabolizator (18-45 %)	Preporučuje se promjena lijeka (prasugrel, tikagrelor)
Spori metabolizator (2-15 %)	Preporučuje se promjena lijeka (prasugrel, tikagrelor)

Troškovi

Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize *CYP2C19* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno siguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Scott SA, Sangkuhl K, Gardner EE, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther. 2011;90(2):328-332. doi:10.1038/clpt.2011.132

[2] Scott SA, Sangkuhl K, Stein CM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94(3):317-323. doi:10.1038/clpt.2013.105

CODEINE

Genetic test to minimize the risks related to therapy with codeine

Drug

What are the indications and mechanisms of action of codeine?

Codeine is a morphine derivative from the class of opiates that due to its analgesic, antitussive and light sedative effects is commonly used for the treatment of dry cough and in combination with other active ingredients, such as paracetamol, acetylsalicylic acid or diclofenac for the treatment of moderately severe to severe pain. Codeine is converted in the liver to a small proportion (approx. 10 %) into the pharmacologically more active morphine. The opioid effect of both opiates is mediated through the binding to opioid receptors, whereby for codeine the affinity to the μ-receptor compared to morphine is much less.

Genes

Which genes influence the effect of codeine?

The enzyme CYP2D6 catalyzes the demethylation reaction of codeine to morphine. Since the latter is the much stronger opiate of the two, the CYP2D6 enzyme activity determines the level of the codeine/morphine ratio and therefore also the strength of the opiate effect. A variety of activity-reducing gene variants as well as activity-increasing gene duplications which cause a large fluctuation range of enzyme activity are known for the *CYP2D6* gene.

Test

What will be tested?

The patient's *CYP2D6* genotype is tested for the most common activity-reducing variants in the *CYP2D6* gene as well as for the number of active gene copies.

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with codeine in order to make a change of therapy with a suitable active ingredient if necessary. It should be noted that ultrarapid metabolizers like children under 2 years of age[1], breastfed infants of mothers who are ultrarapid metabolizers[2], and children following tonsillectomy with or without adenoidectomy are at high risk for serious adverse effects and codeine related deaths[1,3,4].

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[5,6] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for codeine therapy according to the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-2 %)	Avoid codeine use due to the potential for toxicity. Usage of alternative agent necessary
Extensive metabolizer (77-92 %)	Usage according to Summary of Product Characteristics
Intermediate metabolizer (2-11 %)	Usage according to Summary of Product Characteristics If no response, consider alternative analgesics such as morphine or a non-opioid analgesic
Poor metabolizer (5-10 %)	Change of active ingredient recommended

Costs

Costs for the *CYP2D6* genetic analysis will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Ciszkowski C, Madadi P, Phillips MS, et al. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009;361:827–828. doi:10.1056/NEJMc0904266

[2] Willmann, S., Edginton, A.N., Coboeken, K., et al. Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. Clin Pharmacol Ther 2009;86:634–643. doi:10.1038/clpt.2009.151

[3] Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics. 2012;129(5):e1343-e1347. doi:10.1542/peds.2011-2538

[4] Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth. 2007:17:684–687. doi:10.1111/j.1460-9592.2006.02182.x

[5] Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther. 2012;91(2):321-326. doi:10.1038/clpt.2011.287

[6] Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376-382. doi:10.1038/clpt.2013.254

CODEIN

Gentest zur Risikominimierung der Therapie mit Codein

Wirkstoff

Was sind die Indikationen und der Mechanismus der Wirkung von Codein?

Codein ist ein Morphinderivat aus der Klasse der Opiate, das aufgrund seiner analgetischen, antitussiven und leicht sedierenden Wirkung häufig zur Behandlung von Reizhusten und in Kombination mit anderen Wirkstoffen wie Paracetamol, Acetylsalicylsäure oder Diclofenac zur Behandlung von mäßig starken bis starken Schmerzen angewendet wird. Codein wird in der Leber zu einem geringen Anteil (ca. 10 %) in das pharmakologisch aktivere Morphin umgewandelt. Die opioide Wirkung beider Opiate wird durch die Bindung an Opiat-Rezeptoren vermittelt, wobei für Codein die Affinität und Bindungsrate zum μ-Rezeptor im Vergleich zu Morphin wesentlich geringer ist.

Gene

Welche Gene beeinflussen die Wirkung von Codein?

Das Enzym CYP2D6 katalysiert die Demethylierungsreaktion von Codein zu Morphin. Da letzteres das wesentlich stärkere Opiat von beiden ist, bestimmt die CYP2D6-Enzymaktivität den Höhe des Codein/Morphin-Ratios und damit auch die Stärke der Opiatwirkung. Für das *CYP2D6*-Gen sind eine Vielzahl von aktivitätsreduzierenden Genvarianten sowie aktivitätserhöhende Genduplikationen bekannt, die eine große Schwankungsbreite der Enzymaktivität bedingen.

Test

Was wird getestet?

Um die CYP2D6-Metabolisierungstyp zu ermitteln, wird das Erbgut der Patienten sowohl auf die häufigsten aktivitätsmindernden Genvarianten im Gen *CYP2D6*-Gen als auch auf die Anzahl der aktiven Genkopien untersucht.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Codein durchgeführt werden, um gegebenenfalls eine Therapieänderung mit Wirkstoffwechsel in Erwägung zu ziehen. Ultraschnelle Metabolisierer wie Kinder unter 2 Jahren[1], gestillte Säuglinge von Müttern, die ultraschnelle Metablisierer sind[2] und Kinder nach Tonsillektomie mit oder ohne Adenoidektomie stehen unter einem hohem Risiko für codeinbedingte Todesfälle und schwere Arzneimittelnebenwirkungen[1,3,4].

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[5,6] und zeigt für *CYP2D6* das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Codein-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-2 %)	Codein kontraindiziert, Wirkstoffwechsel nötig
Schnelle Metabolisierer (77-92 %)	Therapie gemäß Fachinformation
Intermediäre Metabolisierer (2-11 %)	Therapie gemäß Fachinformation. Ohne erfolgreiches Ansprechen, Wirkstoffwechsel zu alternativen Analgetika (Morphin, nicht-opioides Analgetikum)
Langsame Metabolisierer (5-10 %)	Wirkstoffwechsel empfohlen

Kosten

Die Kosten für die genetische Analyse des *CYP2D6*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Ciszkowski C, Madadi P, Phillips MS, et al. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009;361:827–828. doi:10.1056/NEJMc0904266.

[2] Willmann, S., Edginton, A.N., Coboeken, K., et al. Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. Clin Pharmacol Ther 2009;86:634–643. doi:10.1038/clpt.2009.151.

[3] Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics. 2012;129(5):e1343-e1347. doi:10.1542/peds.2011-2538.

[4] Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth. 2007:17:684–687. doi:10.1111/j.1460-9592.2006.02182.

[5] Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther. 2012;91(2):321-326. doi:10.1038/clpt.2011.287.

[6] Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376-382. doi:10.1038/clpt.2013.254.

KODEIN

Genetički test za smanjenje rizika pri primjeni kodeina

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja kodeina?

Kodein je polusintetski derivat morfina, spada u skupinu opiodnih lijekova. Ima analgetski, antitusivni učinak i lagano sedirajuće djelovanje. Često se kombinira s drugim lijekovima kao što su paracetamol, acetilsalicilna kiselina ili diklofenak u liječenju umjereno jake do jake boli. U jetri se kodein (oko 10 %) metabolizira preko enzima CYP2D6 u svoj aktivni metabolit morfin. Opioidni učinak oba opijata posredovan je vezanjem na opioidne receptore, pri čemu kodein ima značajno manji afinitet za μ-receptor u odnosu na morfin.

Geni

Koji geni utječu na djelovanje kodeina?

Enzim CYP2D6 katalizira demetilaciju kodeina u morfin. Budući da je morfin potentniji opijat od kodeina aktivnost enzima CYP2D6 određuje odnos kodein/morfin i samim time i intenzitet učinka posredovanog ovim lijekovima. Za gen *CYP2D6* su poznate brojne varijante koje umanjuju aktivnost enzima, ali i varijante koje su povezane s većom aktivnost enzima (zbog duplikacije gena) što posljedično doprinosi velikoj varijabilnosti u aktivnosti enzima.

Analiza

Što se analizira?

Da bi se ustanovila sposobnost metaboliziranja lijeka, analiziraju se najučestalije varijante gena *CYP2D6* koje dovode do smanjenja aktivnosti enzima kao i broj aktivnih kopija gena što u konačnici dovodi do povećane aktivnosti enzima.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo provesti prije planirane terapije kodeinom kako bi se eventualno prilagodilo doziranje ili primijenio drugi lijek te time spriječile ozbiljne nuspojave. Treba istaknuti da ultra brzi metabolizatori kojima pripadaju djeca do 2 godine starosti[1], dojenčad majki ultrabrzih metabolizatora[2] i djeca/mladi podvrgnuti tonzilektomiji predstavljaju skupinu visokog rizika[1,3,4].

Posljedice rezultata testova

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su utemeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)* smjernicama[5,6] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje kodeinom ovisno o fenotipu CYP2D6 gena

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizatori (1-2 %)	Izbjegavati primjenu kodeina zbog rizika od toksičnosti. Preporučuje se promjena lijeka
Brzi metabolizatori (77-92 %)	Terapija sukladno uputama o lijeku
Intermedijarni metabolizatori (2-11 %)	Terapija sukladno uputama o lijeku. Ukoliko izostane terapijski odgovor, preporučuje se alternativna analgezija (morfin ili neopioidni analgetik)
Spori metabolizatori (5-10 %)	Preporučuje se promjena lijeka

Troškovi

Troškovi za određivanje genotipa *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Ciszkowski C, Madadi P, Phillips MS, et al. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009;361:827–828. doi:10.1056/NEJMc0904266

[2] Willmann, S., Edginton, A.N., Coboeken, K., et al. Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. Clin Pharmacol Ther 2009;86:634–643. doi:10.1038/clpt.2009.151

[3] Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics. 2012;129(5):e1343-e1347. doi:10.1542/peds.2011-2538

[4] Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth. 2007:17:684–687. doi:10.1111/j.1460-9592.2006.02182.x

[5] Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther. 2012;91(2):321-326. doi:10.1038/clpt.2011.287

[6] Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376-382. doi:10.1038/clpt.2013.254

DESFLURANE

Genetic test to minimize the risk of malignant hyperthermia (MH) related to the usage of desflurane

Drug

What are the indications and mechanisms of action of desflurane?

Desflurane is potent generally safe volatile inhaled anesthetic used for inducing general anesthesia. Its mechanism of action is complex and includes a reduction in junctional conductance by decreasing gap junction channel opening times and increasing gap junction channel closing times. It also activates calcium-dependent ATPase in the sarcoplasmic reticulum by increasing the fluidity of the lipid membrane. Desflurane probably binds to various neurotransmitter receptors (like GABA, glycine, glutamate) and ion channels and interacts with the nerve membranes.

Genes

Which genes influence the effect of desflurane?

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the *RYR1* and *CACNA1S* genes under consideration here predispose individuals to a severe and sometimes lethal hypermetabolic reaction whose symptoms include muscle rigidity, high fever, and a fast heart rate. Complications can include rhabdomyolysis and high blood potassium.

Test

What will be tested?

The genotype of the ryanodine receptor isoform 1 protein (*RYR1*) is tested for one of the 48 causative single-nucleotide variants or one deletion that are designated diagnostic MH mutations[1]. The α1S subunit of the dihydropyridine receptor (CACNA1S) is tested for the 2 known variants that are MH susceptible. Since MH susceptibility is inherited in an autosomal-dominant pattern, a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as diagnostic for the trait.

Indication

When should a test be performed?

Genetic testing should be carried out before the initiation of the scheduled therapy with desflurane in order to predict the risk for MH.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for desflurane usage depending on the phenotype of the RYR1 and CACNA1S genes

RYR1 or CACNA1S Phenotype	Recommended therapy
Malignant hyperthermia susceptible (MHS)	Desflurane is not recommended due to MH susceptibility, use alternative anesthetics
Uncertain susceptibility	Clinical findings, family history, further genetic testing, and other laboratory data should guide the use of desflurane

Nota bene: A negative or inconclusive genetic test cannot be assumed to indicate normal RYR1-related phenotype and should be interpreted in the context of clinical findings, family history, and other laboratory data.

Costs

Costs for the determination of the *RYR1* and *CACNA1S* genotype are reimbursed for patients with a statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

DESFLURAN

Gentest zur Risikominimierung der Entwicklung einer malignen Hyperthermie (MH) bei Einsatz von Desfluran

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Desfluran?

Desfluran ist ein wirksames und allgemein sicheres, flüchtiges Anästhetikum, das zur Einleitung einer Vollnarkose verwendet wird. Sein Wirkungsmechanismus ist komplex und umfasst eine Reduzierung der Verbindungsleitfähigkeit durch verringerte Öffnungszeiten und erhöhte Schließzeiten von *gap junction* Kanälen. Es aktiviert auch die Calcium-abhängige ATPase im sarkoplasmatischen Retikulum, indem es die Fluidität der Lipidmembran erhöht. Es wird hypothetisiert, dass Desfluran an verschiedene Neurotransmitter-Rezeptoren und Ionenkanäle (wie GABA, Glycine, Glutamat) bindet und mit Nervenmembranen interagiert.

Gene

Welche Gene beeinflussen die Wirkung von Desfluran?

Im Gegensatz zu vielen verwertbaren pharmakogenetischen Merkmalen, die den Metabolismus und/oder die Ausscheidung eines Arzneimittels beeinflussen, prädisponieren die hier betrachteten Varianten der Gene *RYR1* und *CACNA1S* zu einer schweren und manchmal tödlichen hypermetabolischen Reaktion, zu deren Symptomen Muskelsteifheit, hohes Fieber und schnelle Herzfrequenz gehören. Weitere Komplikationen können Rhabdomyolyse und hohe Kaliumwerte im Blut darstellen.

Test

Was wird getestet?

Der Genotyp des Ryanodinrezeptor-Isoform-1-Proteins *(RYR1)* wird auf eine der 48 Einzelnukleotidvarianten und eine Deletion getestet, die als diagnostische maligne Hyperthermie-Mutation[1] bezeichnet werden. Die α1S-Untereinheit des Dihydropyridinrezeptors (CACNA1S) wird auf die beiden bekannten Varianten getestet, die für maligne Hyperthermie anfällig sind. Da die Anfälligkeit für maligne Hyperthermie (MHS) in einem autosomal-dominanten Muster vererbt wird, kann ein heterozygoter Genotyp einer pathogenen Variante in *RYR1* als diagnostisch für das Merkmal angesehen werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Desfluran durchgeführt werden, um das Risiko einer bösartigen Hyperthermie zu verringern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Desfluran-Gebrauch mit Phänotyp der RYR1- und CACNA1S-Gene

RYR1 oder CACNA1S Phänotyp	Therapieempfehlung
Maligne Hyperthermie Anfälligkeit (MHS)	Desfluran kontraindiziert, Anästhetikawechsel empfohlen
Unsichere Anfälligkeit	Klinische Befunde, Familienanamnese, weitere Gentests und andere Labordaten sollten den Einsatz von Desfluran anleiten

Nota bene: Ein negativer oder nicht eindeutiger Gentest kann nicht als Hinweis auf einen normalen RYR1-bezogenen Phänotyp angesehen werden und sollte im Zusammenhang mit klinischen Befunden, Familienanamnese und anderen Labordaten interpretiert werden.

Kosten

Die Kosten für die genetische Analyse der *RYR1*- und *CACNA1S*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

DESFLURAN

Genetički test za smanjenje rizika pojave maligne hipertermije pri primjeni desflurana

Lijek

Koje su indikacije i mehanizmi djelovanja desflurana?

Desfluran je potentan i siguran hlapljivi inhalacijski anestetik koji se često koristi za indukciju opće anestezije. Njegov mehanizam djelovanja je kompleksan, a uključuje smanjenje provodljivosti skraćivanjem vremena otvaranja kanala na pukotinskim spojevima (engl. gap junctions) i produljujući vrijeme zatvaranja istih. Također aktivira o kalciju ovisnu ATPazu na sarkoplazmatskom retikulumu povećanjem fluidnosti lipidne membrane. Desfluran se vjerojatno veže na više neurotransmitorskih receptora (poput $GABA_A$, glicinskog i glutamatnog), ionskih kanala te ulazi u interakciju s membranama neurona.

Geni

Koji geni utječu na djelovanje desflurana?

Za razliku od mnogih drugih lijekova kojima genski polimorfizmi utječu na metabolizam ili ekskreciju, polimorfizmi *RYR1* i *CACNA1S* gena su predisponirajući za tešku i smrtonosnu hipermetaboličku reakciju, čiji simptomi uključuju: rigidnost mišića, visoku tjelesnu temperaturu, tahikardiju. Komplikacije uključuju rabdomiolizu i hiperkalemiju.

Analiza

Što se analizira?

Genotip rajanodinskog receptora izoforme 1 *(RYR1)* testira se na jedan od 48 nukleotidnih polimorfizama ili jednu deleciju koje su označene kao dijagnostičke mutacije za malignu hipertermiju[1]. α1S podjedinica dihidropiridinskog receptora (CACNA1S) se testira za jednu od 2 poznate mutacije koje su dijagnostičke za malignu hipertermiju. Budući da se navedeni geni nasljeđuju autosomno dominantno, heterozigotni genotip navedenih gena smatra se kao dijagnoza sklonosti ka malignoj hipertermiji.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka primjene desflurana kako bi se odredila sklonost ka nastanku maligne hipertermije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortiums (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za primjenu desflurana ovisno o genotipu RYR1 i CACNA1S

RYR1 ili CACNA1S fenotip	Preporučena terapija
Osjetljivost za malignu hipertermiju	Ne preporučuje se primjena desflurana; potrebno je korištenje alternativnog anestetika
Neinformativan	Odluka o primjeni desflurana trebala bi se voditi kliničkom slikom, obiteljskom anamnezom, daljnjim genskim testiranjem i ostalim laboratorijskim podatcima

Nota bene: negativan ili neinformativan rezultat testa se ne smije uzeti kao indikacija za normalan fenotip te se treba razmotriti u kontekstu kliničkih nalaza, obiteljske anamneze i ostalih laboratorijskih nalaza.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

DESIPRAMINE

Genetic test to minimize the risks related to therapy with desipramine

Drug

What are the indications and mechanisms of action of desipramine?

Tricyclic antidepressant desipramine is a more selective norepinephrine reuptake inhibitor, though it also inhibits serotonin reuptake, adrenergic, cholinergic mAch, and histamine H1 receptors. It is indicated for the treatment of depression, obsessive-compulsive disorder as well as neuropathic pain and migraine prophylaxis.

Genes

Which genes influence the effect of desipramine?

Desipramine is metabolized via the CYP2D6 enzyme to less-active metabolites. Different variants of the *CYP2D6* gene with wide variability in enzymatic activity are known. They can influence the therapy with desipramine.

Test

What will be tested?

In order to determine the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants in the *CYP2D6* gene *(*1XN, *2, *2XN,3*, *4, *5, *6, *9, *10, *41)*.

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with desipramine in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1,2] and have the highest clinical level of evidence 1A for *CYP2D6*.

Table 1: Recommendations for desipramine therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-20 %)	Usage of desipramine is not recommended, the prescription of an alternative agent is recommended. If desipramine is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Therapeutic drug monitoring is strongly recommended
Normal metabolizer (72-88 %)	Usage according to the Summary of Product Characteristics
Intermediate metabolizer (1-13 %)	Reduction of starting dose of desipramine by 25 %
Poor metabolizer (1-10 %)	Usage of desipramine is not recommended, the prescription of an alternative agent is recommended. If desipramine is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Nota bene: If a patient is treated for neuropathic pain with desipramine and is an intermediate or poor CYP2D6 metabolizer, no dose adjustment is recommended because of a lower prescribed dose initially. Patients should be monitored for potential side effects.

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

DESIPRAMIN

Gentest zur Risikominimierung der Therapie mit Desipramin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Desipramin?

Das trizyklische Antidepressivum Desipramin ist ein selektiverer Norepinephrin-Wiederaufnahmehemmer, hemmt jedoch auch die Serotonin-Wiederaufnahme-, adrenergen, cholinergen mAch- und Histamin-H1-Rezeptoren. Dieser Wirkstoff wird bei der Behandlung von Depressionen und Zwangsstörungen sowie neuropathischen Schmerzen und Migräneprophylaxe eingesetzt.

Gene

Welche Gene beeinflussen die Wirkung von Desipramin?

Desipramine wird durch das CYP2D6-Enzym zu weniger aktiven Metaboliten verstoffwechselt. Es sind verschiedene Varianten des *CYP2D6*-Gens mit einer großen Variabilität der enzymatischen Wirksamkeit bekannt. Sie können für die Therapie mit TCAs von entscheidender Bedeutung sein.

Test

Was wird getestet?

Um den CYP2D6-Metabolismustyp zu bestimmen, wird der Erbgut des Patienten im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Desipramin durchgeführt werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu ändern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)* [1,2] und zeigt das höchste klinische Evidenzlevel 1A für *CYP2D6*.

Tabelle 1: Empfehlungen für die Desipramin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Desipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Desipramin: auf höhere Zieldosis (verglichen zu normalen Metabolisierern) titrieren bei therapeutischem *Drug Monitoring*
Normale Metabolisierer (72-88 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis um 25 % reduzieren bei therapeutischem *Drug Monitoring*
Langsame Metabolisierer (1-10 %)	Desipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Desipramin: Startdosis um 50 % reduzieren bei therapeutischem *Drug Monitoring*

Nota bene: Wenn ein Patient wegen neuropathischer Schmerzen mit Desipramin behandelt wird und ein intermediärer oder schlechter CYP2D6-Metabolisierer ist, wird aufgrund einer anfänglich niedrigeren verschriebenen Dosis keine Dosisanpassung empfohlen. Die Patienten sollten auf mögliche Nebenwirkungen überwacht werden.

Kosten

Die Kosten für die genetische Analyse der *CYP2D6*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2.

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597.

DESIPRAMIN

Genetički test za smanjenje rizika pri primjeni desipramina

Lijek

Koje su indikacije i mehanizmi djelovanja desipramina?

Triciklički antidepresiv desipramin je selektivniji inhibitor ponovne pohrane noradrenalina, ali također inhibira i ponovnu pohranu serotonina, muskarinske receptore za acetilkolin i histaminske H1 receptore. Koristi se za liječenje depresije, opsesivno-kompulzivnog poremećaja, neuropatske boli te za profilaksu migrene.

Geni

Koji geni utječu na djelovanje desipramina?

Desipramin se kao sekundarni amin metabolizira preko CYP2D6 enzima u manje aktivne metabolite. Ovaj enzim determinira učinkovitost i duljinu djelovanja desipramina. Nekoliko genskih polimorfizama dovode do velike varijabilnosti u enzimatskoj funkciji CYP2D6.

Analiza

Što se analizira?

Kako bi se odredio fenotip enzima CYP2D6, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, 9*, *10, *41)*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije desipraminom, kako bi se po potrebi prilagodilo doziranje lijeka ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] te imaju najvišu kliničku razinu dokaza 1A za CYP2D6.

Tablica 1: Preporuke za liječenje desipraminom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-20 %)	Ne preporučuje se liječenje desipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja desipraminom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (77-88 %)	Koristiti lijek prema sažetku opisa svojstava lijeka
Intermedijarni metabolizator (1-13 %)	Smanjenje početne doze desipramina za 25 %
Spori metabolizator (1-10 %)	Ne preporučuje se liječenje desipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja desipraminom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Nota bene: Ukoliko se liječi neuropatska bol, a pacijent je intermedijarni ili sporiji CYP2D6 metabolizator, ne preporučuje se prilagodba doze zbog već inicijalno propisane niže doze. Pacijente treba nadzirati zbog potencijalnih nuspojava.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

DOXEPIN

Genetic test to minimize the risks related to therapy with doxepin

Drug

What are the indications and mechanisms of action of doxepin?

Tricyclic antidepressant doxepin is an inhibitor of both serotonin and norepinephrine reuptake in the presynaptic neuron. It additionally has antiadrenergic, antihistamine, antiserotonergic, and anticholinergic activities. Doxepin is indicated for the treatment of a major depressive disorder, anxiety disorders, and for short-term treatment of insomnia.

Genes

Which genes influence the effect of doxepin?

Doxepin as tertiary amine is metabolized via the enzyme CYP2C19 to a secondary amine. Both are further metabolized via the CYP2D6 enzyme to less-active metabolites. Both enzymes play a decisive role in its efficiency and duration of action to all TCAs. Several variants in the genes of these two enzymes are known in the population. These lead to great variability in the enzymatic efficacy of CYP2C19 and CYP2D6, and can, therefore, be of vital importance for doxepin therapy.

Test

What will be tested?

In order to determine the CYP2C19 as well as the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants *(*2, *3, *17)* and in the *CYP2D6* gene *(*1XN, *2, *2XN, 3*, *4, *5, *6, *9, *10, *41)*.

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with doxepin in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1,2] and have the highest clinical level of evidence 1A for *CYP2D6*, while for *CYP2C19* a low clinical level of evidence 3.

Table 1: Recommendations for doxepin therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-20 %)	Usage of doxepin is not recommended, the prescription of an alternative agent is recommended. If doxepin is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Therapeutic drug monitoring is strongly recommended
Normal metabolizer (72-88 %)	Usage according to the Summary of Product Characteristics
Intermediate metabolizer (1-13 %)	Reduction of starting dose of doxepin by 25 %
Poor metabolizer (1-10 %)	Usage of doxepin is not recommended, the prescription of an alternative agent is recommended. If doxepin is warranted, consider a 50 % reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Table 2: Recommendations for doxepin therapy depending on the phenotype of the CYP2C19 gene

CYP2C19 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (2-5 %)	Usage of doxepin is not recommended, the prescription of an alternative agent is recommended. If doxepin is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Rapid metabolizer (2-30 %)	Usage of doxepin is not recommended, the prescription of an alternative agent is recommended. If doxepin is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Normal metabolizer (72-88 %)	Initiate therapy with recommended starting dose
Intermediate metabolizer (18-45 %)	Initiate therapy with recommended starting dose
Poor metabolizer (2-15 %)	Usage of doxepin is not recommended, the prescription of an alternative agent is recommended. If doxepin is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Nota bene 1: If a patient is treated with lower doxepin doses (e.g. for insomnia) and is a poor CYP2D6/CYP2C19 metabolizer, no dose adjustment is recommended because of a lower prescribed dose initially. Patients should be monitored for potential side effects.

Nota bene 2: The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group has evaluated therapeutic dose recommendations for doxepin based on CYP2C19 metabolizer (UM, IM, PM). They conclude that NO action is required for this gene-drug interaction[3].

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

[3] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf

DOXEPIN

Gentest zur Risikominimierung der Therapie mit Doxepin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Doxepin?

Das trizyklische Antidepressivum Doxepin hemmt die Wiederaufnahme von Serotonin und Noradrenalin im präsynaptischen Neuron. Doxepin hat zusätzlich antiadrenerge, antihistaminische, antiserotonerge und anticholinerge Aktivitäten. Dieser Wirkstoff wird bei der Behandlung von Depressionen und Zwangsstörungen sowie neuropathischen Schmerzen und Migräneprophylaxe und zur kurzfristigen Behandlung von Schlaflosigkeit indiziert.

Gene

Welche Gene beeinflussen die Wirkung von Doxepin?

Doxepin als tertiäres Amin wird über das Enzym CYP2C19 zu sekundärem Amin metabolisiert. Beide werden über das CYP2D6-Enzym zu weniger aktiven Metaboliten weiter metabolisiert. Beide Enzyme spielen eine entscheidende Rolle in der Effizienz und Wirkdauer von Doxepin. Es sind verschiedene Varianten der Gene dieser beiden Enzyme bekannt, welche zu einer großen Variabilität der enzymatischen Wirksamkeit führen.

Test

Was wird getestet?

Um sowohl den CYP2C19- als auch den CYP2D6-Metabolismustyp zu bestimmen, wird das Erbgut des Patienten im *CYP2C19*-Gen *(*2, *3, *17)* und im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet).

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Doxepin durchgeführt werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu ändern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt für *CYP2D6* das höchste klinische Evidenzlevel 1A, für *CYP2C19* ein niedriges klinisches Evidenzlevel 3.

Tabelle 1: Empfehlungen für die Doxepin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Doxepin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Doxepin: auf höhere Zieldosis (verglichen zu normalen Metabolisierern) titrieren bei therapeutischem drug monitoring
Normale Metabolisierer (72-88 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis um 25 % reduzieren bei therapeutischem drug monitoring
Langsame Metabolisierer (1-10 %)	Doxepin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Doxepin: Startdosis um 50 % reduzieren bei therapeutischem drug monitoring

Tabelle 2: Empfehlungen für die Doxepin-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

CYP2C19 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (2-5 %)	Doxepin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Doxepin: therapeutisches drug monitoring
Schnelle Metabolisierer (2-30 %)	Doxepin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Doxepin: therapeutisches drug monitoring
Normale Metabolisierer (35-50 %)	Beginn mit Startdosis
Intermediäre Metabolisierer (18-45 %)	Beginn mit Startdosis
Langsame Metabolisierer (2-15 %)	Doxepin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Doxepin: Reduktion Startdosis um 50 % bei therapeutischem drug monitoring

Nota bene 1: Wenn ein Patient wegen neuropathischer Schmerzen mit Doxepin behandelt wird und ein intermediärer oder schlechter CYP2D6 / CYP2C19-Metabolisierer ist, wird aufgrund einer anfänglich niedrigeren verschriebenen Dosis keine Dosisanpassung empfohlen. Die Patienten sollten auf mögliche Nebenwirkungen überwacht werden.

Nota bene 2: Die Arbeitsgruppe der *Royal Dutch Pharmacists Association - Pharmacogenetics* hat Empfehlungen zur therapeutischen Dosis von Doxepin basierend auf dem CYP2C19-Metabolisierer (UM, IM, PM) bewertet. Sie folgern, dass für diese Gen-Wirkstoff-Wechselwirkung KEINE Aktion erforderlich ist[3].

Kosten

Die Kosten für die genetische Analyse der *CYP2D6*- und *CAP2C19*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

[3] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf

DOKSEPIN

Genetički test za smanjenje rizika pri primjeni doksepina

Lijek

Koje su indikacije i mehanizmi djelovanja doksepina?

Triciklički antidepresiv doksepin je inhibitor ponovne pohrane noradrenalina i serotonina u presinaptičkom neuronu. Također ima antiadrenergička, antihistaminska, antiserotoninska i antikolinergična svojstva. Koristi se za liječenje depresije, anksioznih poremećaja, te za kratkotrajno liječenje nesanice.

Geni

Koji geni utječu na djelovanje doksepina?

Doksepin se kao tercijarni amin metabolizira preko enzima CYP2C19 u sekundarni amin. Oboje se dalje metaboliziraju putem enzima CYP2D6 u manje aktivne metabolite. Oba enzima određuju učinkovitost i duljinu djelovanja doksepina. Nekoliko genskih polimorfizama dovode do velike varijabilnosti u enzimatskoj funkciji CYP2C19 i CYP2D6.

Analiza

Što se analizira?

Kako bi se odredio fenotip enzima CYP2C19 i CYP2D6, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2C19 (*2,*3,*17)* te gena *CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, 9*, *10, *41)*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije doksepinom, kako bi se po potrebi prilagodilo doziranje lijeka ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] te imaju najvišu kliničku razinu dokaza 1A za *CYP2D6* te nisku kliničku razinu dokaza 3 za *CYP2C19*.

Tablica 1: Preporuke za liječenje doksepinom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-20 %)	Ne preporučuje se liječenje doksepinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja doksepinom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (77-88 %)	Koristiti lijek prema sažetku opisa svojstava lijeka
Intermedijarni metabolizator (1-13 %)	Smanjenje početne doze doksepina za 25 %
Spori metabolizator (1-10 %)	Ne preporučuje se liječenje doksepinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja doksepinom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Tablica 2: Preporuke za liječenje doksepinom ovisno o fenotipu CYP2C19

CYP2C19 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (2-5 %)	Ne preporučuje se liječenje doksepinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja doksepinom, preporučuje se terapijsko praćenje lijeka radi modifikacije doze
Brzi metabolizator (2-30 %)	Ne preporučuje se liječenje doksepinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja doksepinom, preporučuje se terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (35-50 %)	Započeti terapiju preporučenom početnom dozom
Intermedijarni metabolizatori (18-45 %)	Započeti terapiju preporučenom početnom dozom
Spori metabolizator (2-15 %)	Ne preporučuje se liječenje doksepinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja doksepinom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Nota bene 1: Ukoliko se pacijent liječi nižim dozama doksepina (npr. zbog insomnije), a da je intermedijarni ili spori CYP2D6 / CYP2C19 metabolizator, ne preporučuje se prilagodba doze zbog već inicijalno propisane niže doze. Pacijente treba nadzirati zbog potencijalnih nuspojava.

Nota bene 2: The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group je evaluirala preporuke doziranja prema CYP2C19 fenotipu (UM, IM, PM). Zaključili su kako NEMA potrebe za terapijskom intervencijom za ovu interakciju gena i lijeka[3].

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa *CYP2C19* i *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

[3] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf

EFAVIRENZ

Genetic test to minimize the risk related to therapy with efavirenz

Drug

What are the indications and mechanisms of action of efavirenz?

Efavirenz is an antiviral agent prescribed for the treatment of infections with the human immunodeficiency virus type 1 (HIV-1). Efavirenz is a non-nucleoside HIV-1 reverse transcriptase inhibitor that suppresses HIV-1 replication in treatment-naïve HIV positive patients. It is combined with other drugs in therapeutic regimens.

Genes

What genes influence the effect of efavirenz?

Efavirenz has well-known side-effects affecting mainly the central nervous system (CNS), and has notably more drug-drug interactions when compared with alternative therapeutical regimens. It is metabolized to inactive metabolites by CYP2B6 enzyme, encoded by the *CYP2B6* gene, which is the main cause of the interactions and side-effects, while CYP2A6, CYP3A4, and CYP1A2 play minor roles.

Test

What is tested?

In order to determine the metabolism type, the patients' genotype of highly polymorphic *CYP2B6* (38 known variant allels) is tested for the most common activity-varying gene variants which are classified into functional groups: normal function (e.g. **1*), decreased function (e.g. **6, *9*), no function (e.g. **18*) and increased function (e.g. **4*).

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with efavirenz in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted according to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for efavirenz therapy depending on the phenotype of the CYP2B6 gene

CYP2B6 phenotype	Recommended therapy
Ultrarapid metabolizer	Initiate efavirenz with standard dosing (600 mg/day)
Rapid metabolizer	Initiate efavirenz with standard dosing (600 mg/day)
Normal metabolizer	Initiate efavirenz with standard dosing (600 mg/day)
Intermediate metabolizer	Consider initiating efavirenz with reduced dosing (400 mg/day)
Poor metabolizer	Consider initiating efavirenz with reduced dosing (400 or 200 mg/day)

Cost

Costs for the determination of the *CYP2B6* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Desta Z, Gammal RS, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. Clin Pharmacol Ther. 2019;106(4):726-733. doi:10.1002/cpt.1477

EFAVIRENZ

Gentest zur Risikominimierung der Therapie mit Efavirenz

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Efavirenz?

Efavirenz ist ein antivirales Mittel, das zur Behandlung von Infektionen mit dem humanen Immundefizienzvirus Typ 1 (HIV-1) verschrieben wird. Efavirenz ist ein nicht-nukleosidischer HIV-Typ-1-Inhibitor für die reverse Transkriptase, der die HIV-1-Replikation bei therapienaiven, HIV-positiven Patienten unterdrückt. Efavirenz verhindert die Integration des HIV-Genoms in das Genom der Wirtszellen und damit die Replikation des Virus.

Gene

Welche Gene beeinflussen die Wirkung von Efavirenz?

Efavirenz hat seit langem bekannte Nebenwirkungen, die hauptsächlich das Zentralnervensystem (ZNS) betreffen. Im Vergleich zu alternativen Therapien weist Efavirenz deutlich mehr Arzneimittelwechselwirkungen auf. Das *CYP2B6*-Gen ist die Hauptursache für die Wechselwirkungen und Nebenwirkungen, bei denen *CYP2A6*, *CYP3A4* und *CYP1A2* eine untergeordnete Rolle spielen.

Test

Was wird getestet?

Um den hochpolymorphen Metabolismustyp *CYP2B6* (38 bekannte Allelvarianten) zu bestimmen, wird der Genotyp des Patienten auf die häufigsten aktivitätsvarianten Genvarianten getestet, die in funktionelle Gruppen eingeteilt sind: normale Funktion (z. B. **1*), verminderte Funktion (z.B. **6, *9*), keine Funktion (z.B. **18*) und erhöhte Funktion (z.B. **4*).

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Efavirenz durchgeführt werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu ändern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Efavirenz-Therapie unter Berücksichtigung des Phänotyp des CYP2B6-Gens

CYP2B6 Phänotyp	Therapieempfehlung
Ultraschnelle Metabolisierer	Anwendung gemäß Fachinformation (600mg/Tag)
Schnelle Metabolisierer	Anwendung gemäß Fachinformation (600mg/Tag)
Normale Metabolisierer	Anwendung gemäß Fachinformation (600mg/Tag)
Intermediäre Metabolisierer	Startdosis reduzieren (400mg/Tag)
Langsame Metabolisierer	Startdosis reduzieren (400 oder 200mg/Tag)

Kosten

Die Kosten für die genetische Analyse der *CYP2B6* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Desta Z, Gammal RS, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. Clin Pharmacol Ther. 2019;106(4):726-733. doi:10.1002/cpt.1477

EFAVIRENZ

Genetički test za smanjenje rizika pri primjeni efavirenza

Lijek

Koje su indikacije i mehanizmi djelovanja efavirenza?

Efavirenz je antivirusni lijek koji se koristi u liječenju infekcije virusom humane imunodeficijencije tip 1 (HIV-1). Efavirenz je nenukleozidni inhibitor reverzne transkriptaze virusa koji suprimira replikaciju HIV-1 u pacijenata koji su HIV-pozitivni, a nisu primali antiretrovirusnu terapiju. Efavirenz se kombinira s drugim lijekovima u visokoaktivnim antiretrovirusnim terapijskim režimima.

Geni

Koji geni utječu na metabolizam efavirenza?

Efavirenz ima dobro poznate nuspojave koje najvećim djelom zahvaćaju središnji živčani sustav. U usporedbi s drugim antiretrovirusnim lijekovima, efavirenz ulazi u znatno više interakcija s ostalim lijekovima. Enzim CYP2B6, koji je kodiran genom *CYP2B6* glavni je za biotransformaciju efavirenza u inaktivne metabolite, dok CYP2A6, CYP3A4 i CYP1A2 imaju manju ulogu. CYP2B6 je najvažniji uzrok interakcija i nuspojava efavirenza.

Analiza

Što se analizira?

Kako bi se odredio tip metabolizma visoko polimorfnog *CYP2B6* gena (38 poznatih varijanti alela), genom pacijenta testira se na najčešće genske varijante koje su povezane s aktivnošću te se sukladno tome klasificiraju u funkcionalne skupine: normalna funkcija (npr. **1*), smanjena funkcija (npr. **6, *9*), nema funkcije (npr. **18*) i povećana funkcija (npr. **4*)

Indikacija

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka liječenja efavirenzom radi određivanja doze lijeka ili mogućeg uvođenja alternativnog lijeka, ukoliko je to potrebno.

Preporuka

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su utemeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje efavirenzom ovisno o CYP2B6 fenotipu

CYP2B6 fenotip	Preporučena terapija
Ultrabrzi metabolizator	Uvesti efavirenz u standardnoj dozi (600 mg/dan)
Brzi metabolizator	Uvesti efavirenz u standardnoj dozi (600 mg/dan)
Normalni metabolizator	Uvesti efavirenz u standardnoj dozi (600 mg/dan)
Intermedijarni metabolizator	Razmotriti uvođenje efavirenza u sniženoj dozi (400 mg/dan)
Spori metabolizator	Razmotriti uvođenje efavirenza u sniženoj dozi (400 ili 200 mg/dan)

Troškovi

Priznavanje i povrat troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje *CYP2B6* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Desta Z, Gammal RS, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. Clin Pharmacol Ther. 2019;106(4):726-733. doi:10.1002/cpt.1477

ENFLURANE

Genetic test to minimize the risk of malignant hyperthermia (MH) related to the therapy with enflurane

Drug

What are the indications and mechanisms of action of enflurane?

Enflurane is generally safe volatile inhaled anesthetic used for inducing general anesthesia. Its mechanism of action is complex and includes a reduction in junctional conductance by decreasing gap junction channel opening times and increasing gap junction channel closing times. It also activates calcium-dependent ATPase in the sarcoplasmic reticulum by increasing the fluidity of the lipid membrane. Enflurane probably binds to various neurotransmitter receptors (like GABA, glycine, glutamate) and ion channels and interacts with the nerve membranes.

Genes

Which genes influence the effect of enflurane?

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the *RYR1* and *CACNA1S* genes under consideration here predispose individuals to a severe and sometimes lethal hypermetabolic reaction whose symptoms include muscle rigidity, high fever, and a fast heart rate. Complications can include rhabdomyolysis and high blood potassium.

Test

What will be tested?

The genotype of the ryanodine receptor isoform 1 protein *(RYR1)* is tested for one of the 48 causative single-nucleotide variants or one deletion that are designated diagnostic malignant hyperthermia (MH) mutations[1]. The α1S subunit of the dihydropyridine receptor (CACNA1S) is tested for the 2 known variants that are MH susceptible. Since MH susceptibility is inherited in an autosomal-dominant pattern, a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as diagnostic for the trait.

Indication

When should a test be performed?

Genetic testing should be carried out before the initiation of the scheduled therapy with enflurane in order to predict the risk of MH.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for enflurane usage depending on the phenotype of the RYR1 and CACNA1S genes

RYR1 or CACNA1S Phenotype	Recommended therapy
Malignant hyperthermia susceptible (MHS)	Enflurane is not recommended due to MH susceptibility, use alternative anesthetics
Uncertain susceptibility	Clinical findings, family history, further genetic testing, and other laboratory data should guide the use of enflurane

Nota bene: A negative or inconclusive genetic test cannot be assumed to indicate normal phenotype and should be interpreted in the context of clinical findings, family history, and other laboratory data.

Costs

Costs for the determination of the *RYR1* and *CACNA1S* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

ENFLURAN

Gentest zur Risikominimierung der Therapie mit Enfluran bei maligner Hyperthermie (MH)

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Enfluran?

Enfluran ist ein weit verbreitetes und allgemein sicheres, flüchtiges Anästhetikum, das zur Einleitung einer Vollnarkose verwendet wird. Sein Wirkungsmechanismus ist komplex und umfasst eine Verringerung der Verbindungsleitfähigkeit durch verringerte Öffnungszeiten und erhöhte Schließzeiten von *gap junction*-Kanälen. Es aktiviert auch die Calcium-abhängige ATPase im sarkoplasmatischen Retikulum, indem es die Fluidität der Lipidmembran erhöht. Es wird hypothetisiert, dass Enfluran an verschiedene Neurotransmitter-Rezeptoren und Ionenkanalen (wie GABA, Glycine, Glutamat) bindet und mit Nervenmembranen interagiert.

Gene

Welche Gene beeinflussen die Wirkung von Enfluran?

Im Gegensatz zu vielen verwertbaren pharmakogenetischen Merkmalen, die den Metabolismus und/oder die Ausscheidung eines Arzneimittels beeinflussen, prädisponieren die hier betrachteten Varianten der Gene *RYR1* und *CACNA1S* zu einer schweren und manchmal tödlichen hypermetabolischen Reaktion, zu deren Symptomen Muskelsteifheit, hohes Fieber und schnelle Herzfrequenz gehören. Weitere Komplikationen können Rhabdomyolyse und hohe Kaliumwerte im Blut darstellen.

Test

Was wird getestet?

Der Genotyp des Ryanodinrezeptor-Isoform-1-Proteins *(RYR1)* wird auf eine der 48 Einzelnukleotidvarianten und eine Deletion getestet, die als diagnostische maligne Hyperthermie-Mutation[1] bezeichnet werden. Die α1S-Untereinheit des Dihydropyridinrezeptors (CACNA1S) wird auf die beiden bekannten Varianten getestet, die für maligne Hyperthermie anfällig sind. Da die Anfälligkeit für maligne Hyperthermie (MHS) in einem autosomal-dominanten Muster vererbt wird, kann ein heterozygoter Genotyp einer pathogenen Variante in *RYR1* als diagnostisch für das Merkmal angesehen werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Desfluran durchgeführt werden, um das Risiko einer bösartigen Hyperthermie zu verringern. Alle nichtdepolarisierenden Muskelrelaxantien außer den Hyperthermie-auslösenden starken, flüchtigen Anästhetika, alle intravenösen Induktionsmittel sowie die verlängerte Inhalationsanästhesie mit nicht auslösenden Mitteln stellen Alternativen dar, die nicht mit bösartiger Hyperthermie assoziiert sind.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Enfluran-Gebrauch mit Phänotyp der RYR1- und CACNA1S-Gene

RYR1 oder CACNA1S Phänotyp	Therapieempfehlung
Maligne Hyperthermie Anfälligkeit (MHS)	Enfluran kontraindiziert, Anästhetikawechsel empfohlen
Unsichere Anfälligkeit	Klinische Befunde, Familienanamnese, weitere Gentests und andere Labordaten sollten den Einsatz von Enfluran anleiten

Nota bene: Ein negativer oder nicht eindeutiger Gentest kann nicht als Hinweis auf einen normalen RYR1-bezogenen Phänotyp angesehen werden und sollte im Zusammenhang mit klinischen Befunden, Familienanamnese und anderen Labordaten interpretiert werden.

Kosten

Die Kosten für die genetische Analyse des CYP2B6 -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

ENFLURAN

Genetički test za smanjenje rizika pojave maligne hipertermije pri primjeni enflurana

Lijek

Koje su indikacije i mehanizmi djelovanja enflurana?

Enfluran je siguran hlapljivi inhalacijski anestetik koji se često koristi za indukciju opće anestezije. Njegov mehanizam djelovanja je kompleksan, a uključuje smanjenje provodljivosti skraćivanjem vremena otvaranja kanala na pukotinskim spojevima (gap junctions) i produljujući vrijeme zatvaranja istih. Također aktivira o kalciju ovisnu ATP-azu na sarkoplazmatskom retikulumu povećanjem fluidnosti lipidne membrane. Enfluran se vjerojatno veže na više neurotransmitorskih receptora (poput $GABA_A$, glicinskog i glutamatnog), ionskih kanala te ulazi u interakciju s membranama neurona.

Geni

Koji geni utječu na djelovanje enflurana?

Za razliku od mnogih drugih lijekova kojima genski polimorfizmi utječu na metabolizam ili ekskreciju, polimorfizmi *RYR1* i *CACNA1S* gena su predisponirajući za tešku i smrtonosnu hipermetaboličku reakciju, čiji simptomi uključuju: rigidnost mišića, visoku tjelesnu temperaturu, tahikardiju. Komplikacije uključuju rabdomiolizu i hiperkalemiju.

Analiza

Što se analizira?

Genotip rajanodinskog receptora izoforme 1 *(RYR1)* testira se na jedan od 48 nukleotidnih polimorfizama ili jednu deleciju koje su označene kao dijagnostičke mutacije za malignu hipertermiju[1]. α1S podjedinica dihidropiridinskog receptora (CACNA1S) se testira za jednu od 2 poznate mutacije koje su dijagnostičke za malignu hipertermiju. Budući da se navedeni geni nasljeđuju autosomno dominantno, heterozigotni genotip navedenih gena smatra se kao dijagnoza sklonosti ka malignoj hipertermiji.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka primjene enflurana kako bi se odredila sklonost ka nastanku maligne hipertermije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortiums (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za primjenu enflurana ovisno o genotipu RYR1 i CACNA1S

RYR1 ili CACNA1S fenotip	Preporučena terapija
Osjetljivost za malignu hipertermiju	Ne preporučuje se primjena enflurana. Potrebno je korištenje alternativnog anestetika
Neinformativan	Odluka o primjeni enflurana trebala bi se voditi kliničkom slikom, obiteljskom anamnezom, daljnjim genskim testiranjem i ostalim laboratorijskim podatcima

Nota bene: negativan ili neinformativan rezultat testa se ne smije uzeti kao indikacija za normalan fenotip te se treba razmotriti u kontekstu kliničkih nalaza, obiteljske anamneze i ostalih laboratorijskih nalaza.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

ESCITALOPRAM

Genetic test to minimize the risks related to therapy with escitalopram

Drug

What are the indications and the mechanism of action of escitalopram?

Escitalopram belongs to the class of drugs called selective serotonin reuptake inhibitors (SSRIs). They are typically used as antidepressants in the treatment of major depressive disorder and anxiety disorders. SSRIs increase the extracellular level of serotonin, by limiting its reuptake into the presynaptic cell, thus increasing the level of serotonin in the synaptic cleft available to bind to the presynaptic and postsynaptic receptors. They have only a weak affinity for the norepinephrine and dopamine transporters.

Genes

Which genes influence the effect of escitalopram?

Escitalopram is extensively metabolized by CYP2C19 enzyme to inactive metabolites. *CYP2C19* genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis.

Test

What will be tested?

Commonly reported *CYP2C19* star-alleles are categorized into functional groups (e.g., normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme. To determine the CYP2C19 metabolism type, the patient's *CYP2C19* genotype (*1, *2, *3, *17) is tested for the most common activity-variant gene variants.

Indications

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with escitalopram in order to change the active agent, as required, so that severe side effects can be avoided.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for therapy with escitalopram depending on CYP2C19 genotype and resulting phenotype

Genotype / Phenotype (metabolizer status frequencies)	Recommended therapy
**17/*17, *1/*17* / Ultrarapid metabolizer (5-30 %)	Change of active agent recommended
**1/*1* / Extensive metabolizer (35-50 %)	Usage according to the Summary of Product Characteristics
**1/*2, *1/*3, *2/*17* / Intermediate metabolizer (18-45 %)	Usage according to the Summary of Product Characteristics
**2/*2, *2/*3, *3/*3* / Poor Metabolizer (2-15 %)	Change of active agent recommended If introducing escitalopram: reduction of inital dose to 50 % of the normal starting dose, titration is needed to higher target doses

Costs

Costs for the determination of enzymatic status are reimbursed for patients with statutory or private health insurance if testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

ESCITALOPRAM

Gentest zur Risikominimierung der Therapie mit Escitalopram

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Escitalopram?

Escitalopram ist ein selektiver Serotonin-Wiederaufnahmehemmer (SSRIs), der als Antidepressiva bei der Behandlung von Depressionen und Angststörungen eingesetzt wird. Der genaue Wirkungsmechanismus von SSRIs ist unbekannt. Es wird angenommen, dass eine Erhöhung des extrazellulären Serotoninspiegel im synaptischen Spalt durch Limitierung der Reabsorption (Wiederaufnahme) in die präsynaptische Zelle erreicht wird. Es sind unterschiedliche Selektivitätsgrade für die anderen Monoamintransporter vorhanden, wobei reine SSRIs nur eine schwache Affinität für die Norepinephrin- und Dopamintransporter aufweisen.

Gene

Welche Gene beeinflussen die Wirkung von Escitalopram?

Escitalopram wird durch das CYP2C19-Enzym weitgehend zu inaktiven Metaboliten metabolisiert. Genetische Varianten von *CYP2D6* und *CYP2C19* werden typischerweise als Haplotypen angegeben, die durch eine spezifische Kombination von Einzelnukleotidpolymorphismen (SNPs) und/oder anderen Sequenzvarianten definiert sind, einschließlich Insertionen und Deletionen, die während der Genotypisierungsanalyse abgefragt werden.

Test

Was wird getestet?

Häufig berichtete CYP2C19-Allele werden basierend auf der vorhergesagten Aktivität des kodierten Enzyms in Phänotypen (ultraschnelle-schnelle-normale-langsame Metabolisierer) eingeteilt. Zur Bestimmung des CYP2C19-Metabolismustyp, wird der Genotyp des Patienten im *CYP2C19*-Gen *(*1, *2, *3, *17)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikationen

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Escitalopram durchgeführt werden, um gegebenfalls den Wirkstoff zu wechseln, um schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Escitalopram-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

Genotyp / Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
**17/*17, *1/*17* / Ultraschnelle Metabolisierer (5-30 %)	Wirkstoffwechsel empfohlen
**1/*1* / Schnelle Metabolisierer (35-50 %)	Therapie gemäß Fachinformation
**1/*2, *1/*3, *2/*17* / Intermediäre Metabolisierer (18-45 %)	Therapie gemäß Fachinformation
**2/*2, *2/*3, *3/*3* / Langsame Metabolisierer (2-15 %)	Wirkstoffwechsel empfohlen Bei Einsatz von Escitalopram: Startdosis um 50 % reduzieren, auf höhere Zieldosis titrieren

Kosten

Die Kosten für die genetische Analyse des *CY2PC19*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

ESCITALOPRAM

Genetički test za smanjenje rizika pri primjeni escitaloprama

Lijek

Koje su indikacije i mehanizmi djelovanja escitaloprama?

Esitalopram pripada skupini lijekova koja se naziva selektivni inhibitori ponovne pohrane serotonina (eng. selective serotonin reuptake inhibitors, SSRI). Ova se skupina lijekova tipično koriste u lije**če**nju depresivnih i anksioznih poremećaja. Escitalopram inhibira ponovni povrat serotonina u presinaptički neuron čime se povećava njegova količina u sinaptičkoj pukotini, kao i presinaptičko i postsinaptičko djelovanje. Također, ima nisku razinu selektivnosti za transportere noradrenalina i dopamina.

Geni

Koji geni utječu na djelovanje escitaloprama?

Escitalopram se ekstenzivno metabolizira putem CYP2C19 enzima do inaktivnih metabolita. *CYP2C19* genetičke varijante tipično se opisuju kao haplotipovi, koji su definirani pomoću specifične kombinacije polimorfizma jednog nukleotida (SNP) i drugih varijacija, uključujući insercije i delecije, koje se ispituju tijekom genotipizacije.

Analiza

Što se analizira?

CYP2C19 aleli označeni zvjezdicom kategoriziraju u funkcionalne skupine (npr. pojačana funkcija, normalna funkcija, oslabljena funkcija) prema predviđenoj aktivnosti kodiranog enzima. Za određivanje vrste CYP2C19 metabolizma, pacijentov *CYP2C19* genotip se testira za česte genske varijante (*1, *2, *3, *17).

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka terapije escitalopramom kako bi se mogao primijeniti zamjenski lijek, ukoliko je potrebno, da se izbjegnu značajne nuspojave.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za terapiju escitalopramom ovisno o aktivnosti enzimskog sustava CYP2C19

***CYP2C19* Genotip / Fenotip (učestalost metabolizatora)**	**Preporučena terapija**
*17/*17, *1/*17 / Ultrabrzi metabolizator (5-30 %)	Preporučuje se primjena zamjenskog lijeka
*1/*1 | Ekstenzivni metabolizator (35-50 %)	Terapija sukladno uputama o lijeku
*1/*2, *1/*3, *2/*17 / Intermedijarni metabolizator (18-45 %)	Terapija sukladno uputama o lijeku
*2/*2, *2/*3, *3/*3 / Spori metabolizator (2-15 %)	Preporučuje se primjena zamjenskog lijeka. Ukoliko se uvodi escitalopram: smanjiti početnu dozu na 50 % normalne doze. Titracija je potrebna za više doze

Troškovi

Troškovi za određivanje *CYP2C19* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje ukoliko je testiranje zatraženo od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

5-FLUOROURACIL AND CAPECITABINE

Genetic test to minimize the risks related to therapy with 5-fluorouracil and capecitabine

Drug

What are the indications and mechanisms of action of 5-fluorouracil and capecitabine?

5-fluorouracil and capecitabine are fluoropyrimidines, the group of cytotoxic agents widely used for the treatment of solid tumors such as colorectal cancer, breast cancer and cancers of the aerodigestive tract. Capecitabine is a prodrug being converted into the active agent 5-fluorouracil in the tumor. The cytostatic effect of 5-fluorouracil results from an inhibition of DNA and RNA synthesis.

Genes

What genes influence the effect of 5-fluorouracil and capecitabine?

As an active agent of capecitabine, 5-fluorouracil is also broken down by the enzyme dihydropyrimidine dehydrogenase (DPD). In the population, the *DPYD* gene located on chromosome 1p22 occurs in several variants. Approximately 10-40 % of fluoropyrimidine-treated patients develop severe and sometimes life-threatening toxicity (neutropenia, nausea, vomiting, severe diarrhea, stomatitis, mucositis, hand-foot syndrome, etc.) due to the genetically reduced enzyme activity.

Test

What is tested?

The genotype of patients is tested with regard to the most common genetic variants (*c.1905+1G>A* also known as **2A, c.1679T>G* or **13, c.2846A>T* and *c.1129-5923C>G* or HapB3) which cause a partial or complete loss of the DPD activity. Considering four variants combined, ~7 % of Europeans carry at least one decreased function *DPYD* variants.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with 5-fluorouracil or capecitabine in order to reduce the risk of severe side effects, as required, by means of an adjustment of the initial dose or by prescribing an alternative active agent.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for the therapy with 5-fluorouracil and/or capecitabine depending on the phenotype of the DPYD gene

DPYD Genotype / Phenotype	Recommended therapy
Wildtype / Normal metabolizer	Usage according to the Summary of Product Characteristics
Risk variant, heterozygous / Intermediate metabolizer	Reduce starting dose by 50 % followed by titration of dose based on toxicity
Defficiency / Poor metabolizer	Usage of 5-flourouracil and capecitabine are not recommended, usage of alternative agents is recommended

Costs

Costs for the *DPYD* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Caudle KE, Thorn CF, Klein TE, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013;94(6):640-645. doi:10.1038/clpt.2013.172

[2] Amstutz U, Henricks LM, Offer SM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210-216. doi:10.1002/cpt.911

5-FLUOROURACIL UND CAPECITABIN

Gentest zur Risikominimierung der Therapie mit 5-Fluoruracil und Capecitabin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von 5-Fluorouracil und Capecitabin?

5-Fluorouracil und Capecitabin sind Fluorpyrimidine, die Gruppe von Zytostatika, die häufig zur Behandlung von soliden Tumoren wie Darmkrebs, Brustkrebs und Krebserkrankungen des Aerodigestivtrakts eingesetzt werden. Capecitabin ist ein Prodrug, das in besonders hoher Konzentration im Tumor in den Wirkstoff 5-Fluoruracil umgewandelt wird. Die zytostatische Wirkung von 5-Fluorouracil beruht auf einer Hemmung der DNA- und RNA-Synthese.

Gene

Welche Gene beeinflussen die Wirkung von 5-Fluorouracil und Capecitabin?

Als Wirkstoff von Capecitabin wird 5-Fluorouracil auch durch das Enzym Dihydropyrimidin-Dehydrogenase (DPD) abgebaut. In der Population kommt das auf Chromosom 1p22 befindliche *DPYD*-Gen in mehreren Varianten vor. Ungefähr 10-40 % der mit Fluorpyrimidin behandelten Patienten entwickeln aufgrund der genetisch reduzierten Enzymaktivität eine schwere und manchmal lebensbedrohliche Toxizität (Neutropenie, Übelkeit, Erbrechen, schwerer Durchfall, Stomatitis, Mukositis, Hand-Fuß-Syndrom usw).

Test

Was wird getestet?

Der Genotyp von Patienten wird auf die häufigsten genetischen Varianten untersucht: *c.1905 + 1G> A (*2A), c.1679T> G (*13), c.2846A> T* und *c.1129-5923 C>G* (HapB3), die einen teilweisen oder vollständigen Verlust der DPYD-Aktivität verursachen. Betrachtet man alle vier Varianten zusammen, tragen ~ 7 % der Europäer mindestens eine der *DPYD*-Varianten mit reduzierter Funktion.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn einer geplanten Therapie mit 5-Fluoruracil oder Capecitabin durchgeführt werden, um das Risiko schwerwiegender Nebenwirkungen durch Anpassung der Anfangsdosis oder Wirkstoffwechsel zu verringern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Therapie mit 5-Fluorouracil und/oder Capecitabin mit DPYD-Genotyp

***DPYD* Genotyp / Phänotyp (Metabolisiererhäufigkeit)**	**Recommended therapy**
Wildtyp / Normale Metabolisierer	Therapie gemäß Fachinformation
Risiko Variante, heterozygous / Iintermediäre Metabolisierer	Startdosis um 50 % reduzieren Dosis basierend auf Toxizität titrieren
Defizienz / Langsame Metabolisierer	Wirkstoffwechsel

Kosten

Die Kosten für die genetische Analyse des *DPYD*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Caudle KE, Thorn CF, Klein TE, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013;94(6):640-645. doi:10.1038/clpt.2013.172

[2] Amstutz U, Henricks LM, Offer SM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210-216. doi:10.1002/cpt.911

5-FLUOROURACIL I KAPECITABIN

Genetički test za smanjenje rizika pri primjeni 5-fluorouracila i kapecitabina

Lijek

Koje su indikacije i mehanizmi djelovanja 5-fluorouracila i kapecitabina?

5-fluorouracil i kapecitabin su fluoropirimidini, koji se naširoko upotrebljavaju u liječenju solidnih tumora kao što su kolorektalni karcinom, karcinom dojke i karcinomi aerodigestivnog trakta. Kapecitabin je prolijek, koji se u jetrima ili u samom tumoru pretvara u aktivni metabolit 5-fluorouracil. Citostatsko djelovanje 5-fluorouracila temelji se na inhibiciji sinteze DNA i RNA.

Geni

Koji geni utječu na djelovanje 5-fluorouracila i kapecitabina?

Kao aktivni metabolit kapecitabina, 5-fluorouracil se metabolizira putem enzima dihidropirimidin dehidrogenaze (DPD). U populaciji, *DPYD* gen lociran na 1p22 kromosomu se pojavljuje u nekoliko varijanti. Otprilike 10-40 % pacijenata liječenih s fluoropirimidinima razviju ozbiljne, ponekad po život opasne nuspojave (neutropenija, mučnina, povraćanje, jaki proljevi, stomatitisi, mukozitisi, sindrom usta-stopalo, itd.), a razlog je genski uvjetovana smanjena enzimska aktivnost.

Analiza

Što se analizira?

Analizira se genotip pacijenta na najučestalije varijante gena (*c.1905+1G>A* poznat kao **2A, c.1679T>G* ili **13, c.2846A>T* i *c.1129-5923C>G* ili HapB3) koje dovode do parcijalnog ili potpunog gubitka DPD aktivnosti. Uzimajući u obzir sve četiri varijante zajedno, oko 7 % Europljana ima bar jednu varijantu *DPYD* sa smanjenom funkcijom.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije 5-fluorouracilom, odnosno kapecitabionom da bi se prilagodbom početne doze ili po potrebi ordiniranjem drugog lijeka smanjio rizik ozbiljnih nuspojava

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Sljedeće preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] i imaju najvišu razinu dokaza 1A.

Tablica 1: Preporuke za liječenje 5-fluorouracilom i/ili kapecitabinom ovisno o genotipu DPYD

***DPYD* Genotip / Fenotip**	**Preporučena terapija**
Divlji tip / Normalni metabolizator	Korištenje sukladno uputama o lijeku
Rizična varijanta, heterozigot / Intermedijarni metabolizator	Potrebno je smanjiti standardnu-početnu dozu za 50 % i potom titrirati ovisno o toksičnosti
Nedostatak / Slab metabolizator	Primjena 5-fluorouracila i kapecitabina se ne preporučuje, preporučuje se primjena zamjenskog lijeka

Troškovi

Priznavanje i povrat troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize *DPYD* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Caudle KE, Thorn CF, Klein TE, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013;94(6):640-645. doi:10.1038/clpt.2013.172

[2] Amstutz U, Henricks LM, Offer SM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210-216. doi:10.1002/cpt.911

FLURBIPROFEN

Genetic test to minimize the risks related to therapy with flurbiprofen

Drug

What are the indications and mechanisms of action of flurbiprofen?

Flurbiprofen is a nonsteroidal drug with antiinflammatory, analgesic, and antipyretic activities. Its therapeutic effects occur via inhibition of prostaglandin biosynthesis from arachidonic acid by the cyclooxygenases (COX) isoforms 1 and 2. Flurbiprofen is non-selective reversible inhibitor of both COX isoforms.

Genes

Which genes influence the effect of flurbiprofen?

Flurbiprofen is metabolized via the enzyme CYP2C9. A decrease in the CYP2C9 function decreases metabolic clearance of flurbiprofen thus prolonging its plasma elimination half-life. Several variants of the *CYP2C9* gene with great variability in the enzymatic activity of CYP2C9 are known in the population.

Test

What is tested?

To determine the CYP2C9 metabolism type, the testing of *CYP2C9* gene variants *(*2, *3)* associated with significantly reduced CYP2C9 enzyme activity is recommended.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the therapy with flurbiprofen, in order to minimize the risk of side effects such as gastrointestinal bleeding, hypertension, myocardial infarction, heart failure, and renal damage through an adjustment of the starting dose or the prescription of alternative therapy.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for flurbiprofen therapy according to the CYP2C9 genotype

***CYP2C9* Genotype / Phenotype**	**Therapy recommendation**
*CYP2C9*1/*1* / Normal metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*2* / Intermediate metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*3, *2/*2* / Intermediate metabolizer	Initiate therapy with the lowest recommended starting dose and titrate upward to clinical effect or maximum recommended dose with caution, especially in individuals with other factors affecting clearance such as hepatic impairment or advanced age
*CYP2C9*2/*3, *3/*3* / Poor metabolizer	Initiate therapy with 25–50 % of the lowest recommended starting dose and titrate dose upward to clinical effect or 25–50 % of the maximum recommended dose with caution. Alternatively, consider the other drug not primarily metabolized by CYP2C9

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

FLURBIPROFEN

Gentest zur Risikominimierung der Therapie mit Flurbiprofen

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Flurbiprofen?

Flurbiprofen ist ein nichtsteroidales Medikament mit entzündungshemmenden, analgetischen und fiebersenkenden Eigenschaften. Seine therapeutischen Wirkungen treten über die Hemmung der Prostaglandin-Biosynthese aus Arachidonsäure durch die Cyclooxygenasen (COX)-Isoformen 1 und 2 auf. Flurbiprofen ist ein nicht selektiver reversibler Inhibitor beider COX-Isoformen.

Gene

Welche Gene beeinflussen die Wirkung von Flurbiprofen?

Flurbiprofen wird über das Enzym CYP2C9 metabolisiert. Eine Abnahme der CYP2C9-Funktion verringert die metabolische Clearance (Ausscheidung) von Flurbiprofen und verlängert so die Halbwertszeit der Plasmaelimination. In der Population sind mehrere Varianten des *CYP2C9*-Gens mit großer Variabilität der enzymatischen Aktivität von CYP2C9 bekannt.

Test

Was wird getestet?

Zur Bestimmung des CYP2C9-Metabolismus wird empfohlen, *CYP2C9*-Genvarianten *(*2, *3)* zu testen, die mit einer signifikant verringerten CYP2C9-Enzymaktivität assoziiert sind.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der Therapie mit Flurbiprofen durchgeführt werden, um das Risiko für Nebenwirkungen wie gastrointestinale Blutungen, Bluthochdruck, Myokardinfarkt, Herzinsuffizienz und Nierenschäden durch Anpassung der Anfangsdosis oder der Verschreibung einer alternativen Behandlung zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Flurbiprofen-Therapie in Abhängigkeit vom CYP2C9-Genotyp

***CYP2C9* Genotyp / Phänotyp**	**Therapieempfehlung**
*CYP2C9*1/*1* / Normale Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*2* / Intermediare metabolizer	Anwendung gemäß Fachinformation
*CYP2C9*1/*3, *2/*2* / Intermediäre Metabolisierer	Start mit der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder empfohlene maximale Dosis, insbesondere bei Vorliegen von Leberfunktionsstörung oder höherem Alter
*CYP2C9*2/*3, *3/*3* / Langsame Metabolisierer	Start mit 25-50 % der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder 25-50 % der empfohlenen maximalen Dosis. Alternativ: Wechsel auf Wirkstoff ohne *CYP2C9*-Metabolismus

Kosten

Die Kosten für die genetische Analyse des *CYP2C9* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

FLURBIPROFEN

Genetički test za smanjenje rizika pri primjeni flurbiprofena

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja flurbiprofena

Flurbiprofen je nesteroidni lijek s analgetskim, protuupalnim i antipiretskim djelovanjem. Njegov mehanizam djelovanja temelji se na inhibiciji biosinteze prostaglandina iz arahidonske kiseline djelovanjem enzima ciklooksigenaze (COX), izoformi 1 i 2. Flurbiprofen je neselektivni reverzibilni inhibitor obje COX izoforme.

Geni

Koji geni utječu na djelovanje flurbiprofena

Flurbiprofen se metabolizira putem enzima CYP2C9. Smanjenje funkcije CYP2C9 usporava eliminaciju flurbiprofena iz organizma i produljuje poluvrijeme eliminacije. Poznato je nekoliko varijanti *CYP2C9* gena s velikom varijabilnošću u enzimskoj aktivnosti CYP2C9 u populaciji.

Analiza

Što se analizira

Kako bi se odredio metabolizam s obzirom na CYP2C9, preporučuje se utvrđivanje prisutnosti varijanti *CYP2C9* gena *(*2, *3)* koje su povezane sa značajno reduciranim kapacitetom enzimske aktivnosti.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo provesti prije započinjanja terapije flurbiprofenom kako bi se smanjio rizik neželjenih nuspojava kao što su gastrointestinalno krvarenje, hipertenzija, infarkt miokarda, srčano zatajenje i bubrežno oštećenje na način da se prilagodi početna doza ili propiše druga terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje flurbiprofenom ovisno o CYP2C9 genotipu

***CYP2C9* genotip / fenotip**	**Preporučena terapija**
*CYP2C9*1/*1* / Normalni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*2* / Intermedijarni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*3, *2/*2* / Intermedijarni metabolizator	Započnite terapiju s najnižom preporučenom dozom i titrirajte do željenog kliničkog učinka ili do najveće preporučene doze s oprezom, osobito u pojedinaca koji imaju rizične faktore koji utječu na eliminaciju lijeka kao što su jetreno oštećenje i starija životna dob
*CYP2C9*2/*3, *3/*3* / Spori metabolizator	Započnite terapiju s 25–50 % najniže preporučene doze i titrirajte s oprezom do željenog kliničkog učinka ili do najviše 25–50 % od maksimalne preporučene doze. Alternativno, odaberite lijek koji se primarno ne metabolizira putem *CYP2C9*

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *CYP2C9* varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *CYP2C9* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

FLUVOXAMINE

Genetic test to minimize the risks related to therapy with fluvoxamine

Drug

What are the indications and mechanisms of action of fluvoxamine?

Fluvoxamine belongs to the of class selective serotonin reuptake inhibitors (SSRIs) which increase the extracellular level of the neurotransmitter serotonin by limiting its reuptake into the presynaptic neuron. Furthermore, it has the highest affinity for sigma1-receptor out of all the SSRIs. By acting as an agonist of this receptor, it may contribute to its antidepressant and anxiolytic effects. Apart from treating depression, it is also used to treat obsessive-compulsive disorder, social anxiety, and post-traumatic stress disorder.

Genes

What genes influence the effect of fluvoxamine?

Fluvoxamine is extensively metabolized by CYP2D6 to inactive compounds. Several variants in the *CYP2D6* gene of these two enzymes are known in the population. These lead to great variability in the enzymatic efficacy and CYP2D6, and can therefore be of great importance for fluvoxamine efficacy and duration of action.

Test

What is tested?

In order to determine the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants in the *CYP2D6* gene *(*1, *1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)*.

Indication

When should a test be carried out?

Patients on a stable and effective dose of an SSRI most likely will not benefit from additional dose modifications based on *CYP2D6* or *CYP2C19* genotype results. The genetic test should be considered before the start of planned therapy with fluvoxamine in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] have the highest clinical level of evidence 1A.

Table 1: Recommendations for fluvoxamine therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-2 %)	No recommendation due to lack of evidence
Extensive metabolizer (77-92 %)	Initiate dose with recommended starting dose
Intermediate metabolizer (2-11 %)	Initiate dose with recommended starting dose
Poor metabolizer (5-10 %)	Consider a 25–50 % reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6

Cost

Costs for the determination of the *CYP2D6* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

FLUVOXAMIN

Gentest zur Risikominimierung der Therapie mit Fluvoxamin

Arzneimittel

Was sind die Indikationen und Wirkmechanismen von Fluvoxamin?

Fluvoxamin ist ein klassenselektiver Serotonin-Wiederaufnahmehemmer (SSRIs), der als Antidepressiva bei der Behandlung von Depressionen, Zwangsstörungen, sozialer Angst und Angststörungen eingesetzt wird. Der genaue Wirkungsmechanismus von SSRIs ist unbekannt. Es wird angenommen, dass eine Erhöhung des extrazellulären Serotoninspiegel im synaptischen Spalt durch Limitierung der Reabsorption (Wiederaufnahme) in die präsynaptische Zelle erreicht wird. Darüber hinaus weist es von allen SSRIs die höchste Affinität zum sigma1-Rezeptor auf. Indem es als Agonist dieses Rezeptors wirkt, kann es zu seiner antidepressiven und anxiolytischen Wirkung beitragen.

Gene

Welche Gene beeinflussen die Wirkung von Fluvoxamin?

Fluvoxamin wird durch CYP2D6 weitgehend zu inaktiven Verbindungen metabolisiert. In der Population sind mehrere Varianten des *CYP2D6*-Gens dieser beiden Enzyme bekannt. Diese führen zu einer großen Variabilität der enzymatischen Wirksamkeit von CYP2D6 und können daher für die Wirksamkeit und Wirkdauer von Fluvoxamin von großer Bedeutung sein.

Test

Was wird getestet?

Um den CYP2D6-Metabolismus-Typ zu bestimmen, wird das Erbgut des Patienten auf die häufigsten aktivitätsvariablen Genvarianten im *CYP2D6*-Gen getestet *(*1, *1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)*.

Indikation

Wann sollte ein Test durchgeführt werden?

Patienten mit einer stabilen und wirksamen Dosis eines SSRI profitieren höchstwahrscheinlich nicht von zusätzlichen Dosisänderungen, die auf den Ergebnissen des *CYP2D6*-Genotyps basieren. Der Gentest sollte vor Beginn der geplanten Therapie mit Fluvoxamin in Betracht gezogen werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu wechseln.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Fluvoxamin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-2 %)	Keine Empfehlung, fehlende Daten
Schnelle Metabolisierer (77-92 %)	Therapie gemäß Fachinformation
Intermediäre Metabolisierer (2-11 %)	Therapie gemäß Fachinformation
Langsame Metabolisierer (5-10 %)	Startdosis um 25–50 % reduzieren, bis Reaktion titrieren oder Wirkstoffwechsel

Kosten

Die Kosten für die genetische Analyse des *CYP2D6* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

FLUVOKSAMIN

Genetički test za smanjenje rizika pri primjeni fluvoksamina

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja fluvoksamina?

Fluvoksamin pripada skupini lijekova poznatih kao selektivni inhibitori ponovne pohrane serotonina (eng. selective serotonin reuptake inhibitors, SSRI). Ovi lijekovi povećavaju izvanstaničnu razinu neurotransmitora serotonina tako što inhibiraju njegovu ponovnu pohranu u presinaptički neuron. Nadalje, fluvoksamin ima najveći afinitet za s1 receptor od svih lijekova ove skupine. Djelovanje na ovaj receptor može doprinijeti njegovom antidepresivnom i anksiolitičkom učinku. Osim depresije, fluvoksamin se koristi za liječenje opsesivno-kompulzivnog poremećaja, socijalne anksioznosti te posttraumatskog stresnog poremećaja.

Geni

Koji geni utječu na učinkovitost fluvoksamina?

Fluvoksamin se ekstenzivno metabolizira putem CYP2D6 enzima do inaktivnih metabolita. Nekoliko genetičkih varijanti *CYP2D6* poznato je u populaciji. Ovo doprinosi velikoj varijabilnosti u učinkovitosti enzima CYP2D6 te može značajno utjecati na učinkovitost fluvoksamina te trajanje djelovanja.

Analiza

Što se analizira?

Da bi se utvrdio tip CYP2D6 metabolizatora, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2D6 (*1, *1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)*.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka terapije fluvoksaminom kako bi se mogao primijeniti zamjenski lijek, ukoliko je potrebno, da se izbjegnu značajne nuspojave.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su utemeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje fluvoksaminom ovisno o genotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizatori (1-2 %)	Nema preporuke s obzirom na nedostatak dokaza
Ekstenzivni metabolizatori (77-92 %)	Početi s preporučenom početnom dozom
Intermedijarni metabolizatori (2-11 %)	Početi s preporučenom početnom dozom
Spori metabolizatori (5-10 %)	Savjetuje se smanjivanje preporučene početne doze za 25-50 % i prilagođavanje do zadovoljavajućeg odgovora. Može se koristiti i terapija zamjenskim lijekom koji se ne metabolizira preko enzima CYP2D6

Troškovi

Troškovi za određivanje *CYP2D6* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

HALOTHANE

Genetic test to minimize the risk of malignant hyperthermia (MH) related to the usage of halothane

Drug

What are the indications and the mechanism of action of halothane?

Halothane is a potent volatile inhalation anesthetic used for the induction and maintenance of general anesthesia. It has a complex mechanism of action and its effects are attributed to binding to different ion channels and receptors, like GABA-A, glycine, NMDA, nAch receptor, causing cell hyperpolarization.

Genes

Which genes influence the effect of halothane?

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the *RYR1* and *CACNA1S* genes under consideration here predispose individuals to a severe and sometimes lethal hypermetabolic reaction whose symptoms include muscle rigidity, high fever, and a fast heart rate. Complications can include rhabdomyolysis and high blood potassium.

Test

What will be tested?

The genotype of the ryanodine receptor isoform 1 protein *(RYR1)* is tested for one of the 48 causative single-nucleotide variants or one deletion that is designated diagnostic MH mutations[1]. The α1S subunit of the dihydropyridine receptor (CACNA1S) is tested for the 2 known variants that are MH susceptible. Since MH susceptibility is inherited in an autosomal-dominant pattern, a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as diagnostic for the trait.

Indication

When should a test be performed?

Genetic testing should be carried out before the initiation of the scheduled therapy with halothane in order to predict the risk of MH.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for halothane usage depending on the phenotype of the RYR1 and CACNA1S genes

RYR1 or CACNA1S Phenotype	Recommended therapy
Malignant hyperthermia susceptible	Halothane is not recommended due to MH susceptibility, use alternative anesthetics
Uncertain susceptibility	Clinical findings, family history, further genetic testing, and other laboratory data should guide the use of volatile anesthetics

Nota bene: A negative or inconclusive genetic test cannot be assumed to indicate a normal phenotype and should be interpreted in the context of clinical findings, family history, and other laboratory data.

Costs

Costs for the determination of the *RYR1* and *CACNA1S* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

HALOTHAN

Gentest zur Risikominimierung der Therapie mit Halothan bei maligner Hyperthermie (MH)

Wirkstoff

Was sind die Indikationen und der Wirkungsmechanismus von Halothan?

Halothan ist ein starkes flüchtiges Inhalationsanästhetikum, das zur Einleitung und Aufrechterhaltung der Vollnarkose verwendet wird. Es hat einen komplexen Wirkmechanismus und seine Wirkungen werden auf die Bindung an verschiedene Ionenkanäle und Rezeptoren wie GABA-A, Glycin, NMDA, nAch-Rezeptor zurückgeführt, was zu einer Zellhyperpolarisation führt.

Gene

Welche Gene beeinflussen die Wirkung von Halothan?

Im Gegensatz zu vielen aktiven pharmakogenetischen Merkmalen, die den Metabolismus und/oder die Ausscheidung eines Arzneimittels beeinflussen, prädisponieren die hier betrachteten Varianten der Gene *RYR1* und *CACNA1S* Individuen zu einer schweren und manchmal tödlichen hypermetabolischen Reaktion, zu deren Symptomen Muskelsteifheit, hohes Fieber und schnelle Herzfrequenz gehören. Weitere Komplikationen können Rhabdomyolyse und hohe Kaliumwerte im Blut darstellen.

Test

Was wird getestet?

Der Genotyp des Ryanodinrezeptor-Isoform-1-Proteins *(RYR1)* wird auf eine der 48 Einzelnukleotidvarianten und eine Deletion getestet, die als diagnostische maligne Hyperthermie (MH)-Mutation[1] bezeichnet werden. Die α1S-Untereinheit des Dihydropyridinrezeptors (CACNA1S) wird auf die beiden bekannten Varianten getestet, die für maligne Hyperthermie anfällig sind. Da die Anfälligkeit für maligne Hyperthermie (MHS) in einem autosomal-dominanten Muster vererbt wird, kann ein heterozygoter Genotyp einer pathogenen Variante in *RYR1* als diagnostisch für das Merkmal angesehen werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Halothan durchgeführt werden, um das Risiko einer bösartigen Hyperthermie zu verringern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für einen Halothan-Einsatz mit Phänotyp der RYR1- und CACNA1S-Gene

RYR1 oder CACNA1S Phänotyp	Therapieempfehlung
Maligne Hyperthermie Anfälligkeit (MHS)	Halothan kontraindiziert, Anästhetikawechsel empfohlen
Unsichere Anfälligkeit	Klinische Befunde, Familienanamnese, weitere Gentests und andere Labordaten sollten den Einsatz von Halothan anleiten

Nota bene: Ein negativer oder nicht eindeutiger Gentest kann nicht als Hinweis auf einen normalen RYR1-bezogenen Phänotyp angesehen werden und sollte im Zusammenhang mit klinischen Befunden, Familienanamnese und anderen Labordaten interpretiert werden.

Kosten

Die Kosten für die genetische Analyse der *RYR1*- und *CACNA1S* -Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

HALOTAN

Genetički test za smanjenje rizika pojave maligne hipertermije pri primjeni halotana

Lijek

Koje su indikacije i mehanizmi djelovanja halotana?

Sevofluran je siguran hlapljivi inhalacijski anestetik koji se često koristi za indukciju opće anestezije. Njegov mehanizam djelovanja je kompleksan, a pripisuje se vezivanju za više ionskih kanala i neurotransmitorskih receptora, poput GABA-A, glicinskog, NMDA i nikotinskog acetilkolinskog, što uzrokuje hiperpolarizaciju stanice.

Geni

Koji geni utječu na djelovanje halotana?

Za razliku od mnogih drugih lijekova kojima genski polimorfizmi utječu na metabolizam ili ekskreciju, polimorfizmi *RYR1* i *CACNA1S* gena su predisponirajući za tešku i smrtonosnu hipermetaboličku reakciju, čiji simptomi uključuju: rigidnost mišića, visoku tjelesnu temperaturu, tahikardiju. Komplikacije uključuju rabdomiolizu i hiperkalemiju.

Analiza

Što se analizira?

Genotip rajanodinskog receptora izoforme 1 *(RYR1)* testira se na jedan od 48 nukleotidnih polimorfizama ili jednu deleciju koje su označene kao dijagnostičke mutacije za malignu hipertermiju[1]. α1S podjedinica dihidropiridinskog receptora (CACNA1S) se testira za jednu od 2 poznate mutacije koje su dijagnostičke za malignu hipertermiju. Budući da se navedeni geni nasljeđuju autosomno dominantno, heterozigotni genotip navedenih gena smatra se kao dijagnoza sklonosti ka malignoj hipertermiji.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka primjene halotana kako bi se odredila sklonost ka nastanku maligne hipertermije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortiums (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za primjenu halotana ovisno o genotipu RYR1 i CACNA1S

RYR1 ili CACNA1S fenotip	Preporučena terapija
Osjetljivost za malignu hipertermiju	Ne preporučuje se primjena halotana. Potrebno je korištenje alternativnog anestetika
Neinformativan	Odluka o primjeni halotana trebala bi se voditi kliničkom slikom, obiteljskom anamnezom, daljnjim genskim testiranjem i ostalim laboratorijskim podatcima

Nota bene: negativan ili neinformativan rezultat testa se ne smije uzeti kao indikacija za normalan fenotip te se treba razmotriti u kontekstu kliničkih nalaza, obiteljske anamneze i ostalih laboratorijskih nalaza.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or *CACNA1S* Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

IBUPROFEN

Genetic test to minimize the risks related to therapy with ibuprofen

Drug

What are the indications and mechanisms of action of ibuprofen?

Ibuprofen is a nonsteroidal drug with analgesic, antiinflammatory and antipyretic effects. Low-dose ibuprofen can be purchased over-the-counter in many countries. Its therapeutic effects occur via inhibition of prostaglandin biosynthesis from arachidonic acid by cyclooxygenases (COX) isoforms 1 and 2. Ibuprofen is a non-selective reversible inhibitor of both COX isoforms.

Genes

Which genes influence the effect of ibuprofen?

CYP2C9 is the primary CYP isoform responsible for ibuprofen clearance. A decrease in the CYP2C9 function decreases the metabolic clearance of ibuprofen thus prolonging its plasma elimination half-life. Several variants of the *CYP2C9* gene with great variability in the enzymatic activity of CYP2C9 are known in the population. CYP2C8 plays a minor role in ibuprofen clearance, catalyzing the biotransformation of R-enantiomer[1].

Test

What is tested?

To determine the CYP2C9 metabolism type, the testing of *CYP2C9* gene variants *(*2, *3)* associated with significantly reduced CYP2C9 enzyme activity is recommended. The *CYP2C9*2* allele is in strong linkage disequilibrium with the *CYP2C8*3* allele, such that > 80 % of individuals who carry the *CYP2C9*2* allele also carry the *CYP2C8*3* allele in many populations, and this should be taken into consideration.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the therapy with ibuprofen, in order to minimize the risk of side effects such as gastrointestinal bleeding, hypertension, myocardial infarction, heart failure, and renal damage through an adjustment of the starting dose or the prescription of alternative therapy.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendation for the *CYP2C9* genotype is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for ibuprofen therapy according to the CYP2C9 genotype

***CYP2C9* Genotype / Phenotype**	**Therapy recommendation**
*CYP2C9*1/*1* / Normal metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*2* / Intermediate metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*3, *2/*2* / Intermediate metabolizer	Initiate therapy with the lowest recommended starting dose and titrate upward to clinical effect or maximum recommended dose with caution, especially in individuals with other factors affecting clearance such as hepatic impairment or advanced age
*CYP2C9*2/*3, *3/*3* / Poor metabolizer	Initiate therapy with 25–50 % of the lowest recommended starting dose and titrate dose upward to clinical effect or 25–50 % of the maximum recommended dose with caution. Alternatively, consider the other drug not primarily metabolized by CYP2C9

Nota bene: Caution should be taken with ibuprofen use in individuals carrying the *CYP2C9*2* allele as it is in linkage disequilibrium with *CYP2C8*3* that may result in impaired R (-) ibuprofen clearance and increased exposure to the parent drug.

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Mazaleuskaya LL, Theken KN, Gong L, et al. PharmGKB summary: ibuprofen pathways. Pharmacogenet Genomics. 2015;25(2):96-106. doi:10.1097/FPC.0000000000000113

[2] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

IBUPROFEN

Gentest zur Risikominimierung der Therapie mit Ibuprofen

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Ibuprofen?

Ibuprofen ist ein nichtsteroidales Medikament mit entzündungshemmender, analgetischer und fiebersenkender Wirkung. Niedrig dosiertes Ibuprofen kann in vielen Ländern rezeptfrei gekauft werden. Seine therapeutischen Wirkungen treten über die Hemmung der Prostaglandin-Biosynthese aus Arachidonsäure durch die Cyclooxygenasen (COX)-Isoformen 1 und 2 auf. Flurbiprofen ist ein nicht selektiver reversibler Inhibitor beider COX-Isoformen.

Gene

Welche Gene beeinflussen die Wirkung von Ibuprofen?

CYP2C9 ist die primäre CYP-Isoform, die für die Ibuprofen-Clearance (Ausscheidung) verantwortlich ist. Eine Abnahme der CYP2C9-Funktion verringert die metabolische Clearance von Ibuprofen und verlängert so die Halbwertszeit der Plasmaelimination. In der Population sind mehrere Varianten des *CYP2C9*-Gens mit großer Variabilität der enzymatischen Aktivität von CYP2C9 bekannt. CYP2C8 spielt eine untergeordnete Rolle bei der Ibuprofen-Clearance und katalysiert die Biotransformation von R-Enantiomer[1].

Test

Was wird getestet?

Zur Bestimmung des CYP2C9-Metabolismus wird empfohlen, *CYP2C9*-Genvarianten *(*2, *3)* zu testen, die mit einer signifikant verringerten CYP2C9-Enzymaktivität assoziiert sind. Das *CYP2C9*2*-Allel befindet sich in einem starken Bindungsungleichgewicht mit dem *CYP2C8*3*-Allel, so dass> 80 % der Personen, die das *CYP2C9*2*-Allel tragen, in vielen Populationen auch das *CYP2C8*3*-Allel tragen, und dies sollte berücksichtigt werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der Therapie mit Ibuprofen durchgeführt werden, um das Risiko für Nebenwirkungen wie gastrointestinale Blutungen, Bluthochdruck, Myokardinfarkt, Herzinsuffizienz und Nierenschäden durch Anpassung der Anfangsdosis oder der Verschreibung einer alternativen Behandlung zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Ibuprofen-Therapie in Abhängigkeit vom CYP2C9-Genotyp

***CYP2C9* Genotyp / Phänotyp**	**Therapieempfehlung**
*CYP2C9*1/*1* / Normale Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*2* / Intermediare metabolizer	Anwendung gemäß Fachinformation
*CYP2C9*1/*3, *2/*2* / Intermediäre Metabolisierer	Start mit der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder empfohlene maximale Dosis, insbesondere bei Vorliegen von Leberfunktionsstörung oder höherem Alter
*CYP2C9*2/*3, *3/*3* / Langsame Metabolisierer	Start mit 25-50 % der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder 25-50 % der empfohlenen maximalen Dosis Alternativ: Wechsel auf Wirkstoff ohne CYP2C9-Metabolismus

Nota bene: Bei der Anwendung von Ibuprofen bei Personen, die das *CYP2C9*2*-Allel tragen, ist Vorsicht geboten, da es sich im Bindungsungleichgewicht mit *CYP2C8*3* befindet, was zu einer beeinträchtigten R (-) Ibuprofen-Clearance und einer erhöhten Exposition gegenüber dem Ausgangsarzneimittel führen kann.

Kosten

Die Kosten für die genetische Analyse des *CYP2C9* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Mazaleuskaya LL, Theken KN, Gong L, et al. PharmGKB summary: ibuprofen pathways. Pharmacogenet Genomics. 2015;25(2):96-106. doi:10.1097/FPC.0000000000000113

[2] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

IBUPROFEN

Genetički test za smanjenje rizika pri primjeni ibuprofena

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja ibuprofena?

Ibuprofen je nesteroidni lijek s analgetskim, protuupalnim i antipiretskim djelovanjem. Ibuprofen u niskim dozama može se izdati bez liječničkog recepta (over-the-counter) u mnogim zemljama. Njegov mehanizam djelovanja temelji se na inhibiciji biosinteze prostaglandina iz arahidonske kiseline djelovanjem enzima ciklooksigenaze (COX), izoformi 1 i 2. Ibuprofen je neselektivni, reverzibilni inhibitor obje COX izoforme.

Geni

Koji geni utječu na djelovanje ibuprofena?

Ibuprofen se primarno metabolizira putem enzima CYP2C9. Smanjenje funkcije CYP2C9 usporava eliminaciju ibuprofena iz organizma i produljuje poluvrijeme eliminacije. Poznato je nekoliko varijanti *CYP2C9* gena s velikom varijabilnošću u enzimskoj aktivnosti CYP2C9 u populaciji. CYP2C8 ima manju ulogu u eliminaciji ibuprofena, katalizirajući biotransformaciju R-enantiomera[1].

Analiza

Što se analizira?

Kako bi se odredio metabolizam s obzirom na CYP2C9, preporučuje se utvrđivanje prisutnosti varijanta *CYP2C9* gena *(*2, *3)* koje su povezane sa značajno reduciranim kapacitetom enzimske aktivnosti.

*CYP2C9 * 2* alel je snažno povezan s varijantom *CYP2C8 * 3* alela na način da više od 80 % pojedinaca koji imaju *CYP2C9*2* alel također imaju i *CYP2C8 * 3* alel u mnogim populacijama što bi dodatno trebalo uzeti u obzir.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije ibuprofenom kako bi se smanjio rizik neželjenih nuspojava kao što su gastrointestinalno krvarenje, hipertenzija, infarkt miokarda, srčano zatajenje i bubrežno oštećenje na način da se prilagodi početna doza ili propiše druga terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje ibuprofenom ovisno o CYP2C9 genotipu

***CYP2C9* genotip / fenotip**	**Preporučena terapija**
*CYP2C9*1/*1* / Normalni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*2* / Intermedijarni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*3, *2/*2* / Intermedijarni metabolizator	Započnite terapiju s najnižom preporučenom dozom i titrirajte do željenog kliničkog učinka ili do najveće preporučene doze s oprezom, osobito u pojedinaca koji imaju rizične faktore koji utječu na eliminaciju lijeka kao što su jetreno oštećenje i starija životna dob
*CYP2C9*2/*3, *3/*3* / Spori metabolizator	Započnite terapiju s 25–50 % najniže preporučene doze i oprezno titrirajte do željenog kliničkog učinka ili do najviše 25–50 % od maksimalne preporučene doze. Alternativno, odaberite lijek koji se primarno ne metabolizira putem CYP2C9

Nota bene: Oprez je potreban u pojedinaca koji nose *CYP2C9*2* alel s obzirom na poveznicu s *CYP2C8*3* alelom što može rezultirati smanjenom eliminacijom R (-) ibuprofena i većoj izloženosti osnovnom lijeku.

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *CYP2C9* varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *CYP2C9* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Mazaleuskaya LL, Theken KN, Gong L, et al. PharmGKB summary: ibuprofen pathways. Pharmacogenet Genomics. 2015;25(2):96-106. doi:10.1097/FPC.0000000000000113

[2] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

IMIPRAMINE

Genetic test to minimize the risks related to therapy with imipramine

Drug

What are the indications and mechanism of action of imipramine?

Tricyclic antidepressant imipramine is an inhibitor of both serotonin and norepinephrine reuptake in the presynaptic neuron. It also blocks muscarinic acetylcholine, H1 histamine, D2 dopamine and adrenergic receptors. Imipramine is indicated for the treatment of depression, some anxiety disorders, childhood enuresis, as well as neuropathic pain.

Genes

Which genes influence the effect of imipramine?

Imipramine as tertiary amine is metabolized via the enzyme CYP2C19 to active metabolite desipramine. Both are further metabolized via CYP2D6 enzyme to less-active metabolites. Both enzymes play a decisive role in its efficiency and duration of action to all TCAs. Several variants in the genes of these two enzymes are known. These leads to great variability in the enzymatic efficacy of CYP2C19 and CYP2D6.

Test

What will be tested?

In order to determine the CYP2C19 as well as the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants in the *CYP2C19* gene *(*2, *3, *17)* and in the *CYP2D6* gene *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)*.

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with imipramine in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1,2] and have the highest clinical level of evidence 1A for *CYP2D6* and medium clinical level of evidence 2A for *CYP2C19*.

Table 1: Recommendations for imipramine therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolism status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-20 %)	Usage of imipramine is not recommended, prescription of an alternative agent is recommended. If imipramine is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Therapeutic drug monitoring is strongly recommended
Normal metabolizer (72-88 %)	Usage according to the Summary of Product Characteristic
Intermediate metabolizer (1-13 %)	Reduction of starting dose of imipramine by 25 %
Poor metabolizer (1-10 %)	Usage of imipramine is not recommended, the prescription of an alternative agent is recommended. If imipramine is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Table 2: Recommendations for imipramine therapy depending on the phenotype of the CYPC19 gene

CYP2C19 Phenotype (metabolism status frequencies)	Recommended therapy
Ultrarapid metabolizer (2-5 %)	Usage of imipramine not recommended, the prescription of an alternative agent is recommended. If imipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Rapid metabolizer (2-30 %)	Usage of imipramine not recommended, the prescription of an alternative agent is recommended. If imipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Normal metabolizer (35-50 %)	Initiate therapy with a recommended starting dose
Intermediate metabolizer (18-45 %)	Initiate therapy with a recommended starting dose
Poor metabolizer (2-15 %)	Usage of imipramine is not recommended, the prescription of an alternative agent is recommended. If imipramine is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Nota bene: If a patient is treated with lower doses of imipramine and is an intermediate or poor CYP2D6/CYP2C19 metabolizer, no dose adjustment is recommended because of a lower prescribed dose initially. Patients should be monitored for potential side effects.

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

IMIPRAMIN

Gentest zur Risikominimierung der Therapie mit Imipramin

Wirkstoff

Was sind die Indikationen und der Wirkungsmechanismus von Imipramin?

Das trizyklische Antidepressivum Imipramin hemmt die Wiederaufnahme von Serotonin und Noradrenalin in das präsynaptische Neuron. Es blockiert auch Muskarinacetylcholin, H1-Histamin, D2-Dopamin und adrenerge Rezeptoren. Dieser Wirkstoff wird bei der Behandlung von Depressionen, Zwangsstörungen und Enuresis im Kindesalter sowie neuropathischen Schmerzen und Migräneprophylaxe eingesetzt.

Gene

Welche Gene beeinflussen die Wirkung von Imipramin?

Imipramin als tertiäres Amin wird über das Enzym CYP2C19 zum aktiven Metaboliten Desipramin metabolisiert. Beide werden über das CYP2D6-Enzym zu weniger aktiven Metaboliten weiter metabolisiert. Beide Enzyme spielen eine entscheidende Rolle für die Effizienz und Wirkdauer aller TCAs. Es sind verschiedene Varianten der Gene dieser beiden Enzyme bekannt, welche zu einer großen Variabilität der enzymatischen Wirksamkeit von CYP2C19 und CYP2D6 führen.

Test

Was wird getestet?

Um sowohl den CYP2C19- als auch den CYP2D6-Metabolismustyp zu bestimmen, wird das Erbgut des Patienten im *CYP2C19*-Gen *(*2, *3, *17)* und im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Imipramin durchgeführt werden, um eine Dosisanpassung vorzunehmen und gegebenfalls einen Wirkstoffwechsel in Erwägung zu ziehen, um schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt für *CYP2D6* das höchste klinische Evidenzlevel 1A, für *CYP2C19* ein mittleres klinisches Evidenzlevel 2A.

Tabelle 1: Empfehlungen für die Imipramin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Imipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Imipramin: Titration auf höhere Zieldosis (verglichen zu normalen Metabolisierern) bei therapeutischem *Drug Monitoring*
Normale Metabolisierer (72-88 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis um 25 % reduzieren bei therapeutischem *Drug Monitoring*
Langsame Metabolisierer (1-10 %)	Imipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Imipramin: Startdosis um 50 % reduzieren bei therapeutischem *Drug Monitoring*

Tabelle 2: Empfehlungen für die Imipramin-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

CYP2C19 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (2-5 %)	Imipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Imipramin: therapeutisches *Drug Monitoring*
Schnelle Metabolisierer (2-30 %)	Imipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Imipramin: therapeutisches *Drug Monitoring*
Normale Metabolisierer (35-50 %)	Beginn mit Startdosis
Intermediäre Metabolisierer (18-45 %)	Beginn mit Startdosis
Langsame Metabolisierer (2-15 %)	Imipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Imipramin: Reduktion Startdosis um 50 % bei therapeutischem *Drug Monitoring*

Nota bene: Wenn ein Patient mit niedrigeren Imipramin-Dosen behandelt wird und ein intermediärer oder schlechter CYP2D6 / CYP2C19-Metabolisierer ist, wird aufgrund einer anfänglich niedrigeren verschriebenen Dosis keine Dosisanpassung empfohlen. Die Patienten sollten auf mögliche Nebenwirkungen überwacht werden.

Kosten

Die Kosten für die genetische Analyse der *CYP2D6*- und *CAP2C19*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

IMIPRAMIN

Genetički test za smanjenje rizika pri primjeni imipramina

Lijek

Koje su indikacije i mehanizmi djelovanja imipramina?

Triciklički antidepresiv imipramin je inhibitor ponovne pohrane noradrenalina i serotonina u presinaptičkom neuronu. Također blokira muskarinske kolinergičke, H1-histaminske, D2-dopaminske i adrenergične receptore. Koristi se za liječenje depresije, anksioznih poremećaja, noćne enureze u djece, te za liječenje neuropatske boli.

Geni

Koji geni utječu na djelovanje imipramina?

Imipramin se kao tercijarni amin metabolizira preko enzima CYP2C19 u aktivni metabolit desipramin. Oboje se dalje metaboliziraju putem enzima CYP2D6 u manje aktivne metabolite. Oba enzima određuju učinkovitost i duljinu djelovanja imipramina. Nekoliko genskih polimorfizama dovode do velike varijabilnosti u enzimatskoj funkciji CYP2C19 i CYP2D6.

Analiza

Što se analizira?

Kako bi se odredio fenotip enzima CYP2C19 i CYP2D6, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2C19 (*2,*3,*17)* te gena *CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, 9*, *10, *41)*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije imipraminom, kako bi se po potrebi prilagodilo doziranje lijeka ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] te imaju najvišu kliničku razinu dokaza 1A za *CYP2D6* te srednju kliničku razinu dokaza 2A za *CYP2C19*.

Tablica 1: Preporuke za liječenje imipraminom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-20 %)	Ne preporučuje se liječenje imipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja imipraminom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (77-88 %)	Koristiti lijek prema sažetku opisa svojstava lijeka
Intermedijarni metabolizator (1-13 %)	Smanjenje početne doze imipramina za 25 %
Spori metabolizator (1-10 %)	Ne preporučuje se liječenje imipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja imipraminom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Tablica 2: Preporuke za liječenje imipraminom ovisno o fenotipu CYP2C19

CYP2C19 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (2-5 %)	Ne preporučuje se liječenje imipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja imipraminom preporučuje se terapijsko praćenje lijeka radi modifikacije doze
Brzi metabolizator (2-30 %)	Ne preporučuje se liječenje imipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja imipraminom preporučuje se terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (35-50 %)	Započeti terapiju preporučenom početnom dozom
Intermedijarni metabolizator (18-45 %)	Započeti terapiju preporučenom početnom dozom
Spori metabolizator (2-15 %)	Ne preporučuje se liječenje imipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja imipraminom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Nota bene: Ukoliko se primjenjuju niže doze, a pacijent je intermedijarni ili spori CYP2D6, odnosno CYP2C19 metabolizator, ne preporučuje se prilagodba doze zbog već inicijalno propisane niže doze. Pacijente treba nadzirati zbog potencijalnih nuspojava.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa *CYP2C19* i *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

ISOFLURANE

Genetic test to minimize the risk of malignant hyperthermia (MH) related to the usage of isoflurane

Drug

What are the indications and mechanism of action of isoflurane?

Isoflurane is generally a safe volatile inhaled anesthetic used for inducing general anesthesia. Its mechanism of action is complex and includes a reduction in junctional conductance by decreasing gap junction channel opening times and increasing gap junction channel closing times. It also activates calcium-dependent ATPase in the sarcoplasmic reticulum by increasing the fluidity of the lipid membrane. Isoflurane probably binds to various neurotransmitter receptors (like GABA, glycine, glutamate) and ion channels and interacts with the nerve membranes.

Genes

Which genes influence the effect of isoflurane?

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the *RYR1* and *CACNA1S* genes under consideration here predispose individuals to a severe and sometimes lethal hypermetabolic reaction whose symptoms include muscle rigidity, high fever, and a fast heart rate. Complications can include rhabdomyolysis and high blood potassium.

Test

What will be tested?

The genotype of the ryanodine receptor isoform 1 protein *(RYR1)* is tested for one of the 48 causative single-nucleotide variants or one deletion that are designated diagnostic MH mutations[1]. The α1S subunit of the dihydropyridine receptor *(CACNA1S)* is tested for the 2 known variants that are MH susceptible. Since MH susceptibility is inherited in an autosomal-dominant pattern, a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as diagnostic for the trait.

Indication

When should a test be performed?

Genetic testing should be carried out before the initiation of the scheduled usage of isoflurane in order to predict the risk of MH.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for isoflurane usage depending on the phenotype of the RYR1 and CACNA1S genes

RYR1 or CACNA1S Phenotype	Recommended therapy
Malignant hyperthermia susceptible	Isoflurane is not recommended due to MH susceptibility, use alternative anesthetics
Uncertain susceptibility	Clinical findings, family history, further genetic testing, and other laboratory data should guide the use of isoflurane

Nota bene: A negative or inconclusive genetic test cannot be assumed to indicate normal phenotype and should be interpreted in the context of clinical findings, family history, and other laboratory data.

Costs

Costs for the determination of the *RYR1* and *CACNA1S* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

ISOFLURAN

Gentest zur Risikominimierung der Therapie mit Isofluran bei maligner Hyperthermie (MH)

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Isofluran?

Isofluran ist ein weit verbreitetes und allgemein sicheres flüchtiges Inhalationsanästhetikum, das zur Einleitung einer Vollnarkose verwendet wird. Sein Wirkungsmechanismus ist komplex und umfasst eine Verringerung der Verbindungsleitfähigkeit durch verringerte Öffnungszeiten und erhöhte Schließzeiten von *gap junction*-Kanälen. Es aktiviert auch die Calcium-abhängige ATPase im sarkoplasmatischen Retikulum, indem es die Fluidität der Lipidmembran erhöht. Es wird hypothetisiert, dass Isofluran an verschiedene Neurotransmitter-Rezeptoren und Ionenkanäle (wie GABA, Glycine, Glutamat) binden und mit den Nervenmembranen interagiert.

Gene

Welche Gene beeinflussen die Wirkung von Isofluran?

Im Gegensatz zu vielen verwertbaren pharmakogenetischen Merkmalen, die den Metabolismus und/oder die Ausscheidung eines Arzneimittels beeinflussen, prädisponieren die hier betrachteten Varianten der Gene *RYR1* und *CACNA1S* zu einer schweren und manchmal tödlichen hypermetabolischen Reaktion, zu deren Symptomen Muskelsteifheit, hohes Fieber und schnelle Herzfrequenz gehören. Weitere Komplikationen können Rhabdomyolyse und hohe Kaliumwerte im Blut darstellen.

Test

Was wird getestet?

Der Genotyp des Ryanodinrezeptor-Isoform-1-Proteins *(RYR1)* wird auf eine der 48 Einzelnukleotidvarianten und eine Deletion getestet, die als diagnostische maligne Hyperthermie (MH)-Mutation[1] bezeichnet werden. Die α1S-Untereinheit des Dihydropyridinrezeptors *(CACNA1S)* wird auf die beiden bekannten Varianten getestet, die für maligne Hyperthermie anfällig sind. Da die Anfälligkeit für maligne Hyperthermie (MHS) in einem autosomal-dominanten Muster vererbt wird, kann ein heterozygoter Genotyp einer pathogenen Variante in *RYR1* als diagnostisch für das Merkmal angesehen werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn des geplanten Gebrauchs von Isofluran durchgeführt werden, um das Risiko einer bösartigen Hyperthermie zu verringern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für einen Isofluran-Einsatz mit Phänotyp der RYR1- und CACNA1S-Gene

RYR1 oder CACNA1S Phänotyp	Therapieempfehlung
Maligne Hyperthermie Anfälligkeit (MHS)	Isofluran kontraindiziert, Anästhetikawechsel empfohlen
Unsichere Anfälligkeit	Klinische Befunde, Familienanamnese, weitere Gentests und andere Labordaten sollten den Einsatz von Isofluran anleiten

Nota bene: Ein negativer oder nicht eindeutiger Gentest kann nicht als Hinweis auf einen normalen Phänotyp angesehen werden und sollte im Zusammenhang mit klinischen Befunden, Familienanamnese und anderen Labordaten interpretiert werden.

Kosten

Die Kosten für die genetische Analyse der *RYR1*- und *CACNA1S* -Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

IZOFLURAN

Genetički test za smanjenje rizika pojave maligne hipertermije pri primjeni izoflurana

Lijek

Koje su indikacije i mehanizmi djelovanja izoflurana?

Izofluran je siguran hlapljivi inhalacijski anestetik koji se često koristi za indukciju opće anestezije. Njegov mehanizam djelovanja je kompleksan, a uključuje smanjenje provodljivosti skraćivanjem vremena otvaranja kanala na pukotinskim spojevima (gap junctions) i produljujući vrijeme zatvaranja istih. Također aktivira o kalciju ovisnu ATP-azu na sarkoplazmatskom retikulumu povećanjem fluidnosti lipidne membrane. Izofluran se vjerojatno veže na više neurotransmitorskih receptora (poput GABA, glicinskog i glutamatnog), ionskih kanala te ulazi u interakciju s membranama neurona.

Geni

Koji geni utječu na djelovanje izoflurana?

Za razliku od mnogih drugih lijekova kojima genski polimorfizmi utječu na metabolizam ili ekskreciju, polimorfizmi *RYR1* i *CACNA1S* gena su predisponirajući za tešku i smrtonosnu hipermetaboličku reakciju, čiji simptomi uključuju: rigidnost mišića, visoku tjelesnu temperaturu, tahikardiju. Komplikacije uključuju rabdomiolizu i hiperkalemiju.

Analiza

Što se analizira?

Genotip rajanodinskog receptora izoforme 1 *(RYR1)* testira se na jedan od 48 nukleotidnih polimorfizama ili jednu deleciju koje su označene kao dijagnostičke mutacije za malignu hipertermiju[1]. α1S podjedinica dihidropiridinskog receptora *(CACNA1S)* se testira za jednu od 2 poznate mutacije koje su dijagnostičke za malignu hipertermiju. Budući da se navedeni geni nasljeđuju autosomno dominantno, heterozigotni genotip navedenih gena smatra se kao dijagnoza sklonosti ka malignoj hipertermiji.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka primjene izoflurana kako bi se odredila sklonost ka nastanku maligne hipertermije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortiums (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za primjenu izoflurana ovisno o genotipu RYR1 i CACNA1S

RYR1 ili CACNA1S fenotip	Preporučena terapija
Osjetljivost za malignu hipertermiju	Ne preporučuje se primjena izoflurana. Potrebno je korištenje alternativnog anestetika
Neinformativan	Odluka o primjeni izoflurana trebala bi se voditi kliničkom slikom, obiteljskom anamnezom, daljnjim genskim testiranjem i ostalim laboratorijskim podatcima

Nota bene: negativan ili neinformativan rezultat testa se ne smije uzeti kao indikacija za normalan fenotip te se treba razmotriti u kontekstu kliničkih nalaza, obiteljske anamneze i ostalih laboratorijskih nalaza.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

IVACAFTOR

Genetic test to minimize the risks related to therapy with ivacaftor

Drug

What are the indications and mechanisms of action of ivacaftor?

Ivacaftor is used for the treatment of cystic fibrosis (mucoviscidosis) among patients with certain mutations in the *CFTR* gene. Genetic modifications in the *CFTR* gene on the CFTR protein level lead to loss of function in the chloride channels in the cell membranes of certain somatic cells, whereby viscous secretions occur, including the bronchial mucosa of the lungs, as a result of the insufficient moisture content. Ivacaftor is a CFTR potentiator and leads to an improved function of the misdirected chloride channels among patients with certain mutations in the *CFTR* gene, but can only alleviate the clinical symptoms.

Genes

Which genes influence the effect of ivacaftor?

More than 2,000 mutations of the *CFTR* gene in connection with cystic fibrosis are known at present. According to the present state of knowledge, the pharmacological efficacy of ivacaftor is so far only limited to patients with certain pathogenic variants in Table 1.

Test

What will be tested?

The patient's genotype will be tested for the *CFTR* gene variants which are sensitive to ivacaftor.

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with ivacaftor in order to ensure the therapeutic efficacy of ivacaftor.

Consequences and test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines[1], and the update to the CPIC guidelines (May 2019)[2], and have the highest level of clinical evidence 1A.

Table 1: Recommendations for ivacaftor therapy subject to CFTR genotype

***CFTR* Genotype**	**Recommended therapy**
Homozygosity or heterozygosity for *G551D-CFTR* variants: *G551D / F508del, G551D / G551D,* rs75527207 genotype *AA* or *AG*	Usage according to the Summary of Product Characteristics for patients older than 6 years, without associated diseases. It is recommended to adjust the therapeutic dose of ivacaftor in patients with liver damage
Negative for *G551D-CFTR: F508del / R553X,* rs75527207 genotype *GG*	Ivacaftor not recommended
Homozygosity for *F508del-CFTR (F508del / F508del),* rs113993960, or rs199826652 genotype *del / del*	Ivacaftor is not recommended
Homozygosity or heterozygosity for following *CFTR* variants: *E56K, P67L, R74W, D110E, D110H, R117C, R117H, G178R, E193K, L206W, R347H, R352Q, A455E, S549N, S549R, G551S, D579G, S945L, S997F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, G1244E, S1251N, S1255P, D1270N, G1349D, 2789+5G->A, 3272-26A->G, 3849+10kbC->T, 711+1G->T, E831X*	Usage according to the Summary of Product Characteristics

Costs

Costs of genetic testing will be reimbursed for statutory and privately insured patients whose testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Clancy JP, Johnson SG, Yee SW, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for ivacaftor therapy in the context of CFTR genotype. Clin Pharmacol Ther. 2014;95(6):592-597. doi:10.1038/clpt.2014.54

[2] https://www.pharmgkb.org/guidelineAnnotation/PA166114461

IVACAFTOR

Gentest zur Risikominimierung der Therapie mit Ivacaftor

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Ivacaftor?

Ivacaftor wird zur Behandlung der zystischen Fibrose (Mukoviszidose) bei Patienten mit bestimmten Mutationen im *CFTR*-Gen eingesetzt. Genetische Veränderungen des *CFTR*-Gens auf CFTR-Proteinebene führen zu einem Funktionsverlust der Chloridkanäle in den Zellmembranen bestimmter somatischer Zellen, wodurch infolge des zu geringen Wassergehalts zähflüssige Sekrete in der Bronchialschleimhaut der Lunge entstehen. Der Wirkstoff Ivacaftor ist ein CFTR-Potentiator und führt bei Patienten mit bestimmten Mutationen im *CFTR*-Gen zu einer verbesserten Funktion der mutierten Chloridkanäle, kann jedoch die klinischen Symptome nur mildern.

Gene

Welche Gene beeinflussen die Wirkung von Ivacaftor?

Gegenwärtig sind mehr als 2.000 Mutationen des *CFTR*-Gens im Zusammenhang mit Mukoviszidose bekannt. Nach dem gegenwärtigen Kenntnisstand ist die pharmakologische Wirksamkeit von Ivacaftor bislang nur auf Patienten mit bestimmten pathogenen Varianten in Tabelle 1 beschränkt.

Test

Was wird getestet?

Der Erbgut des Patienten wird auf die für Ivacaftor sensitiven *CFTR*-Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Ivacaftor durchgeführt werden, um die therapeutische Wirksamkeit von Ivacaftor abzusichern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und der letzten Aktualisierung zur CPIC-Richtlinie (Mai 2019)[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Ivacaftor-Therapie mit CFTR-Genotyp

***CFTR* Genotyp**	**Therapieempfehlung**
Homozygotie / Heterozygotie für *G551D-CFTR*-Varianten: *G551D / F508del, G551D / G551D,* rs75527207 Genotyp *AA* oder *AG*	Therapie gemäß Fachinformation für Patienten älter als 6 Jahre ohne weitere Krankheiten Dosisanpassung bei Patienten mit Leberschäden
Negativ für *G551D-CFTR: F508del / R553X,* rs75527207 Genotyp *GG*	Ivacaftor nicht empfohlen
Homozygotie für *F508del-CFTR, rs113993960* oder rs199826652 Genotyp *del / del*	Ivacaftor nicht empfohlen
Homozygotie / Heterozygotie für *CFTR*-Varianten: *E56K, P67L, R74W, D110E, D110H, R117C, R117H, G178R, E193K, L206W, R347H, R352Q, A455E, S549N, S549R, G551S, D579G, S945L, S997F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, G1244E, S1251N, S1255P, D1270N, G1349D, 2789+5G->A, 3272-26A->G, 3849+10kbC->T, 711+1G->T, E831X*	Therapie gemäß Fachinformation

Kosten

Die Kosten für die genetische Analyse des *CFTR* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Clancy JP, Johnson SG, Yee SW, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for ivacaftor therapy in the context of CFTR genotype. Clin Pharmacol Ther. 2014;95(6):592-597. doi:10.1038/clpt.2014.54

[2] https://www.pharmgkb.org/guidelineAnnotation/PA166114461

IVAKAFTOR

Genetički test za smanjenje rizika pri primjeni ivakaftora

Lijek

Koje su indikacije i mehanizmi djelovanja lijeka ivakaftora?

Ivakaftor se koristi u liječenju cistične fibroze kod pacijenata s određenim patogenim varijantama u genu *CFTR*. Genetičke promjene u genu *CFTR* rezultiraju na proteinskoj razini gubitkom funkcije kloridnog kanala u staničnoj membrani određenih tjelesnih stanica, pri čemu uslijed nedostatnog sadržaja vode nastaje žilavi sekret, između ostaloga i u bronhima. Ivakaftor stimulira CFTR protein i kod pacijenata s određenim mutacijama gena *CFTR* dovodi do poboljšane funkcije kloridnih kanala te može samo ublažiti kliničke simptome.

Geni

Koji geni utječu na djelovanje ivakaftora?

Poznato je više od 2000 patogenih varijanti gena *CFTR* koje su povezane s cističnom fibrozom. Trenutno je farmakološka djelotvornost ivakaftora ograničena na pacijente s određenim patogenim varijantama navedenima u Tablici 1.

Analiza

Što se analizira?

Analizira se genotip bolesnika na *CFTR* varijante gena na koje ivakaftor djeluje.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka planirane terapije ivakaftorom kako bi se osigurao terapijski učinak ivakaftora.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1], dopunama smjernica (svibanj 2019)[2], te imaju najveću razinu dokaza 1A.

Tablica 1: Preporuke za liječenje ivakaftorom prema CFTR genotipu

CFTR genotip	Preporučena terapija
Homozigot ili heterozigot za *G551D-CFTR* varijante: *G551D / F508del, G551D / G551D,* rs75527207 genotip *AA* or *AG*	Koristiti sukladno uputama o lijeku za pacijente starije od 6 godina, bez pridruženih bolesti. Preporučuje se prilagoditi terapijsku dozu ivakaftora kod pacijenata s jetrenim oštećenjem
Negativni za *G551D-CFTR: F508del / R553X,* rs75527207 genotip *GG*	Ivakaftor se ne preporučuje
Homozigot za *F508del-CFTR (F508del / F508del),* rs113993960, ili rs199826652 genotip *del / del*	Ivakaftor se ne preporučuje
Homozigot ili heterozigot za sljedeće *CFTR* varijante: *E56K, P67L, R74W, D110E, D110H, R117C, R117H, G178R, E193K, L206W, R347H, R352Q, A455E, S549N, S549R, G551S, D579G, S945L, S997F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, G1244E, S1251N, S1255P, D1270N, G1349D, 2789+5G->A, 3272-26A->G, 3849+10kbC->T, 711+1G->T, E831X*	Koristiti prema uputama o lijeku

Troškovi

Troškovi genskog testa će biti refundirani pacijentima s državnim i privatnim osiguranjem ukoliko je testiranje indicirano od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Clancy JP, Johnson SG, Yee SW, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for ivacaftor therapy in the context of CFTR genotype. Clin Pharmacol Ther. 2014;95(6):592-597. doi:10.1038/clpt.2014.54

[2] https://www.pharmgkb.org/guidelineAnnotation/PA166114461

LORNOXICAM

Genetic test to minimize the risks related to therapy with lornoxicam

Drug

What are the indications and mechanisms of action of lornoxicam?

Lornoxicam is a nonsteroidal drug with analgesic, anti-inflammatory and antipyretic properties. Its therapeutic effects occur via inhibition of prostaglandin biosynthesis from arachidonic acid by cyclooxygenases (COX) isoforms 1 and 2. Lornoxicam is a potent non-selective reversible inhibitor of both COX isoforms.

Genes

Which genes influence the effect of lornoxicam?

Lornoxicam is metabolized via the enzyme CYP2C9. A decrease in the CYP2C9 function decreases metabolic clearance of lornoxicam thus prolonging its plasma elimination half-life. Several variants of the gene with great variability in the enzymatic activity of CYP2C9 are known in the population.

Test

What is tested?

To determine the CYP2C9 metabolism type, the testing of *CYP2C9* gene variants *(*2, *3)* associated with significantly reduced CYP2C9 enzyme activity is recommended.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the therapy with lornoxicam, in order to minimize the risk of side effects such as gastrointestinal bleeding, hypertension, myocardial infarction, heart failure, and renal damage through an adjustment of the starting dose or the prescription of alternative therapy.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for lornoxicam therapy according to the CYP2C9 genotype

***CYP2C9* Genotype / Phenotype**	**Therapy recommendation**
*CYP2C9*1/*1* / Normal metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*2* / Intermediate metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*3, *2/*2* / Intermediate metabolizer	Initiate therapy with the lowest recommended starting dose and titrate upward to clinical effect or maximum recommended dose with caution, especially in individuals with other factors affecting clearance such as hepatic impairment or advanced age
*CYP2C9*2/*3, *3/*3* / Poor metabolizer	Initiate therapy with 25–50 % of the lowest recommended starting dose and titrate dose upward to clinical effect or 25–50 % of the maximum recommended dose with caution. Alternatively, consider the other drug not primarily metabolized by CYP2C9

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with a statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for treatment is not affected.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

LORNOXICAM

Gentest zur Risikominimierung der Therapie mit Lornoxicam

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Lornoxicam?

Lornoxicam ist ein nichtsteroidales Medikament mit entzündungshemmenden, analgetischen und fiebersenkenden Eigenschaften. Seine therapeutischen Wirkungen treten über die Hemmung der Prostaglandin-Biosynthese aus Arachidonsäure durch die Cyclooxygenasen (COX)-Isoformen 1 und 2 auf. Lornoxicam ist ein starker nicht selektiver reversibler Inhibitor beider COX-Isoformen.

Gene

Welche Gene beeinflussen die Wirkung von Lornoxicam?

Lornoxicam wird über das Enzym CYP2C9 metabolisiert. Eine Abnahme der CYP2C9-Funktion verringert die metabolische Clearance (Ausscheidung) von Lornoxicam und verlängert so die Halbwertszeit der Plasmaelimination. In der Population sind mehrere Varianten des *CYP2C9*-Gens mit großer Variabilität der enzymatischen Aktivität von CYP2C9 bekannt.

Test

Was wird getestet?

Zur Bestimmung des CYP2C9-Metabolismus wird empfohlen, *CYP2C9*-Genvarianten *(*2,*3)* zu testen, die mit einer signifikant verringerten *CYP2C9*-Enzymaktivität assoziiert sind.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der Therapie mit Lornoxicam durchgeführt werden, um das Risiko für Nebenwirkungen wie gastrointestinale Blutungen, Bluthochdruck, Myokardinfarkt, Herzinsuffizienz und Nierenschäden durch Anpassung der Anfangsdosis oder der Verschreibung einer alternativen Behandlung zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Lornoxicam-Therapie in Abhängigkeit vom CYP2C9-Genotyp

***CYP2C9* Genotyp / Phänotyp**	**Therapieempfehlung**
*CYP2C9*1/*1* / Normale Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*2* / Intermediare Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*3, *2/*2* / Intermediäre Metabolisierer	Start mit der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder empfohlene maximale Dosis, insbesondere bei Vorliegen von Leberfunktionsstörung oder höherem Alter
*CYP2C9*2/*3, *3/*3* / Langsame Metabolisierer	Start mit 25-50 % der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder 25-50 % der empfohlenen maximalen Dosis Alternativ: Wechsel auf Wirkstoff ohne CYP2C9-Metabolismus

Kosten

Die Kosten für die genetische Analyse des *CYP2C9* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

LORNOKSIKAM

Genetički test za smanjenje rizika pri primjeni lornoksikama

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja lornoksikama?

Lornoksikam je nesteroidni lijek s analgetskim, protuupalnim i antipiretskim djelovanjem. Njegov mehanizam djelovanja temelji se na inhibiciji biosinteze prostaglandina putem arahidonske kiseline djelovanjem enzima ciklooksigenaze (COX), izoforma 1 i 2. Lornoksikam je potentni neselektivni reverzibilni inhibitor obje COX izoforme.

Geni

Koji geni utječu na djelovanje lornoksikama?

Lornoksikam se metabolizira putem enzima CYP2C9. Smanjenje funkcije CYP2C9 usporava eliminaciju lornoksikama iz organizma i produljuje poluvrijeme eliminacije. Poznato je nekoliko varijanti *CYP2C9* gena s velikom varijabilnošću u enzimskoj aktivnosti CYP2C9 u populaciji.

Analiza

Što se analizira?

Kako bi se odredio metabolizam s obzirom na CYP2C9, preporučuje se utvrđivanje prisutnosti varijanta *CYP2C9* gena *(*2, *3)* koje su povezane sa značajno reduciranim kapacitetom enzimske aktivnosti.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije lornoksikamom kako bi se smanjio rizik neželjenih nuspojava kao što su gastrointestinalno krvarenje, hipertenzija, infarkt miokarda, srčano zatajenje i bubrežno oštećenje na način da se prilagodi početna doza ili propiše druga terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje lornoksikamom ovisno o CYP2C9 genotipu

***CYP2C9* genotip / fenotip**	**Preporučena terapija**
*CYP2C9*1/*1* / Normalni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*2* / Intermedijarni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*3, *2/*2* / Intermedijarni metabolizator	Započnite terapiju s najnižom preporučenom dozom i titrirajte do željenog kliničkog učinka ili do najveće preporučene doze s oprezom, osobito u pojedinaca koji imaju rizične faktore koji utječu na eliminaciju lijeka kao što su jetreno oštećenje i starija životna dob
*CYP2C9*2/*3, *3/*3* / Spori metabolizator	Započnite terapiju s 25–50 % najniže preporučene doze i oprezno titrirajte do željenog kliničkog učinka ili do 25–50 % od maksimalne preporučene doze. Alternativno, odaberite lijek koji se primarno ne metabolizira putem CYP2C9

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *CYP2C9* varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *CYP2C9* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

MELOXICAM

Genetic test to minimize the risks related to therapy with meloxicam

Drug

What are the indications and mechanisms of action of meloxicam?

Meloxicam is a nonsteroidal drug with analgesic, anti-inflammatory and antipyretic properties. Its therapeutic effects occur via inhibition of prostaglandin biosynthesis from arachidonic acid by cyclooxygenases (COX) isoforms 1 and 2. Meloxicam preferentially inhibits COX-2 isoform.

Genes

Which genes influence the effect of meloxicam?

Meloxicam is metabolized via the enzyme CYP2C9. A decrease in the CYP2C9 function decreases the metabolic clearance of meloxicam thus prolonging its plasma elimination half-life. Several variants of the gene with great variability in the enzymatic activity of CYP2C9 are known in the population.

Test

What is tested?

To determine the CYP2C9 metabolism type, the testing of *CYP2C9* gene variants *(*2,*3)* associated with significantly reduced CYP2C9 enzyme activity is recommended.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the therapy with meloxicam, in order to minimize the risk of side effects such as gastrointestinal bleeding, hypertension, myocardial infarction, heart failure, and renal damage through an adjustment of the starting dose or the prescription of alternative therapy.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for meloxicam therapy according to the CYP2C9 genotype

***CYP2C9* Genotype / Phenotype**	**Recommended therapy**
*CYP2C9*1/*1* / Normal metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*2* / Intermediate metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*3, *2/*2* / Intermediate metabolizer	Initiate therapy with 50 % of the lowest recommended starting dose and titrate dose upward to clinical effect or 50 % of the maximum recommended dose with caution. Alternatively, consider the other drug not primarily metabolized by CYP2C9
*CYP2C9*2/*3, *3/*3* / Poor metabolizer	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants in vivo or choose an NSAID metabolized by CYP2C9 but with a shorter half-life

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

MELOXICAM

Gentest zur Risikominimierung der Therapie mit Meloxicam

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Meloxicam?

Meloxicam ist ein nichtsteroidales Medikament mit entzündungshemmenden, analgetischen und fiebersenkenden Eigenschaften. Seine therapeutischen Wirkungen treten über die Hemmung der Prostaglandin-Biosynthese aus Arachidonsäure durch die Cyclooxygenasen (COX) -Isoformen 1 und 2 auf. Meloxicam hemmt vorzugsweise die COX-2-Isoform.

Gene

Welche Gene beeinflussen die Wirkung von Meloxicam?

Meloxicam wird über das Enzym CYP2C9 metabolisiert. Eine Abnahme der CYP2C9-Funktion verringert die metabolische Clearance (Ausscheidung) von Meloxicam und verlängert so die Halbwertszeit der Plasmaelimination. In der Population sind mehrere Varianten des *CYP2C9*-Gens mit großer Variabilität der enzymatischen Aktivität von CYP2C9 bekannt.

Test

Was wird getestet?

Zur Bestimmung des CYP2C9-Metabolismus wird empfohlen, *CYP2C9*-Genvarianten *(*2, *3)* zu testen, die mit einer signifikant verringerten CYP2C9-Enzymaktivität assoziiert sind.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der Therapie mit Meloxicam durchgeführt werden, um das Risiko für Nebenwirkungen wie gastrointestinale Blutungen, Bluthochdruck, Myokardinfarkt, Herzinsuffizienz und Nierenschäden durch Anpassung der Anfangsdosis oder der Verschreibung einer alternativen Behandlung zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Meloxicam-Therapie in Abhängigkeit vom CYP2C9-Genotyp

***CYP2C9* Genotyp / Phänotyp**	**Therapieempfehlung**
*CYP2C9*1/*1* / Normale Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*2* / Intermediare Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*3, *2/*2* / Intermediäre Metabolisierer	Start mit der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder empfohlene maximale Dosis, insbesondere bei Vorliegen von Leberfunktionsstörung oder höherem Alter
*CYP2C9*2/*3, *3/*3* / Langsame Metabolisierer	Start mit 25-50 % der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder 25-50 % der empfohlenen maximalen Dosis Alternativ: Wechsel auf Wirkstoff ohne CYP2C9-Metabolismus

Kosten

Die Kosten für die genetische Analyse des *CYP2C9* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

MELOKSIKAM

Genetički test za smanjenje rizika pri primjeni meloksikama

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja meloksikama?

Meloksikam je nesteroidni lijek s analgetskim, protuupalnim i antipiretskim djelovanjem. Njegov mehanizam djelovanja temelji se na inhibiciji biosinteze prostaglandina iz arahidonske kiseline djelovanjem enzima ciklooksigenaze (COX), izoformi 1 i 2. Meloksikam selektivnije inhibira COX-2 izoformu.

Geni

Koji geni utječu na djelovanje meloksikama?

Meloksikam se metabolizira putem enzima CYP2C9. Smanjenje funkcije CYP2C9 usporava eliminaciju meloksikama iz organizma i produljuje poluvrijeme eliminacije. Poznato je nekoliko varijanti *CYP2C9* gena s velikom varijabilnošću u enzimskoj aktivnosti CYP2C9 u populaciji.

Analiza

Što se analizira?

Kako bi se odredio metabolizam s obzirom na CYP2C9, preporučuje se utvrđivanje prisutnosti varijanti *CYP2C9* gena *(*2, *3)* koje su povezane sa značajno reduciranim kapacitetom enzimske aktivnosti.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije meloksikamom kako bi se smanjio rizik neželjenih nuspojava kao što su gastrointestinalno krvarenje, hipertenzija, infarkt miokarda, srčano zatajenje i bubrežno oštećenje, na način da se prilagodi početna doza ili propiše druga terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje meloksikamom ovisno o CYP2C9 genotipu

***CYP2C9* genotip / fenotip**	**Preporučena terapija**
*CYP2C9*1/*1* / Normalni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*2* / Intermedijarni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*3, *2/*2* / Intermedijarni metabolizator	Započnite terapiju s 50 % najniže preporučene doze i oprezno titrirajte do željenog kliničkog učinka ili do 50 % od najviše preporučene doze. Alternativno, odaberite lijek koji se primarno ne metabolizira putem CYP2C9
*CYP2C9*2/*3, *3/*3* / Spori metabolizator	Potrebno je odabrati neki od lijekova koji se ne metaboliziraju putem CYP2C9 ili čiji metabolizam nije pod značajnim utjecajem *CYP2C9* genotipa ili one s kraćim poluvremenom eliminacije

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *CYP2C9* varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *CYP2C9* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

6-MERCAPTOPURINE

Genetic test to minimize the risks related to therapy with 6-mercaptopurin

Drug

What are the indications and mechanisms of action of 6-mercaptopurine?

6-mercaptopurine is a purine analogue and inhibits purine synthesis as well as DNA and RNA synthesis. It is used to treat malignant and non-malignant conditions due to its cytotoxic and imunosuppressive effects.

Genes

What genes influence the effect of 6-mercaptopurine?

The enzyme thiopurine methyltransferase (TPMT) is responsible for the inactivation of 6-mercaptopurine through methylation of the sulfhydryl group. In the case of a TPMT deficiency, toxic metabolites develop during the breakdown process which can cause myelosuppression in the hematopoietic tissue with life-threatening side effects. In the population, there are known activity-reducing variants for the *TPMT* gene which require an adjustment of the dose in order to increase the tolerability with regard to the active agent.

As a nucleoside diphosphatase, NUDT15 catalyzes the conversion of the cytotoxic thioguanine triphosphate (TGTP) metabolites to the less toxic thioguanine monophosphate. Genetic variants in *NUDT15* have been identified that strongly influence thiopurine tolerance in patients with acute lymphoblastic leukemia (ALL) and those with inflammatory bowel disease. In the case of genetically caused *NUDT15* deficiency, toxic by-products increasingly accumulate which can lead to myelosuppression with life-threatening side effects due to their cytotoxic potential.

Test

What is tested?

The genotype of patients is examined with regard to the most frequent clinically relevant *TPMT* gene variants *(*2, *3A, *3B, *3C, *4)* which, in the compound heterozygous or homozygous state, lead to a complete loss of the TPMT enzyme activity.

The genotype of patients is also examined with regard to the most common clinically relevant *NUDT15* gene variants *(*2, *3)* which in, compound heterozygous or homozygous state, lead to a partial or complete loss of the NUDT15 enzyme activity.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with 6-mercaptopurine in order to reduce the risk of myelosuppression (disturbance of hematopoiesis), as required, by means of an adjustment of the initial dose or by prescribing an alternative active agent. Inherited TPMT deficiency is the primary genetic cause of thiopurine intolerance in Europeans and Africans, whereas risk alleles in *NUDT15* explain the majority of thiopurine-related myelosuppression in Asians and are also common in Hispanics.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for 6-mercaptopurine therapy depending on the TPMT genotype

***TPMT* Genotype / Phenotype**	**Recommended therapy**
Wild type / Normal metabolizer	Use according to the Summary of Product Characteristics
Risk variant, heterozygous / Intermediate metabolizer	Reduce the starting dose by 30-80 % Adjust the dose to the degree of myelosuppression
Risk variant, compound heterozygous or homozygous / Poor metabolizer	For malignant conditions: drastic reduction of the initial dose (10-fold reduction and only on 3 days/week), adjust doses based on the degree of myelosuppression For non-malignant conditions: Consider alternative nonthiopurine immunosuppressant therapy

Table 2: Recommendations for 6-mercaptopurine therapy depending on the NUDT15 genotype

***NUDT15* Genotype / Phenotype**	**Recommended therapy**
Wild type / Normal metabolizer	Use according to the Summary of Product Characteristics
Risk variant, heterozygous / Intermediate metabolizer	Reduce the starting dose by 30-80 % Adjust the dose to the degree of myelosuppression
Risk variant, compound heterozygous or homozygous / Poor metabolizer	For malignancy: drastic reduction of the initial dose (use 10 mg/m^2/day instead of 75 mg/m^2/day), adjust doses based on the degree of myelosuppression For nonmalignant conditions: consider alternative nonthiopurine immunosuppressant therapy

Costs

Costs for the *TPMT* and *NUDT15* genes analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

6-MERCAPTOPURIN

Gentest zur Risikominimierung der Therapie mit 6-Mercaptopurin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von 6-Mercaptopurin?

6-Mercaptopurin ist ein zytotoxischer, immunsuppressiver Wirkstoff, der vorrangig zur Behandlung von akuter und chronischer myeloischer Leukämie eingesetzt wird. 6-Mercaptopurin ist ein Purinanalogon und hemmt die Purinsynthese sowie die DNA-und RNA-Synthese. So wird die Vermehrung von Immunzellen verhindert.

Gene

Welche Gene beeinflussen die Wirkung von 6-Mercaptopurin?

Das Enzym Thiopurinmethyltransferase (TPMT) inaktiviert 6-Mercaptopurin durch Methylierung der Sulfhydrylgruppe. Bei einem Mangel an TPMT entstehen im Abbauprozess toxische Metaboliten, die im hämatopoetischen Gewebe eine Myelosuppression mit lebensbedrohlichen Nebenwirkungen auslösen können. Für das *TPMT*-Gen sind in der Bevölkerung aktivitätsmindernde Genvarianten bekannt, die eine Dosisanpassung erforderlich machen, um die Verträglichkeit des Wirkstoffs zu erhöhen.

Die Nucleosiddiphosphatase/Nudix-Hydrolase 15 (NUDT15) katalysiert die Umwandlung der zytotoxischen Thioguanintriphosphat (TGTP)-Metaboliten in das weniger toxische Thioguaninmonophosphat (TGMP). Es gibt genetische Varianten von *NUDT15*, die Thiopurintoleranz bei Patienten mit akuter lymphoblastischer Leukämie (ALL) und bei Patienten mit entzündlichen Darmerkrankungen stark beeinflussen. Bei genetisch bedingtem funktionellem *NUDT15*-Mangel reichern sich toxische Nebenprodukte an, die zu einer Myelosuppression mit lebensbedrohlichen Nebenwirkungen führen können.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit 6-Mercaptopurin durchgeführt werden, um gegebenfalls durch eine Anpassung der Startdosis oder die Verordnung eines alternativen Wirkstoffs das Risiko einer Myelosuppression zu senken. Bei 30-60 % der Patienten mit einem heterozygoten *TPMT*-Risikogenotyp ist die Standarddosis mit dem Risiko von Nebenwirkungen verbunden. Der angeborene TMPT-Mangel ist die primäre genetische Ursache für die Thiopurin-Intoleranz bei Europäern und Afrikanern, während bei Asiaten und Hispanics Risiko-Allele in *NUDT15* die Mehrheit der Thiopurin-bedingten Myelosuppression erklären.

Test

Was wird getestet?

Der Genotyp von Patienten wird auf die häufigsten klinisch relevanten *TPMT*-Genvarianten *(*2, *3A, *3B, *3C, *4)* untersucht, die im compound heterozygoten oder homozygoten Zustand zu einem vollständigen Verlust der TPMT-Enzymaktivität führen. Zudem wird der Genotyp von Patienten auf die häufigsten klinisch relevanten *NUDT15*-Genvarianten *(*2, *3)* untersucht, die im compound heterozygoten oder homozygoten Zustand zu einem partiellen oder vollständigen Verlust der *NUDT15*-Enzymaktivität führen.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die 6-Mercaptopurin-Therapie in Abhängigkeit vom TPMT-Genotyp

TPMT Genotyp / Phänotyp	Therapieempfehlung
Wildtyp / Normale Metabolisierer	Anwendung gemäß der Fachinformation
Risikovariante, heterozygot / Intermediäre Metabolisierer	Startdosis um 30-80 % reduzieren Anpassung der Dosis an Grad der Myelosuppression
Risikovariante, compound heterozygot oder homozygot / Langsame Metabolisierer	Bei malignen Erkrankungen: Startdosis drastisch reduzieren (10-fach reduziert und nur an 3 Tagen/Woche), Anpassung der Dosis an Grad der Myelosuppression Bei nicht malignen Erkrankungen: Wirkstoffwechsel mit nicht-Thiopurin-Immunspressiva empfohlen

Tabelle 2: Empfehlungen für die 6-Mercaptopurin-Therapie in Abhängigkeit vom NUDT15-Genotyp

***NUDT15* Genotyp / Phänotyp**	**Therapieempfehlung**
Wildtyp / Normale Metabolisierer	Anwendung gemäß der Fachinformation
Risikovariante, heterozygot / Intermediäre Metabolisierer	Startdosis um 30-80 % reduzieren Anpassung der Dosis an Grad der Myelosuppression
Risikovariante, compound heterozygot oder homozygot / Langsame Metabolisierer	Bei nicht malignen Erkrankungen: Wirkstoffwechsel mit nicht-Thiopurin-Immunspressiva empfohlen Bei malignen Erkrankungen: Startdosis drastisch reduzieren (10-fach reduziert, Anpassung der Dosis an Grad der Myelosuppression)

Kosten

Die Kosten für die genetische Analyse des *TMPT*-Gens und des *NUDT15*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

6-MERKAPTOPURIN

Genetički test za smanjenje rizika pri primjeni 6-merkaptopurina

Lijek

Koje su indikacije i mehanizmi djelovanja 6-merkaptopurina?

6-merkaptopurin je purinski analog koji inhibira sintezu purina te posljedično i sintezu DNA i RNA. Koristi se za terapiju malignih i nemalignih stanja zbog svojeg citotoksičnog i imunosupresivnog djelovanja.

Geni

Koji geni utječu na djelovanje 6-merkaptopurina?

Enzim tiopurin metiltransferaza (TPMT) inaktivira 6-merkaptopurin putem metilacije sulfhidrilne skupine. Nedostatak TPMT dovodi do odgođene razgradnje aktivne tvari, pri čemu može doći do teške, po život opasne supresije koštane srži. U gotovo svim populacijama poznate su varijante gena *TPMT* koje dovode do smanjene aktivnosti enzima i stoga je potrebno prilagoditi doziranje 6-merkaptopurina da bi se povećala podnošljivost.

NUDT15, nukleozidna difosfataza, enzim je koji katalizira konverziju citotoksičnog metabolita tiogvanin trifosfata (TGTP) u manje toksičan tiogvanin monofosfat. Genetske varijante u *NUDT15* snažno utječu na toleranciju na tiopurine kod pacijenata koji boluju od akutne limfoblastične leukemije (ALL) i upalnih bolesti crijeva. Smanjena aktivnost NUDT15 također za posljedicu ima akumulaciju toksičnih metabolita koji mogu dovesti do oštećenja funkcije koštane srži (mijelosupresija) s nuspojavama opasnim po život.

Test

Što se analizira?

Analizira se genotip pacijenta na najučestalije klinički relevantne varijante gena *TPMT (*2, *3A, *3B, *3C i *4)* koji u kombiniranih (združenih) heterozigota "compound heterozygous" ili homozigota vode do potpunog gubitka aktivnosti enzima TPMT.

Također se analiziraju najučestalije klinički relevantne varijante gena *NUDT15 (*2, *3)* koje kombinirane (združene) u heterozigota ili homozigota za posljedicu imaju djelomični ili potpuni gubitak aktivnosti enzima NUDT15.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije sa 6-merkaptopurinom da bi se smanjio rizik supresije koštane srži (poremećaj hematopoeze) putem prilagođavanja početne doze ili ordiniranjem alternativnog lijeka. Genetički uvjetovana smanjena aktivnost TMPT kao primarni uzrok nepodnošenja tiogvanina češća je u Europljana i Afrikanaca dok rizični aleli u *NUDT15* objašnjavaju većinu supresija koštane srži povezanih s terapijom tiopurinima u Azijata i Hispanoamerikanaca.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Postupak je temeljen na preporukama smjernica the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] uz najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenjem 6-merkaptopurinom ovisno o TPMT genotipu

***TPMT* Genotip / Fenotip**	**Preporučena terapija**
Divlji tip / Normalni metabolizator	Terapija sukladno uputama o lijeku
Rizična varijanta, heterozigot / Intermedijarni metabolizator	Početna doza trebala bi iznositi 30-80 % normalne doze lijeka. Potrebno je podešavanje doze s obzirom na stupanj mijelosupresije
Rizična varijanta, recipročni/translokacijski heterozigoti ("compound heterozygous") ili homozigot / Spori metabolizator	Za maligna stanja: drastična redukcija incijalne doze (10-struko reducirana doza i samo 3 dana/tjedno), potrebno je podešavanje doze s obzirom na stupanj mijelosupresije Za nemaligna stanja: razmotriti alternativnu imunosupresivnu terapiju koja nije iz skupine tiopurina

Tablica 2: Preporuke za liječenjem 6-merkaptopurinom ovisno o NUDT15 genotipu

***NUDT15* Genotip / Fenotip**	**Preporučena terapija**
Divlji tip / Normalni metabolizator	Terapija sukladno uputama o lijeku
Rizična varijanta, heterozigot / Intermedijarni metabolizator	Početna doza trebala bi iznositi 30-80 % prosječne doze lijeka, potrebno je podešavanje doze s obzirom na stupanj mijelosupresije
Rizična varijanta, recipročni/translokacijski heterozigoti ("compound heterozygous") ili homozigot / Spori metabolizator	Za malignitete: drastična redukcija početne doze (započeti 10 mg/m^2/dan umjesto 75 mg/m^2/dan), potrebno je podešavanje doze s obzirom na stupanj mijelosupresije Za nemaligna stanja: razmotriti alternativnu imunosupresivnu terapiju koja nije iz skupine tiopurina

Troškovi

Priznavanje i povrat troškova za analizu *TPMT* i *NUDT15* varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

METHOXYFLURANE

Genetic test to minimize the risk of malignant hyperthermia (MH) related to the usage of methoxyflurane

Drug

What are the indications and mechanism of action of methoxyflurane?

Methoxyflurane is generally a safe volatile inhaled anesthetic used for inducing general anesthesia. Its mechanism of action is complex and includes a reduction in junctional conductance by decreasing gap junction channel opening times and increasing gap junction channel closing times. It also activates calcium-dependent ATPase in the sarcoplasmic reticulum by increasing the fluidity of the lipid membrane. Methoxyflurane probably binds to various neurotransmitter receptors (like GABA, glycine, glutamate) and ion channels and interacts with the nerve membranes.

Genes

Which genes influence the effect of methoxyflurane?

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the *RYR1* and *CACNA1S* genes under consideration here predispose individuals to a severe and sometimes lethal hypermetabolic reaction whose symptoms include muscle rigidity, high fever, and a fast heart rate. Complications can include rhabdomyolysis and high blood potassium.

Test

What will be tested?

The genotype of the ryanodine receptor isoform 1 protein *(RYR1)* is tested for one of the 48 causative single-nucleotide variants or one deletion that are designated diagnostic MH mutations[1]. The α1S subunit of the dihydropyridine receptor *(CACNA1S)* is tested for the 2 known variants that are MH susceptible. Since MH susceptibility is inherited in an autosomal-dominant pattern, a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as diagnostic for the trait.

Indication

When should a test be performed?

Genetic testing should be carried out before the initiation of the scheduled therapy with methoxyflurane in order to predict the risk of MH.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for methoxyflurane usage depending on the phenotype of the RYR1 and CACNA1S genes

RYR1 or CACNA1S Phenotype	Recommended therapy
Malignant hyperthermia susceptible	Methoxyflurane is not recommended due to MH susceptibility, use alternative anesthetics
Uncertain susceptibility	Clinical findings, family history, further genetic testing, and other laboratory data should guide the use of methoxyflurane

Nota bene: A negative or inconclusive genetic test cannot be assumed to indicate normal phenotype and should be interpreted in the context of clinical findings, family history, and other laboratory data.

Costs

Costs for the determination of the *RYR1* and *CACNA1S* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

METHOXYFLURAN

Gentest zur Risikominimierung der Therapie mit Methoxyfluran bei maligner Hyperthermie (MH)

Wirkstoff

Was sind die Indikationen und der Wirkungsmechanismus von Methoxyfluran?

Methoxyfluran ist ein weit verbreitetes und allgemein sicheres flüchtiges Inhalationsanästhetikum, das zur Einleitung einer Vollnarkose verwendet wird. Sein Wirkungsmechanismus ist komplex und umfasst eine Verringerung der Verbindungsleitfähigkeit durch verringerte Öffnungszeiten und erhöhte Schließzeiten von *gap junction*-Kanälen. Es aktiviert auch die Calcium-abhängige ATPase im sarkoplasmatischen Retikulum, indem es die Fluidität der Lipidmembran erhöht. Es wird hypothetisiert, dass Methoxyfluran an verschiedene Neurotransmitter-Rezeptoren und Ionenkanäle (wie GABA, Glycin, Glutamat) bindet und mit Nervenmembranen interagiert.

Gene

Welche Gene beeinflussen die Wirkung von Methoxyfluran?

Im Gegensatz zu vielen verwertbaren pharmakogenetischen Merkmalen, die den Metabolismus und/oder die Ausscheidung eines Arzneimittels beeinflussen, prädisponieren die hier betrachteten Varianten der Gene *RYR1* und *CACNA1S* zu einer schweren und manchmal tödlichen hypermetabolischen Reaktion, zu deren Symptomen Muskelsteifheit, hohes Fieber und schnelle Herzfrequenz gehören. Weitere Komplikationen können Rhabdomyolyse und hohe Kaliumwerte im Blut darstellen.

Test

Was wird getestet?

Der Genotyp des Ryanodinrezeptor-Isoform-1-Proteins *(RYR1)* wird auf eine der 48 Einzelnukleotidvarianten und eine Deletion getestet, die als diagnostische maligne Hyperthermie (MH)-Mutation[1] bezeichnet werden. Die α1S-Untereinheit des Dihydropyridinrezeptors *(CACNA1S)* wird auf die beiden bekannten Varianten getestet, die für maligne Hyperthermie anfällig sind. Da die Anfälligkeit für maligne Hyperthermie (MHS) in einem autosomal-dominanten Muster vererbt wird, kann ein heterozygoter Genotyp einer pathogenen Variante in *RYR1* als diagnostisch für das Merkmal angesehen werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Methoxyfluran durchgeführt werden, um das Risiko einer bösartigen Hyperthermie zu verringern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für einen Methoxyfluran-Einsatz mit Phänotyp der RYR1- und CACNA1S-Gene

RYR1 oder CACNA1S Phänotyp	Therapieempfehlung
Maligne Hyperthermie Anfälligkeit (MHS)	Methoxyfluran kontraindiziert, Anästhetikawechsel empfohlen
Unsichere Anfälligkeit	Klinische Befunde, Familienanamnese, weitere Gentests und andere Labordaten sollten den Einsatz von Methoxyfluran anleiten

Nota bene: Ein negativer oder nicht eindeutiger Gentest kann nicht als Hinweis auf einen normalen Phänotyp angesehen werden und sollte im Zusammenhang mit klinischen Befunden, Familienanamnese und anderen Labordaten interpretiert werden.

Kosten

Die Kosten für die genetische Analyse der *RYR1*- und *CACNA1S* -Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

METOKSIFLURAN

Genetički test za smanjenje rizika pojave maligne hipertermije pri primjeni metoksiflurana

Lijek

Koje su indikacije i mehanizmi djelovanja metoksiflurana?

Metoksifluran je siguran hlapljivi inhalacijski anestetik koji se često koristi za indukciju opće anestezije. Njegov mehanizam djelovanja je kompleksan, a uključuje smanjenje provodljivosti skraćivanjem vremena otvaranja kanala na pukotinskim spojevima (gap junctions) i produljujući vrijeme zatvaranja istih. Također aktivira o kalciju ovisnu ATPazu na sarkoplazmatskom retikulumu povećanjem fluidnosti lipidne membrane. Metoksifluran se vjerojatno veže na više neurotransmitorskih receptora (poput GABA, glicinskog i glutamatnog), ionskih kanala te ulazi u interakciju s membranama neurona.

Geni

Koji geni utječu na djelovanje metoksiflurana?

Za razliku od mnogih drugih lijekova kojima genski polimorfizmi utječu na metabolizam ili ekskreciju, polimorfizmi *RYR1* i *CACNA1S* gena su predisponirajući za tešku i smrtonosnu hipermetaboličku reakciju, čiji simptomi uključuju: rigidnost mišića, visoku tjelesnu temperaturu, tahikardiju. Komplikacije uključuju rabdomiolizu i hiperkalemiju.

Analiza

Što se analizira?

Genotip rajanodinskog receptora izoforme 1 *(RYR1)* testira se na jedan od 48 nukleotidnih polimorfizama ili jednu deleciju koje su označene kao dijagnostičke mutacije za malignu hipertermiju[1]. α1S podjedinica dihidropiridinskog receptora *(CACNA1S)* se testira za jednu od 2 poznate mutacije koje su dijagnostičke za malignu hipertermiju. Budući da se navedeni geni nasljeđuju autosomno dominantno, heterozigotni genotip navedenih gena smatra se kao dijagnoza sklonosti ka malignoj hipertermiji.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka primjene metoksiflurana kako bi se odredila sklonost ka nastanku maligne hipertermije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortiums (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za primjenu metoksiflurana ovisno o genotipu RYR1 i CACNA1S

RYR1 ili CACNA1S fenotip	Preporučena terapija
Osjetljivost za malignu hipertermiju	Ne preporučuje se primjena metoksiflurana. Potrebno je korištenje alternativnog anestetika
Neinformativan	Odluka o primjeni metoksiflurana trebala bi se voditi kliničkom slikom, obiteljskom anamnezom, daljnjim genskim testiranjem i ostalim laboratorijskim podatcima

Nota bene: negativan ili neinformativan rezultat testa se ne smije uzeti kao indikacija za normalan fenotip te se treba razmotriti u kontekstu kliničkih nalaza, obiteljske anamneze i ostalih laboratorijskih nalaza.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

NORTRIPTYLINE

Genetic test to minimize the risks related to therapy with nortriptyline

Drug

What are the indications and mechanism of action of nortriptyline?

Tricyclic antidepressant nortriptyline is a secondary amine, an active metabolite of amitriptyline. Nortriptyline is both, serotonin and norepinephrine reuptake inhibitor in the presynaptic neuron indicated for the treatment of depression, anxiety disorders, nocturnal enuresis, as well as neuropathic pain and migraine prophylaxis.

Genes

Which genes influence the effect of nortriptyline?

Nortriptyline is metabolized via the CYP2D6 enzyme to less-active metabolites. Different variants of the *CYP2D6* gene with wide variability in enzymatic activity are known. They can be crucial for therapy with nortriptyline.

Test

What will be tested?

In order to determine the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants in the *CYP2D6* gene *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41).*

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with nortriptyline in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1,2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for nortriptyline therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-20 %)	Usage of nortriptyline is not recommended, the prescription of an alternative agent is recommended. If nortriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Therapeutic drug monitoring is strongly recommended
Normal metabolizer (72-88 %)	Usage according to the Summary of Product Characteristics
Intermediate metabolizer (1-13 %)	Reduction of starting dose of nortriptyline by 25 %
Poor metabolizer (1-10 %)	Usage of nortriptyline is not recommended, the prescription of an alternative agent is recommended. If nortriptyline is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Nota bene: If a patient is treated for neuropathic pain with nortriptyline and is an intermediate or poor CYP2D6 metabolizer, no dose adjustment is recommended because of a lower prescribed dose initially. Patients should be monitored for potential side effects.

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget will not be burdened.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

NORTRIPTYLIN

Gentest zur Risikominimierung der Therapie mit Nortriptylin

Wirkstoff

Was sind die Indikationen und der Wirkungsmechanismus von Nortriptylin?

Das trizyklische Antidepressivum Nortriptylin ist ein sekundäres Amin, ein aktiver Metabolit von Amitriptylin. Es hemmt die Wiederaufnahme von Serotonin und Noradrenalin im präsynaptischen Neuron. Dieser Wirkstoff wird bei der Behandlung von Depressionen, nächtlicher Enuresis und Zwangsstörungen sowie neuropathischen Schmerzen und Migräneprophylaxe eingesetzt.

Gen

Welche Gene beeinflussen die Wirkung von Nortriptylin?

Nortriptylin wird durch das CYP2D6-Enzym zu weniger aktiven Metaboliten verstoffwechselt. Es sind verschiedene Varianten des *CYP2D6*-Gens mit einer großen Variabilität der enzymatischen Wirksamkeit bekannt. Sie können für die Therapie mit TCAs von entscheidender Bedeutung sein.

Test

Was wird getestet?

Um den CYP2D6-Metabolismustyp zu bestimmen, wird der Erbgut des Patienten im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Nortriptylin durchgeführt werden, um die Dosierung anzupassen oder gegebenenfalls einen Wirkstoffwechsel vorzunehmen.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Nortriptylin-Therapie nach Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Nortriptylin kontrainidziert, Wirkstoffwechsel empfohlen Bei Einsatz von Nortriptylin: auf höhere Zieldosis (verglichen zu schnellen Metabolisierern) titrieren, bei therapeutischem *Drug Monitoring*
Schnelle Metabolisierer (77-88 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis um 25 % reduzieren
Langsame Metabolisierer (1-10 %)	Nortriptylin kontrainidziert, Wirkstoffwechsel empfohlen Bei Einsatz von Nortriptylin: Startdosis um 50 % reduzieren, bei therapeutischem *Drug Monitoring*

Nota bene: Wenn ein Patient wegen neuropathischer Schmerzen mit Nortriptylin behandelt wird und ein intermediärer oder langsamer CYP2D6-Metabolisierer ist, wird aufgrund einer anfänglich niedrigeren verschriebenen Dosis keine Dosisanpassung empfohlen. Die Patienten sollten auf mögliche Nebenwirkungen überwacht werden.

Kosten

Die Kosten für genetische Analysen werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Untersuchung von einem Arzt verordnet wurde. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

NORTRIPTILIN

Genetički test za smanjenje rizika pri primjeni nortriptilina

Lijek

Koje su indikacije i mehanizmi djelovanja nortriptilina?

Triciklički antidepresiv nortriptilin je sekundarni amin, aktivni metabolit amitriptilina. Nortriptilin je inhibitor ponovne pohrane serotonina i noradrenalina u presinaptičkom neuronu. Koristi se za liječenje depresije, anksioznih poremećaja, nokturalne enureze, neuropatske boli te za profilaksu migrene.

Geni

Koji geni utječu na djelovanje nortriptilina?

Nortriptilin se kao sekundarni amin metabolizira preko enzima CYP2D6 u manje aktivne metabolite. Ovaj enzim određuje učinkovitost i duljinu djelovanja nortriptilina. Nekoliko genskih polimorfizama dovode do velike varijabilnosti u enzimatskoj funkciji CYP2D6.

Analiza

Što se analizira?

Kako bi se odredio fenotip enzima CYP2D6, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, 9*, *10, *41).*

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije nortriptilinom, kako bi se po potrebi prilagodilo doziranje lijeka ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje nortriptilinom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-20 %)	Ne preporučuje se liječenje nortriptilinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja nortriptilinom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizator (77-88 %)	Koristiti lijek prema sažetku opisa svojstava lijeka
Intermedijarni metabolizator (1-13 %)	Smanjenje početne doze nortriptilina za 25 %
Spori metabolizator (1-10 %)	Ne preporučuje se liječenje nortriptilinom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja nortriptilinom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Nota bene: Ukoliko se liječi neuropatska bol, a pacijent je intermedijarni ili spori CYP2D6 metabolizator, ne preporučuje se prilagodba doze zbog već inicijalno propisane niže doze. Pacijente treba nadzirati zbog potencijalnih nuspojava.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa CYP2D6 bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

ONDANSETRON

Genetic test to minimize the risks related to therapy with ondansetron

Drug

What are the indications and mechanisms of action of ondansetron?

Ondansetron suppresses nausea and vomiting by selectively blocking 5-HT3 receptors centrally and peripherally, thereby preventing serotonin-mediated emetogenic signaling. Ondansetron is used in the prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting.

Genes

What genes influence the effect of ondansetron?

The 5-HT3 receptor antagonists are generally well tolerated. Ondansetron has been associated with cardiac adverse events such as corrected QT prolongation. Ondansetron is metabolized to four inactive metabolites by multiple CYP enzymes, including CYP3A4, CYP1A2, and CYP2D6, followed by glucuronide conjugation to metabolites not clinically relevant for pharmacologic activity. *CYP2D6* gene is a highly polymorphic gene with over 100 known allelic variants and subvariants. Increased activity of CYP2D6 is associated with higher clearance of ondansetron and decreased therapeutic response, while reduced enzyme activity increases the risk for adverse effects.

Test

What is tested?

The patient's genotype is analyzed for the most common *CYP2D6* variants like *CYP2D6 *1* and **2* that are associated with normal functions, *CYP2D6 *9, *10* and **41* that are associated with reduced functions, *CYP2D6 *3, *4, *5, *6* that are associated with complete lack of functions, while *CYP2D6 *1xN,* where xN represents the copy number of the *CYP2D6* gene, is associated with an increase in function.

Indication

When should a test be carried out?

It is recommended to do pharmacogenetic *CYP2D6* analysis in patients with inadequate therapeutic response to ondansetron, patients suffering side effects, patients which are preparing for chemotherapy, radiotherapy or surgical procedure after which nausea and vomiting are expected.

Consequences and test results

How does the therapy need to be adjusted to the test result?

The following recommendations are based on the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for the therapy with ondansetron depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid Metabolizer (1-20 %)	Usage of ondansetron is not recommended Prescription of an alternative agent is recommended
Normal Metabolizer (72-88 %)	Usage according to the Summary of Product Characteristics
Intermediate Metabolizer (1-13 %)	Insufficient evidence demonstrating clinical impact Initiate therapy with the recommended starting dose
Poor Metabolizer (1-10 %)	Insufficient evidence demonstrating clinical impact Initiate therapy with the recommended starting dose

Cost

Costs for the *CYP2D6* gene analysis will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened.

[1] Bell GC, Caudle KE, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017;102(2):213-218. doi:10.1002/cpt.598

ONDANSETRON

Gentest zur Risikominimierung der Therapie mit Ondansetron

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Ondansetron?

Ondansetron ist ein Antagonist des 5-HT_3-Rezeptors. Ondansetron unterdrückt Übelkeit und Erbrechen, indem es selektiv an 5-HT_3-Rezeptoren bindet und so die Serotonin-vermittelte emetogene Signalübertragung verhindert. Dieser Wirkstoff wird zur Vorbeugung von durch Chemotherapie induzierter, strahleninduzierter und postoperativer Übelkeit und Erbrechen eingesetzt.

Gene

Welche Gene beeinflussen die Wirkung von Ondansetron?

Die 5-HT_3-Rezeptorantagonisten sind allgemein gut verträglich. Leichte Kopfschmerzen, Verstopfung und vorübergehende Erhöhungen der Leberenzyme sind häufige Nebenwirkungen. Ondansetron wurde auch mit kardialen unerwünschten Ereignissen wie Herzrhythmusstörungen aufgrund einer korrigierten QT-Verlängerung in Verbindung gebracht. Ondansetron wird durch mehrere CYP-Enzyme, einschließlich CYP3A4, CYP1A2 und CYP2D6, zu vier inaktiven Metaboliten metabolisiert, gefolgt von einer Glucuronid-Konjugation an Metaboliten, die für die pharmakologische Aktivität klinisch nicht relevant sind. Das *CYP2D6*-Gen ist ein hochpolymorphes Gen mit über 100 bekannten Allelvarianten und Subvarianten. Eine erhöhte Aktivität von CYP2D6 ist mit einer höheren Clearance von Ondasetron und einer verringerten therapeutischen Reaktion verbunden, während eine verringerte Enzymaktivität das Risiko für Nebenwirkungen erhöht.

Test

Was wird getestet?

Das Erbgut des Patienten wird auf die häufigsten *CYP2D6*-Genvarian*ten überprüft: CYP2D6 *1* und *2* sind mit normalen Funktionen assoziiert; *CYP2D6 *9, *10, *41* sind mit reduzierten Funktionen assoziiert; *CYP2D6 *3, *4, *5, *6*, sind mit völligem Mangel an Funktionen assoziiert; *CYP2D6 *1xN* ist mit einer Funktionssteigerung verbunden.

Indikation

Wann sollte ein Test durchgeführt werden?

Es wird empfohlen, eine pharmakogenetische *CYP2D6*-Analyse bei Patienten mit unzureichender therapeutischer Reaktion auf Ondansetron, Patienten mit Nebenwirkungen, Patienten, die sich auf eine Chemotherapie, Strahlentherapie oder einen chirurgischen Eingriff vorbereiten, nach denen Übelkeit und Erbrechen zu erwarten sind, durchzuführen.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Ondansetron-Therapie nach Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Wirkstoffwechsel empfohlen
Schnelle Metabolisierer (72-88 %)	Therapie gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis gemäß Fachinformation, unzureichende klinische Evidenz
Langsame Metabolisierer (1-10 %)	Startdosis gemäß Fachinformation, unzureichende klinische Evidenz

Kosten

Die Kosten für genetische Analysen des *CYP2D6*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Untersuchung von einem Arzt verordnet wurde. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Bell GC, Caudle KE, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017;102(2):213-218. doi:10.1002/cpt.598

ONDANSETRON

Genetički test za minimiziranje rizika povezanih uz terapiju ondansetronom

Lijek

Koje su indikacije i mehanizmi djelovanja ondansetrona?

Ondansetron smanjuje mučninu i povraćanje selektivno inhibirajući 5-HT3 receptore središnje i periferno, na taj način prevenira emetogene signale posredovane serotoninom. Ondasetron se koristi u prevenciji mučnina i povraćanja koji nastaju kao posljedica kemoterapije, radioterapije ili postoperativno.

Geni

Koji geni utječu na djelovanje ondansetrona?

Antagonist 5-HT3 receptora općenito se dobro podnose. Ondansetron je povezan s kardiološkim nuspojavama poput produljenja QT intervala. Ondasetron se metabolizira u četiri inaktivna metabolita putem brojnih CYP enzima, uključujući CYP3A4, CYP1A2 i CYP2D6, nakon čega slijedi konjugacija u glukuronidne metabolite koji nemaju farmakološki relevantnu aktivnost. *CYP2D6* je visoko polimorfan gen s preko 100 poznatih alelnih varijanti i subvarijanti. Povećana aktivnost CYP2D6 je povezana s višim klirensom ondansetrona i smanjenim terapijskim odgovorom, dok smanjena enzimska aktivnost povećava rizik od nuspojava.

Analiza

Što se analizira?

Genotip se analizira na najčešće varijante *CYP2D6* poput *CYP2D6 *1* i *2* koje su povezane s normalnom funkcijom, *CYP2D6 *9, *10 i *41* koje su povezane sa smanjenom funkcijom, *CYP2D6 *3, *4, *5, *6* koje su povezane s potpunim gubitkom funkcije, dok je *CYP2D6 *1xN*, gdje xN prezentira broj kopija *CYP2D6* gena, povezan s povećanom funkcijom.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti kod pacijenata koji nemaju odgovarajući terapijski odgovor na ondansetron ili nuspojave, zatim kod pacijenata koji se pripremaju za početak kemoterapije, radioterapije ili operativni zahvat nakon kojeg se očekuje pojava mučnine ili povraćanja.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] i imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje ondansetronom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-20 %)	Nije preporučena upotreba ondansetrona, preporučuje se upotreba alternativnog lijeka
Normalni metabolizator (77-88 %)	Terapija sukladno uputama o lijeku
Intermedijarni metabolizator (1-13 %)	Započinjanje terapije s preporučenom početnom dozom zbog nedovoljno dokaza o utjecaju genotipa na djelovanje lijeka
Spori metabolizator (1-10 %)	Započinjanje terapije s preporučenom startnom dozom zbog nedovoljno dokaza o utjecaju genotipa na djelovanje lijeka

Troškovi

Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Bell GC, Caudle KE, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017;102(2):213-218. doi:10.1002/cpt.598

OXCARBAZEPINE

Genetic test to minimize the risks related to therapy with oxcarbazepine

Drug

What are the indications and the mechanisms of action of oxcarbazepine?

Oxcarbazepine is a frequently prescribed anticonvulsant drug and is used for the treatment of different forms of epilepsy, neuropathic pain, bipolar disorders and for co-treatment during alcohol withdrawal. Oxcarbazepine suppresses the excitability of nerve cells by blocking the sodium channels of the cell membrane. It furthermore inhibits the release of the neurotransmitter glutamate.

Genes

What genes influence the effect of oxcarbazepine?

Approximately 5-10 percent of patients present with different side effects under oxcarbazepine therapy, such as central nervous disorders, problems with the gastrointestinal tract or hematopoietic changes. Furthermore, the drug can cause severe immunological hypersensitivity reactions in patients who carry the alleles *HLA-A*31:01* (*HLA-A* gene) or *HLA-B*15:02* (*HLA-B* gene) which manifest as DRESS (drug reaction with eosinophilia and systemic symptoms), MPE (maculopapular exanthema), SJS (Stevens-Johnson syndrome) and TEN (toxic epidermal necrolysis).

Test

What is tested?

The genotype of patients is tested with regard to the alleles *HLA-B*15:02* in the *HLA-B* gene.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with oxcarbazepine in order to change the active agent, as required, so that the severe side effects can be avoided.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on the guidelines of *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] for *HLA* Genotype and have the highest clinical level of evidence 1A.

Table 1: Recommendations for oxcarbazepine therapy depending on the HLA-B genotype

***HLA* Genotype**	**Recommended therapy**
*HLA-B*15:02* negative	The usage according to the Summary of Product Characteristics
*HLA-B*15:02* positive	Usage of oxcarbazepine in drug-naïve patients is not recommended The prescription of an alternative agent is recommended

Nota bene: Patients who have been continuously taking oxcarbazepine for longer than 3 months without developing cutaneous reactions are at extremely low risk of adverse events in the future, regardless of *HLA-B*15:02* status.

Costs

Costs for the determination of the *HLA-B* gene are reimbursed for patients with statutory or private health insurance if testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581. doi:10.1002/cpt.1004.

OXCARBAZEPIN

Gentest zur Risikominimierung der Therapie mit Oxcarbazepin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Oxcarbazepin?

Oxacarbazepin ist ein häufig verschriebenes Antikonvulsivum. Es wird zur Behandlung verschiedener Formen der Epilepsie, bei Neuralgien, der bipolaren Störung und zur Begleitung des Alkoholentzugs eingesetzt. Oxacarbazepin unterdrückt die Erregbarkeit von Neuronen durch eine Blockade der Natriumkanäle in der Zellmembran. Es inhibiert zudem die Freisetzung des Neurotransmitters Glutamat.

Gene

Welche Gene beeinflussen die Wirkung von Oxcarbazepin?

Etwa 5-10 % der Patienten erleiden bei einer Oxacarbazepin-Therapie verschiedenartige Nebenwirkungen, wie zentralnervöse Störungen, Beschwerden im Magen-Darm-Trakt, Blutbildungsveränderungen und weiteres. Demgegenüber kann das Medikament bei Patienten, die Träger des *HLA*-Allels *HLA-B*15:02* (*HLA-B*-Gen) sind, schwerste immunologische Überempfindlichkeitsreaktionen auslösen, die sich als Arzneimittelreaktion mit Eosinophilie und systemischen Symptomen (DRESS), makulopapuläres Exanthem (MPE), Stevens-Johnson-Syndrom (SJS) oder toxische epidermale Nekrolyse (TEN) manifestieren.

Test

Was wird getestet?

Das Erbgut der Patienten wird auf das Allel *HLA-B*15:02* (*HLA-B*-Gen) getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Oxacarbazepin durchgeführt werden, um gegebenfalls einen Wirkstoffwechsel vorzunehmen und schwere Nebenwirkungen zu vermeiden.

Konseuqenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] für den *HLA*-Genotyp und die Verwendung von Carbamazepin und Oxcarbazepin: Update[2] 2018. Die Empfehlungen zeigt für *HLA-B* das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Oxacarbazepin-Therapie in Abhängigkeit vom HLA-Gen A- und B-Genotyp

***HLA* Genotyp**	**Therapieempfehlung**
*HLA-B*15:02* negativ	Anwendung gemäß Fachinformationen
*HLA-B*15:02* positiv	Oxacarbazepin kontraindiziert, Wirkstoffwechsel empfohlen

Nota bene: Patienten, die Oxcarbazepin länger als 3 Monate kontinuierlich eingenommen haben ohne Hautreaktionen zu entwickeln, weisen unabhängig vom *HLA-B*15:02*-Status ein äußerst geringes Risiko für unerwünschte Ereignisse in der Zukunft auf.

Kosten

Die Kosten für die genetische Analyse des *HLA-B*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581. doi:10.1002/cpt.1004.

OKSKARBAZEPIN

Genetički test za smanjenje rizika pri primjeni lijeka okskarbazepina

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja okskarbazepina?

Okskarbazepin je često ordinirani antikonvulzivni lijek. Primjenjuje se u liječenju različitih oblika epilepsije, zatim kod neuropatske boli, bipolarnih poremećaja te kod sindroma ustezanja od alkohola. Okskarbazepin suprimira podražljivost živčanih stanica putem blokade natrijskih kanala unutar stanične membrane, te inhibira oslobađanje neurotransmitora glutamata.

Geni

Koji geni utječu na djelovanje okskarbazepina?

Tijekom liječenja okskarbazepinom, 5-10 % pacijenata žali se na različite nuspojave, kao što su smetnje središnjeg živčanog sustava, problemi s probavnim sustavom ili hematopoetske promjene. Nadalje, ovaj lijek može kod pacijenata koji su nositelji alela *HLA-A*31:01* (gen *HLA-A*) ili alela *HLA-B*15:02* (gen *HLA-B*) izazvati teške imunološke reakcije preosjetljivosti koje se manifestiraju kao reakcija na lijek s eozinofilijom i sistemskim simptomima (eng. drug reaction with eosinophilia and systemic symptoms, DRESS), makulopapularni osip (eng. maculopapular exanthema, MPE), Steven-Johnsonov sindrom (eng. Stevens-Johnson syndrome, SJS) i toksična epidermalna nekroliza (eng. toxic epidermal necrolysis, TEN).

Analiza

Što se analizira?

Analizira se genotip pacijenata, odnosno alel *HLA-B*15:02* (gen *HLA-B*).

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka liječenja okskarbazepinom, kako bi se pravovremeno ordinirala zamjenska terapija i izbjegle teške nuspojave.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] za *HLA* genotip. Preporuke imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za terapiju okskarbazepinom ovisno o HLA-B genotipu

***HLA* genotip**	**Preporučena terapija**
*HLA-B*15:02* negativan	Korištenje sukladno uputama o lijeku
*HLA-B*15:02* pozitivan	Korištenje okskarbazepina u pacijenata koji ga nisu prije uzimali se ne preporučuje već se preporučuje primjena zamjenskog lijeka

Troškovi

Troškovi za određivanje *HLA-B* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje ukoliko je testiranje zatraženo od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581. doi:10.1002/cpt.1004

PAROXETINE

Genetic test to minimize the risks related to therapy with paroxetine

Drug

What are the indications and mechanisms of action of paroxetine?

Paroxetine belongs to the class of selective serotonin reuptake inhibitors (SSRIs) which increase the extracellular level of serotonin by limiting its reuptake into the presynaptic neuron. It is one of the most specific and most potent SSRIs. Furthermore, it also inhibits the reuptake of norepinephrine to a lesser extent. Apart from treating depression, it is also used to treat obsessive-compulsive disorder (OCD), post-traumatic stress disorder, panic disorder, social anxiety disorder and other conditions.

Genes

Which genes influence the effect of paroxetine?

Paroxetine's metabolism via the enzyme CYP2D6 plays a decisive role in its efficiency and duration of action. Several variants of genes of this enzyme are known in the population. These lead to a great variability in the enzymatic efficacy of CYP2D6, and can therefore be of great importance for paroxetine therapy.

Test

What will be tested?

In order to determine the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants in the *CYP2D6* gene *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)*.

Indication

When should a test be performed?

Patients on a stable and effective dose of an SSRI most likely will not benefit from additional dose modifications based on *CYP2D6* genotype results. The genetic test should be considered before the start of planned therapy with paroxetine in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for paroxetine therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolism status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-12 %)	No recommendation due to insignificant clinical evidence
Extensive metabolizer (77-92 %)	Usage according to the Summary of Product Characteristics
Intermediate metabolizer (2-11 %)	Usage according to the Summary of Product Characteristics
Poor metabolizer (5-10 %)	Select alternative drug not predominantly metabolized by CYP2D6 or if paroxetine use warranted, consider a 50 % reduction of recommended starting dose and titrate to the response

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

PAROXETIN

Gentest zur Risikominimierung der Therapie mit Paroxetin

Wirkstoff

Was sind die Indikationen und der Wirkungsmechanismus von Paroxetin?

Paroxetin gehört zu den klassenselektiven Serotonin-Wiederaufnahmehemmern (SSRIs), sodass der extrazelluläre Spiegel des Neurotransmitters Serotonin erhöht wird. Indem es als Agonist dieses Rezeptors wirkt, kann es zu seiner antidepressiven und anxiolytischen Wirkung beitragen. Es ist eines der spezifischsten und wirksamsten SSRIs. Durch den Ausgleich des Serotoninspiegels wirkt es als Antidepressivum. Neben der Behandlung von Depressionen wird es zur Behandlung von Zwangsstörungen (OCD), Panikstörungen, sozialen Angststörungen, generalisierten Angststörungen, posttraumatischen Belastungsstörungen und Fibromyalgie eingesetzt.

Gene

Welche Gene beeinflussen die Wirkung von Paroxetin?

Der Metabolismus von Paroxetin über das Enzym CYP2D6 entscheidet über die Effizienz und Wirkdauer. In der Population sind mehrere Varianten des Gens mit großer Variabilität der enzymatischen Wirksamkeit bekannt. Diese führen zu einer großen Variabilität der enzymatischen Wirksamkeit von *CYP2D6* und können daher für die Paroxetin-Therapie von großer Bedeutung sein.

Test

Was wird getestet?

Um den CYP2D6-Metabolismus-Typ zu bestimmen, wird das Erbgut des Patienten auf die häufigsten aktivitätsvariablen Genvarianten im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Patienten mit einer stabilen und wirksamen Dosis eines SSRI profitieren höchstwahrscheinlich nicht von zusätzlichen Dosisänderungen, die auf den Ergebnissen des *CYP2D6*-Genotyps basieren. Der Gentest sollte vor Beginn der geplanten Therapie mit Paroxetin in Betracht gezogen werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu wechseln.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Paroxetin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisiererhäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-2 %)	Keine Empfehlung, fehlende klinische Daten
Schnelle Metabolisierer (77-92 %)	Therapie gemäß Fachinformation
Intermediäre Metabolisierer (2-11 %)	Therapie gemäß Fachinformation
Langsame Metabolisierer (5-10 %)	Startdosis um 25–50 % reduzieren, bis Reaktion titrieren oder Wirkstoffwechsel

Kosten

Die Kosten für die genetische Analyse des *CYP2D6* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147.

PAROKSETIN

Genetički test za smanjenje rizika pri primjeni paroksetina

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja paroksetina?

Paroksetin pripada skupini lijekova poznatih kao selektivni inhibitori ponovne pohrane serotonina (eng. selective serotonin reuptake inhibitors, SSRI) koji povećavaju izvanstaničnu razinu neurotransmitora serotonina tako što inhibiraju njegovu ponovnu pohranu u presinaptički neuron. Paroksetin je jedan je od najpotentnijih i lijekova te skupine koji u manjoj mjeri inhibira i ponovnu pohranu noradrenalina. Osim depresije, koristi se za liječenje opsesivno-kompulzivnog poremećaja, posttraumatskog stresnog poremećaja, paničnih poremećaja, socijalne anksioznosti i ostalih anksioznih stanja.

Geni

Koji geni utječu na učinkovitost paroksetina?

Metabolizam paroksetina odvija se preko enzima CYP2D6 koji ima ključnu ulogu u učinkovitosti i trajanju djelovanja lijeka. Populacijske studije su utvrdile postojanje nekoliko genskih varijanti koje mijenjaju aktivnost enzima CYP2D6 što dovodi do velike varijabilnosti u djelovanju paroksetina.

Analiza

Što se analizira?

Da bi se utvrdila vrsta CYP2D6 metabolizatora, analizira se genotip bolesnika na najučestalije polimorfizme gena *CYP2D6 (*1, *1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)*.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Pacijenti na stabilnoj i učinkovitoj dozi paroksetina najvjerojatnije neće imati koristi od dodatnog prilagođavanja doze istoga temeljem rezultata genetičkog testa za *CYP2D6*. Genetički test potrebno je razmotriti prije početka planirane terapije paroksetinom, kako bi se po potrebi prilagodila doza ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su utemeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje paroksetinom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-12 %)	Bez preporuka s obzirom na nedovoljne kliničke dokaze
Ekstenzivni metabolizator (77-92 %)	Terapija sukladno uputama o lijeku
Intermedijarni metabolizatori (2-11 %)	Terapija sukladno uputama o lijeku
Spori metabolizatori (5-0 %)	Primijeniti zamjenski lijek koji se ne metabolizira dominantno putem CYP2D6 ili u slučaju korištenja paroksetina preporučuje se smanjenje početne doze za 50 % i prilagođavanje do zadovoljavajućeg odgovora

Troškovi

Troškovi za određivanje *CYP2D6* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje ukoliko je testiranje zatraženo od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

PHENPROCOUMON

Genetic test to minimize the risks related to therapy with phenprocoumon

Drug

What are the indications and mechanisms of action of phenprocoumon?

Phenprocoumon is a long-acting anticoagulant with a narrow therapeutic index prescribed for prophylaxis and treatment of venous thromboembolism (DVT), in the prevention of systematic embolism associated with atrial fibrillation and cardiac valve replacement, stroke, reinfarction or sudden cardiac death in patients with acute myocardial infarction. Large interpatient variability in the phenprocoumon concentrations implicates either lack of anticoagulant effect or serious drug adverse events and complications (bleeding). As a vitamin K antagonist, phenprocoumon suppresses the activation of the coagulation factors II, VII, IX and X as well as the synthesis of the anticoagulant proteins C and S. In comparison to the related coumarins, phenprocoumon exhibit a longer half-life. It has been shown to produce more stable anticoagulation compared to warfarin and acenocoumarol.

Genes

Which genes influence the effect of phenprocuomon?

VKORC1 gene has the most significant impact on phenprocoumon dosage. *VKORC1* encodes the vitamin K-epoxide reductase complex, the target enzyme of phenprocoumon. A common variant upstream of *VKORC1* on position *1639 G>A* is significantly associated with phenprocoumon sensitivity and patients carrying such polymorphism (*1639 A/A* and *A/G*) require progressively lower phenprocoumon doses than homozygotes (*1639 G/G*). *CYP2C9* encodes for hepatic drug-metabolizing enzyme with two common gene variants in *CYP2C9*2* and **3* that influence the enzymatic activity among individuals of European and East Asian ancestry. In contrast to warfarin dosing, neither of these gene variants nor variants in genes *CYP4F2*3* and *CYP2C cluster* (rs12777823) have influence on dose requirements.

Test

What will be tested?

To determine the optimal phenprocoumon dose, the most common risk variants of the *VKORC1 1639G>A*, is tested.

Indication

When should a test be performed?

The genetic test should be performed before a planned therapy with phenprocoumon in order to quickly achieve stable INR (international normalized ratio) values through dose adjustment if necessary and to avoid bleeding, specifically in individuals who are carriers of multiple allelic variants. The risk of developing complications is the greatest for phenprocoumon starting dosing.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following procedure takes place in accordance with *Royal Dutch Pharmacists Association - Pharmacogenetics Working Group* (DPWG) guidelines[1,2] for phenprocoumon and has the clinical level of evidence 1B to VKORC1.

Table 1: Recommendations for phenprocoumon dosing based on genotype for adult patients

Genotype	Recommended therapy
VKORC1 (1639G>A) AA	50 % of the standard initial dose of phenprocoumon. More frequent INR monitoring
VKORC1 (1639G>A) AG	No recommendation
*CYP2C9 *2, *3*	No recommendation
*CYP2C9 *5, *6, *8, *11*	No recommendation
*CYP4F2*3*	No recommendation
CYP2C cluster (rs 12777823)	No recommendation

Costs

Costs for the *VKORC1* genetic analysis will be reimbursed for statutory and privately insured patients if physician prescribes the testing, although most insurance plans do not currently pay for phenprocoumon pharmacogenetic testing.

[1] https://www.knmp.nl/producten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics

[2] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf

PHENPROCOUMON

Gentest zur Risikominimierung der Therapie mit Phenprocoumon

Wirkstoff

Was sind Indikationen und Wirkmechanismen von Phenprocoumon?

Phenprocoumon ist ein lang wirkendes Antikoagulans mit einem engen therapeutischen Index, das zur Prophylaxe und Behandlung von venösen Thromboembolien (DVT) verschrieben wird, um systematische Embolien im Zusammenhang mit Vorhofflimmern und Herzklappenersatz, Schlaganfall, Reinfarkt oder plötzlichem Herztod bei Patienten mit akutem Myokardinfarkt zu verhindern. Eine große Variabilität der Phenprocuomon-Konzentrationen impliziert entweder einen Mangel an gerinnungshemmender Wirkung oder in den Patienten schwerwiegende unerwünschte Ereignisse und Komplikationen (Blutungen). Als Vitamin-K-Antagonist unterdrückt Phenprocoumon die Aktivierung der Gerinnungsfaktoren II, VII, IX und X sowie die Synthese der Antikoagulansproteine C und S. Im Vergleich zu den verwandten Cumarinen Acenocoumarol und Warfarin besitzt Phenprocoumon eine längere Halbwertszeit. Es wurde gezeigt, dass es im Vergleich zu Warfarin und Acenocoumarol eine stabilere Antikoagulation herstellt.

Gene

Welche Gene beeinflussen die Wirkung von Phenprocoumon?

Die *VKORC1*- und *CYP2C9*-Gene beeinflussen maßgeblich die Phenprocoumon-Metabolisierung. *VKORC1* codiert den Vitamin K-Epoxid-Reduktase-Komplex, das Zielenzym von Phenprocoumon. Eine häufige Variante stromaufwärts von *VKORC1* an Position *1639 G>A* ist signifikant mit der Phenprocoumon-Sensitivität assoziiert, und Patienten mit einem solchen Polymorphismus (*1639 A/A*) benötigen zunehmend niedrigere Phenprocoumon-Dosen als Homozygote (*1639 G/G*). *CYP2C9* kodiert für ein für die Dosisvariabilität wichtiges hepatisches Arzneimittel metabolisierendes Enzym mit zwei häufigen Genvarianten in *CYP2C9*2* und **3*, die die enzymatische Aktivität bei Personen europäischer und ostasiatischer Abstammung beeinflussen. Zusätzlich leisten identifizierte Genvarianten in den Genen *CYP4F2*3* und im *CYP2C-Cluster* (rs12777823) einen geringen Beitrag zum Dosisbedarf.

Test

Was wird getestet?

Um die am besten geeignete Phenprocoumon-Dosis zu bestimmen, wird die häufigste Risikovariante von *VKORC1 1639G>A* im Erbgut der Patienten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor einer geplanten Therapie mit Phenprocoumon durchgeführt werden, um bei Bedarf durch Dosisanpassung schnell konstante INR-Werte (*International Normalized Ratio*) zu erreichen und Nebenwirkungen (Blutungen) zu vermeiden. Das Risiko, Komplikationen zu entwickeln, ist bei Beginn der Phenprocoumon-Dosierung am größten. Beachtet werden sollte eine Einführung von Phenprocoumon in die Therapie und eine Titration seiner stabilen Dosis sowie einige individuelle Faktoren: Alter, Geschlecht, Körpergewicht, Rasse, interagierende Medikamente (insbesondere Amiodaron), Vitamin-K-Aufnahme (Lebensmittel, insbesondere Zitrusfrüchte (Grapefruit), grünes Gemüse), Rauchen und Komorbiditäten.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] für Phenprocoumon und zeigt das höchste klinische Evidenzlevel 1B für *VKOCR1*.

Tabelle 1: Empfehlungen für die Phenprocoumon-Dosierung mit VKORC1-CYP2C9-CYP4F2-CYP2C cluster-Genotyp für erwachsene Patienten

Genotyp	Therapieempfehlung
VKORC1 (1639G>A) AA	50 % der Standard-Anfangsdosis von Phenprocoumon. Häufigere INR-Überwachung
VKORC1 (1639G>A) AG	Keine Empfehlung
*CYP2C9 *2, *3*	Keine Empfehlung
*CYP2C9 *5,*6, *8, *11*	Keine Empfehlung
*CYP4F2*3*	Keine Empfehlung
CYP2C cluster (rs 12777823)	Keine Empfehlung

Kosten

Die Kosten für die genetische Analyse der *VKORC1*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird, obwohl die meisten Versicherungspläne derzeit nicht für pharmakogenetische Warfarin-Tests bezahlen. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] https://www.knmp.nl/producten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics

[2] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf

FENPROKUMON

Genetički test za smanjenje rizika pri primjeni fenprokumona

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja fenprokumona?

Fenprokumon je dugodjelujući antikoagulans s uskom terapijskom širinom u liječenju i prevenciji duboke venske tromboze (DVT) i plućne embolije, u prevenciji sustavne embolije kod pacijenata s atrijskom fibrilacijom i umjetnim srčanim zaliscima, prevenciji moždanog udara, ponovnog infarkta ili iznenadne smrti u pacijenata s akutnim infarktom miokarda. Velika interindividualna varijabilnost u odgovoru na terapiju fenprokumonom može utjecati ili na izostanak antikoagulacijskog učinka ili često potencira niz nuspojava, kao i opasnost od krvarenja. Kao antagonist vitamina K, fenprokumon smanjuje aktivaciju faktora zgrušavanja II, VII, IX i X, ali i sintezu antikoagulacijskih proteina C i S.

Geni

Koji geni utječu na djelovanje fenprokumona?

Na doziranje fenprokumona najznačajnije utječe gen *VKORC1*. Enzim vitamin K-epoksid reduktaza kompleks ciljno je mjesto djelovanja fenprokumona kojeg kodira *VKORC1*. Jednonukleotidni polimorfizam na poziciji 1639 je supstitucija aminokiseline gvanin u adenin *(1639G>A)* koji je povezan s povećanom osjetljivošću na fenprokumon pa nositelji ovog polimorfizma *(1639 A/A i A/G)* zahtjevaju niže doze fenprokumona u odnosu na pojedince koji su homozigoti *(1639 G/G)*. *CYP2C9* kodira za jetreni enzim koji metabolizira fenprokumon. Na enzimsku aktivnost utječu polimorfizmi gena *CYP2C9 2** i *3** koji su najčešće zastupljeni kod populacije europskog i istočno-azijskog porijekla. Navedeni *CYP2C9* polimorfizmi, kao i varijante u genima *CYP4F2*3* i *CYP2C klastera* (rs12777823) nemaju utjecaj na doziranje fenprokumona.

Analiza

Što se analizira?

Da bi se ustanovila optimalna doza lijeka, analiziraju se najučestalije rizične varijante gena *VKORC1 1639G>A.*

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije a fenprokumonom kako bi se prilagodilo doziranje i postigao terapijski INR (međunarodno normalizirani omjer) 2-3 te izbjegle nuspojave krvarenja, osobito kod nositelja višestrukih alelnih varijanti. Rizik razvoja komplikacija najveći je u samom početku primjene fenprokumona.

Posljedice rezultata testova

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke za doziranje fenprokumona ovisno o *VKORC1* genotipu su utemeljene na smjernicama *Royal Dutch Pharmacists Association - Pharmacogenetics Working Group* (DPWG) guidelines[1,2] i imaju kliničku razinu dokaza 1B.

Tablica 1: Preporuke za doziranje fenprokumona bazirane prema genotipu za odrasle

Genotip	Preporučena terapija
VKORC1 (1639G>A) AA	Početi terapiju s 50 % od standardne početne doze fenprokumona; potrebno je češće praćenje INR-a
VKORC1 (1639G>A) AG	Nema preporuka
*CYP2C9 *2, *3*	Nema preporuka
*CYP2C9 *5, *6, *8, *11*	Nema preporuka
*CYP4F2*3*	Nema preporuka
CYP2C klaster (rs 12777823)	Nema preporuka

Troškovi

Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize gena bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje, iako većina osiguranja za sada ne plaća farmakogenomsko testiranje fenprokumona.

[1] https://www.knmp.nl/producten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics

[2] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-november-2018.pdf

PHENYTOIN

Genetic test to minimize the risks related to therapy with phenytoin

Drug

What are the indications and the mechanism of action of phenytoin?

Phenytoin is an antiepileptic and antiarrhythmic agent for the treatment of epilepsies and cardiac arrhythmias. The anticonvulsant effect of phenytoin is based on its function as a sodium channel blocker, whereby the membrane potential of central and peripheral nerve cells is stabilized.

Genes

Which genes influence the effect of phenytoin?

The tolerance to phenytoin is significantly influenced by variations in the *HLA-B* and *CYP2C9* gene. In addition to a variety of adverse effects, the most severe cutaneous hypersensitivity reactions can arise among carriers of the *HLA-B*15:02* genotype under phenytoin therapy. The *HLA-B*15:02* allele is more commonly found in the Asian population (1-10 %) than among Europeans (<0.1 %). However, activity-reducing variants which can lead to partial or complete loss of CYP2C9 function, the enzyme that catalyzes the biotransformation of phenytoin in the liver, are known in all ethnic groups and can lead to various adverse effects.

Test

What will be tested?

The patient's genotype (especially among Asians) is tested for the *HLA-B*15:02* allele (*HLA-B* gene). However, the testing of activity-reducing *CYP2C9* gene variants (*2,*3) is recommended for all ethnic groups.

Indications

When should a test be performed?

The genetic test should be performed before the start of planned therapy with phenytoin in order to predict and reduce the risk of serious adverse effects through an adjustment of the starting dose or the prescription of an alternative active ingredient.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for phenytoin therapy subject to HLA-B genotype

***HLA-B* Genotype**	**Recommended therapy**
*HLA-B*15:02*, negative	Usage according to the Summary of Product Characteristics
*HLA-B*15:02*, heterozygous or homozygous	The usage of phenytoin is not recommended. Prescription of an alternative agent is recommended

Table 2: Recommendations for phenytoin therapy depending on the phenotype of the CYP2C9 gene

CYP2C9 Phenotype (metabolizer status frequencies)	**Recommended therapy**
Normal (extensive) metabolizer (64-91 %)	Usage according to the Summary of Product Characteristics
Intermediate metabolizer (8-36 %)	Reduction of starting dose by 25 %
Poor metabolizer (0.1-4 %)	Reduction of starting dose by 50 %

Nota bene: The frequencies of the *CYP2C9**2 and *3 alleles and diplotypes differ among racial/ethnic groups[2].

Costs

Costs for the *HLA-B* genotyping and the *CYP2C9* genetic analysis will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

[1] Caudle KE, Rettie AE, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guidelines for *CYP2C9* and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014;96(5):542-548. doi:10.1038/clpt.2014.159

[2] https://www.pharmgkb.org/page/cyp2c9RefMaterials

PHENYTOIN

Gentest zur Risikominimierung der Therapie mit Phenytoin

Wirkstoff

Was sind die Indikationen und der Wirkmechanismus von Phenytoin?

Phenytoin wird als Antiepileptikum und Antiarrhythmikum zur Behandlung von Epilepsien und Herzrhythmusstörungen eingesetzt. Die krampflösende Wirkung von Phenytoin beruht auf einer Hemmung von Natriumkanälen, wodurch das Membranpotential zentraler und peripherer Nervenzellen stabilisiert wird.

Gene

Welche Gene beeinflussen die Wirkung von Phenytoin?

Die Verträglichkeit von Phenytoin wird maßgeblich durch die Genotypen der *HLA-B*- und *CYP2C9*-Gene beeinflusst. Unter Phenytoin-Therapie können eine Reihe von Nebenwirkungen (Bradykardie, Tremor, Ataxie, Nystagmus, uvm.) sowie schwerwiegende Hautüberempfindlichkeitsreaktionen bei Trägern des *HLA-B*15:02*-Genotyps auftreten. Das *HLA-B*15:02*-Allel tritt in der asiatischen Bevölkerung (1-10 %) häufiger auf im Vergleich zu Europäern (<0,1 %). In Bezug auf das *CYP2C9*-Gen, das die Biotransformation von Phenytoin in der Leber katalysiert, sind jedoch in allen ethnischen Gruppen aktivitätsreduzierende Varianten bekannt, die zu einem teilweisen oder vollständigen Verlust der CYP2C9-Funktion und damit zu verschiedenen nachteiligen Auswirkungen führen können.

Test

Was wird getestet?

Der Genotyp des Patienten (insbesondere bei Asiaten) wird auf das *HLA-B*15:02*-Allel (*HLA-B*-Gen) getestet. Die Prüfung aktivitätsreduzierender *CYP2C9*-Genvarianten *(*2, *3)* wird jedoch für alle ethnischen Gruppen empfohlen.

Indikationen

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Phenytoin durchgeführt werden, um möglicherweise das Risiko schwerwiegender Nebenwirkungen durch Anpassung der Startdosis oder Wirkstoffwechsel zu verringern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Phenytoin-Therapie mit HLA-B-Genotyp

***HLA-B* Genotyp**	**Therapieempfehlung**
*HLA-B*15:02* negativ	Anwendung gemäß Fachinformation
*HLA-B*15:02* positiv, heterozygot oder homozygot	Phenytoin kontraindiziert, Wirkstoffwechsel

Tabelle 2: Empfehlungen für eine Phenytoin-Therapie in Abhängigkeit vom Phänotyp des CYP2C9-Gens

CYP2C9 Phänotyp (Metabolisiererhäufigkeit)	**Therapieempfehlung**
Schnelle Metabolisierer (64-91 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (8-36 %)	Startdosis um 25 % reduzieren
Langsame Metabolisierer (0,1-4 %)	Startdosis um 50 % reduzieren

Nota bene: Die Häufigkeit der *CYP2C9*2*- und **3*-Allele und -Diplotypen unterscheidet sich zwischen Rassen / ethnischen Gruppen[2].

Kosten

Die Kosten für die genetischen Analysen der *CYP2C9*- und *HLA-B*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Caudle KE, Rettie AE, Whirl-Carrillo M, et al. *Clinical pharmacogenetics implementation consortium* guidelines for *CYP2C9* and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014;96(5):542-548. doi:10.1038/clpt.2014.159

[2] https://www.pharmgkb.org/page/cyp2c9RefMaterials

FENITOIN

Genetički test za smanjenje rizika pri primjeni fenitoina

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja fenitoina?

Fenitoin se koristi u liječenju epilepsije te poremećaja srčanog ritma. Mehanizam antikonvulzivnog djelovanja fenitoina zasniva se na inhibiciji o naponu-ovisnih natrijskih kanala na membranama stanica središnjeg i perifernog živčanog sustava, što dovodi do stabilizacije membranskog potencijala.

Geni

Koji geni utječu na djelovanje fenitoina?

Odgovor na liječenje fenitoinom pod značajnim je utjecajem varijacija u *HLA-B* i *CYP2C9* genima. Uz brojne neželjene učinke, teške kožne reakcije preosjetljivosti mogu se javiti kod osoba *s HLA-B*15:02* genotipom. *HLA-B*15:02* alel veće je učestalosti u Azijata (1-10 %) nego u Europljana (<0,1 %). Ipak, varijante *CYP2C9* gena koje mogu dovesti do djelomičnog ili potpunog manjka funkcije CYP2C9, te posljedično do brojnih neželjenih učinaka, uočene su u svim populacijama. CYP2C9 odgovoran je za biotransformaciju fenitoina u jetri.

Analiza

Što se analizira?

Analiziraju se genske varijante *HLA-B, HLA-B*15:02* (osobito kod Azijata) i genske varijante *CYP2C9*2*, i *CYP2C9*3* kod svih populacija.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije uvođenja fenitoina u terapiju kako bi se smanjio rizik razvoja neželjenih učinaka na način da se prilagodi doza ili odabere drugi lijek.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Terapijske preporuke navedene u tekstu ispod temelje se na smjernicama *Clinical pharmacogenetics implementation consortium Guidelines (CPIC)*[1] i imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za terapiju fenitoinom ovisno o HLA-B genotipu

***HLA-B* genotip**	**Preporučena terapija**
*HLA-B*15:02*, negativan	Upotreba u skladu s uputama o lijeku
*HLA-B*15:02*, heterozigot ili homozigot	Upotreba fenitoina nije preporučena Preporučuje se odabrati drugi lijek

Tablica 2: Preporuke za terapiju fenitoinom ovisno o fenotipu CYP2C9

CYP2C9 fenotip (učestalost fenotipa)	**Preporučena terapija**
Normalan (ekstenzivni) metabolizator (64-91 %)	Upotreba u skladu s uputama o lijeku
Intermedijarni metabolizator (8-36 %)	Smanjiti početnu dozu za 25 %
Spori metabolizator (0,1-4 %)	Smanjiti početnu dozu za 50 %

Nota bene: Učestalost *CYP2C9*2* and **3* alela i diplotipova razlikuje se ovisno o rasnoj i etničkoj pripadnosti[2].

Troškovi

Troškovi genetičkog testa će biti refundirani pacijentima s državnim i privatnim osiguranjem ukoliko je testiranje indicirano od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Caudle KE, Rettie AE, Whirl-Carrillo M, et al. *Clinical pharmacogenetics implementation consortium* guidelines for *CYP2C9* and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014;96(5):542-548. doi:10.1038/clpt.2014.159

[2] https://www.pharmgkb.org/page/cyp2c9RefMaterials

PIROXICAM

Genetic test to minimize the risks related to therapy with piroxicam

Drug

What are the indications and the mechanisms of action of piroxicam?

Piroxicam is a nonsteroidal drug with analgesic, anti-inflammatory and antipyretic properties. Its therapeutic effects occur via inhibition of prostaglandin biosynthesis from arachidonic acid by cyclooxygenases 1 and 2 (COX-1 and COX-2). Piroxicam is a reversible non-selective inhibitor of both COX isoforms.

Genes

Which genes influence the effect of piroxicam?

Piroxicam is metabolized via the enzyme CYP2C9. A decrease in the CYP2C9 function decreases the metabolic clearance of piroxicam thus prolonging its plasma elimination half-life. Several variants of the gene with great variability in the enzymatic activity of CYP2C9 are known in the population.

Test

What is tested?

To determine the CYP2C9 metabolism type, the testing of *CYP2C9* gene variants *(*2,*3)* associated with significantly reduced *CYP2C9* enzyme activity is recommended.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the therapy with piroxicam, in order to minimize the risk of side effects such as gastrointestinal bleeding, hypertension, myocardial infarction, heart failure, and renal damage through an adjustment of the starting dose or the prescription of alternative therapy.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for piroxicam therapy according to the CYP2C9 genotype

***CYP2C9* Genotype / Phenotype**	**Therapy recommendation**
*CYP2C9*1/*1* / Normal metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*2* / Intermediate metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*3, *2/*2* / Intermediate metabolizer	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants or choose a drug metabolized by CYP2C9 but with a shorter half-life
*CYP2C9*2/*3, *3/*3* / Poor metabolizer	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants or choose a drug metabolized by CYP2C9 but with a shorter half-life

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

PIROXICAM

Gentest zur Risikominimierung der Therapie mit Piroxicam

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Piroxicam?

Piroxicam ist ein nichtsteroidales Medikament mit entzündungshemmenden, analgetischen und fiebersenkenden Eigenschaften. Seine therapeutischen Wirkungen treten über die Hemmung der Prostaglandin-Biosynthese aus Arachidonsäure durch die Cyclooxygenasen (COX)-Isoformen 1 und 2 auf. Piroxicam ist ein reversibler nichtselektiver Inhibitor beider COX-Isoformen..

Gene

Welche Gene beeinflussen die Wirkung von Piroxicam?

Piroxicam wird über das Enzym CYP2C9 metabolisiert. Eine Abnahme der CYP2C9-Funktion verringert die metabolische Clearance (Ausscheidung) von Piroxicam und verlängert so die Halbwertszeit der Plasmaelimination. In der Population sind mehrere Varianten des *CYP2C9*-Gens mit großer Variabilität der enzymatischen Aktivität von CYP2C9 bekannt.

Test

Was wird getestet?

Zur Bestimmung des CYP2C9-Metabolismus wird empfohlen, *CYP2C9*-Genvarianten *(*2, *3)* zu testen, die mit einer signifikant verringerten CYP2C9-Enzymaktivität assoziiert sind.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der Therapie mit Lornoxicam durchgeführt werden, um das Risiko für Nebenwirkungen wie gastrointestinale Blutungen, Bluthochdruck, Myokardinfarkt, Herzinsuffizienz und Nierenschäden durch Anpassung der Anfangsdosis oder der Verschreibung einer alternativen Behandlung zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Piroxicam-Therapie in Abhängigkeit vom CYP2C9-Genotyp

***CYP2C9* Genotyp / Phänotyp**	**Therapieempfehlung**
*CYP2C9*1/*1* / Normale Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*2* / Intermediäre Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*3, *2/*2* / Intermediäre Metabolisierer	Start mit der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder empfohlene maximale Dosis, insbesondere bei Vorliegen von Leberfunktionsstörung oder höherem Alter
*CYP2C9*2/*3, *3/*3* / Langsame Metabolisierer	Start mit 25-50 % der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder 25-50 % der empfohlenen maximalen Dosis Alternativ: Wechsel auf Wirkstoff ohne CYP2C9-Metabolismus

Kosten

Die Kosten für die genetische Analyse des *CYP2C9* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

PIROKSIKAM

Genetički test za smanjenje rizika pri primjeni piroksikama

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja piroksikama?

Piroksikam je nesteroidni lijek s analgetskim, protuupalnim i antipiretskim djelovanjem. Njegov mehanizam djelovanja temelji se na inhibiciji biosinteze prostaglandina putem arahidonske kiseline djelovanjem enzima ciklooksigenaze (COX), izoformi 1 i 2. Piroksikam je reverzibilni ne-selektivni inhibitor obje COX izoforme.

Geni

Koji geni utječu na djelovanje piroksikama?

Piroksikam se metabolizira putem enzima CYP2C9. Smanjenje funkcije CYP2C9 usporava eliminaciju piroksikama iz organizma i produljuje poluvrijeme eliminacije. Poznato je nekoliko varijanti *CYP2C9* gena s velikom varijabilnošću u enzimskoj aktivnosti CYP2C9 u populaciji.

Test

Što se analizira?

Kako bi se odredio metabolizam s obzirom na CYP2C9, preporučuje se utvrđivanje prisutnosti varijanti *CYP2C9* gena *(*2, *3)* koje su povezane sa značajno reduciranim kapacitetom enzimske aktivnosti.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije piroksikamom kako bi se smanjio rizik neželjenih nuspojava kao što su gastrointestinalno krvarenje, hipertenzija, infarkt miokarda, srčano zatajenje i bubrežno oštećenje na način da se prilagodi početna doza ili propiše druga terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje piroksikamom ovisno CYP2C9 genotipu

***CYP2C9* genotip / fenotip**	**Preporučena terapija**
*CYP2C9*1/*1* / Normalni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*2* / Intermedijarni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*3, *2/*2* / Intermedijarni metabolizator	Potrebno je odabrati lijek koji se ne metabolizira putem CYP2C9 ili čiji metabolizam ne ovisi značajno o *CYP2C9* genotipu ili lijek s kraćim poluvremenom eliminacije
*CYP2C9*2/*3, *3/*3* / Spori metabolizator	Potrebno je odabrati lijek koji se ne metabolizira putem CYP2C9 ili čiji metabolizam ne ovisi značajno o *CYP2C9* genotipu ili lijek s kraćim poluvremenom eliminacije

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *CYP2C9* varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *CYP2C9* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

RASBURICASE

Genetic test to minimize the risks related to therapy with rasburicase

Drug

What are the indications and mechanisms of action of rasburicase?

Rasburicase is an enzyme, recombinant urate oxidase. It catalyses the enzymatic oxidation of uric acid to allantoin, a hydrophilic substance which can easily be excreted in the urine via the kidneys. Rasburicase is approved for prophylaxis and treatment of hyperuricemia during chemotherapy in adults and children with lymphoma, leukemia, and solid tumors. Rasburicase has also been used in newborns who have high uric acid associated with kidney injury.

Genes

What genes influence the effect of rasburicase?

The enzymatic oxidation of uric acid leads to an increase in the production of oxygen radicals and hydrogen peroxide which means higher oxidative stress. Glucose 6-phosphate dehydrogenase (G6PD) produces NADPH which is required to protect erythrocytes from oxidative stress. G6PD-deficient erythrocytes have a much reduced capacity for NADPH production; therefore, they are defective in handling oxidative stress and are thus more susceptible to drug-induced lysis (including from rasburicase), which can manifest clinically as hemolytic anemia or methemoglobinemia.

Test

What is tested?

The genotype of the patient is tested with regard to the *G6PD* gene.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with rasburicase in order to change the active agent, as required, so that severe side effects can be avoided.

Consequences and test results

How does the therapy need to be adjusted to the results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and updated data (September 2018) from G6PD Definition Table[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for rasburicase therapy depending on the G6PD phenotype of the G6PD gene

G6PD Phenotype	Recommended therapy
Normal	Usage according to the Summary of Product Characteristics
Deficient or deficient with chronic nonspherocytic hemolytic anemia	The usage of rasburicase is not recommended. The prescription of an alternative agent is recommended
Variable	To ascertain that G6PD status is normal, enzyme activity must be measured

Cost

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Relling MV, McDonagh EM, Chang T, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014;96(2):169-174. doi:10.1038/clpt.2014.97

[2] https://cpicpgx.org/guidelines/guideline-for-rasburicase-and-g6pd/

RASBURICASE

Gentest zur Risikominimierung der Therapie mit Rasburicase

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Rasburicase?

Rasburicase ist eine rekombinante Uratoxidase. Es katalysiert die enzymatische Oxidation von Harnsäure zu Allantoin, einer hydrophilen Substanz, die leicht über die Nieren im Urin ausgeschieden werden kann. Rasburicase ist zur Prophylaxe und Behandlung von Hyperurikämie während der Chemotherapie bei Erwachsenen und Kindern mit Lymphom, Leukämie und soliden Tumoren zugelassen. Der Wirkstoff wurde auch bei Neugeborenen mit hohem Harnsäuregehalt im Zusammenhang mit Nierenverletzungen angewendet.

Gene

Welche Gene beeinflussen die Wirkung von Rasburicase?

Die enzymatische Oxidation von Harnsäure führt zu erhöhter Produktion von Sauerstoffradikalen und Wasserstoffperoxid, was einen höheren oxidativen Stress bedeutet. Glucose-6-phosphat-Dehydrogenase (G6PD) produziert das nötige NADPH, um Erythrozyten vor oxidativem Stress zu schützen. G6PD-defiziente Erythrozyten besitzen eine geringe Kapazität für die NADPH-Produktion. Diese Defizienz führt zu erhöhtem oxidativem Stress und Anfälligkeit von medikamenteninduzierter Lyse (einschließlich Rasburicase), die sich klinisch als hämolytische Anämie oder Methämoglobinämie manifestieren kann.

Test

Was wird getestet?

Das Erbgut des Patienten wird hinsichtlich des *G6PD*-Gens getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Rasburicase durchgeführt werden, um gegebenfalls den Wirkstoff zu wechseln, damit schwerwiegende Nebenwirkungen vermieden werden können.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und den aktualisierten Daten (September 2018) aus der *G6PD*-Definitionstabelle[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Rasburicase-Therapie mit G6PD-Phänotyp

G6PD Phänotyp	Therapieempfehlung
Normal	Anwendung gemäß Fachinformation
Mangel oder Mangel an chronischer nicht-sphärozytischer hämolytischer Anämie	Rasburicase kontraindiziert, Wirkstoffwechsel
Variabel	Messung Enzymaktivität

Kosten

Die Kosten für die genetische Analyse des *G6PD*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Relling MV, McDonagh EM, Chang T, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014;96(2):169-174. doi:10.1038/clpt.2014.97

[2] https://cpicpgx.org/guidelines/guideline-for-rasburicase-and-g6pd/

RASBURIKAZA

Genetički test za smanjenje rizika pri primjeni rasburikaze

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja rasburikaze?

Razburikaza je enzim, rekombinantna urat-oksidaza. Rasburikaza katalizira enzimsku oksidaciju mokraćne kiseline u alantoin, vodotopljiv produkt koji se lako izlučuje iz organizma bubrežnim putem. Odobrena je za prevenciju i liječenje hiperuricemije kod odraslih i djece oboljelih od limfoma, leukemije ili solidnih tumora. Također se koristi kod novorođenčadi koja ima visoke koncentracije mokraćne kiseline povezane sa zatajenjem bubrega.

Geni

Koji geni utječu na djelovanje rasburikaze?

Enzimska razgradnja mokraćne kiseline dovodi do povećanog stvaranja oksidansa (uključujući vodikov peroksid i kisikove radikale). Glukoza-6-fosfat-dehidrogenaza (G6PD) proizvodi NADPH, ključan za zaštitu eritrocita od oksidativnog stresa. Eritrociti koji imaju deficijenciju G6PD imaju smanjeni kapacitet proizvodnje NADPH, stoga su u nemogućnosti nositi se s oksidativnim stresom zbog čega se povećava mogućnost njihove lize potaknuta lijekovima (uključivo i rasburikazu), koja se klinički manifestira kao akutna hemolitička anemija ili methemoglobinemija.

Analiza

Što se analizira?

Analizira se genotip *G6PD*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije uvođenja terapije rasburikazom, kako bi se mogao propisati drugi lijek s manjim rizikom od nuspojava.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke se temelje na *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines[1] i novim podacima (rujan 2018) o definiraju *G6PD* alela[2] te imaju najvišu razinu kliničke značajnosti 1A.

Tablica 1: Preporuke za korištenje rasburikaze ovisno o G6PD fenotipu

G6PD fenotip	Preporučena terapija
Normalan	Upotreba u skladu s uputama o lijeku
Deficijentan ili deficijentan s kroničnom nesferocitnom hemolitičkom anemijom	Upotreba rasburikaze se ne preporučuje Preporučuje se upotreba alternativnog lijeka
Varijabilan	Potrebno je određivanje enzimske aktivnosti G6PD kako bi se dokazao normalni fenotip G6PD

Troškovi

Troškovi genetičkog testa bit će refundirani pacijentima s državnim i privatnim osiguranjem ukoliko je testiranje indicirano od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Relling MV, McDonagh EM, Chang T, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014;96(2):169-174. doi:10.1038/clpt.2014.97

[2] https://cpicpgx.org/guidelines/guideline-for-rasburicase-and-g6pd/

RIBAVIRINE AND PEGINTERFERON α

Genetic test to minimize the risks related to therapy with ribavirin and peginterferon α

Drug

What are the indications and mechanisms of action of ribavirin and peginterpheron α?

Ribavirin is a virostatic agent is used in combination therapy with peginterferon α-2a and 2b for the treatment of chronic hepatitis C (type 1). Ribavirin belongs to the group of nucleoside analogues and blocks viral RNA and DNA synthesis as an antimetabolite. Ribavirin is excreted at a slow rate and accumulates intracellularly.

The peginterferons α-2a and 2b have antiviral and anti-proliferative properties. Their effect is based on the tissue-specific binding to specific interferon receptors on the cell surface. Intracellular signal pathways that inhibit the cell growth and thereby also virus replication are regulated as a result. The exact mechanism of action is not known. Through the binding of the polyethylene glycol to interferons (pegylation), a significantly slower release of interferons is achieved and the effect is prolonged by 5 hours in comparison with native interferon α-2a.

Genes

Which genes influence the effect of ribavirine and peginterpheron α

The therapeutic success of ribavirin and peginterferon α is significantly associated with the genotype of the variant *c.151-152C>T* (rs12979860) in the *interferon lambda-3* (*IFNL3*) gene. The IFNL3 protein is primarily formed in the liver and in the epithelial cells. Therapeutic success is prognosticated based on the sustained virological response (SVR) rate, which is defined by the lack of viral RNA in the blood serum after 12-24 weeks of treatment.

Test

What will be tested?

The patient's genotype is tested for the risk *IFNL3* variant c.151-152C>T.

Indication

When should be a test performed?

The genetic test should be performed before the start of planned combination therapy with ribavirin and peginterferon α in order to assess the benefit of therapy.

Consequences and test results

How does the therapy have to be adapted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium* guidelines[1] and has the highest level of evidence 1A.

Table 1: Recommendations for ribavirine/peginterferon therapy subject to IFNL3 genotype

***IFNL3* Genotype**	**Prognosis of therapeutic success under ribavirine/peginterpheron α**
Wild type	The therapeutic success of 70 % is estimated, higher SVR rates are expected
Risk variant, homozygous or heterozygous	The therapeutic success of 30 % is estimated, lower SVR rates are expected, the benefit of therapy is questionable

Nota bene: SVR, sustained virologic response is defined by undetectable serum viral RNA 12–24 weeks after the end of treatment.

Costs

Costs for the *IFNL3* genotyping will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

[1] Muir AJ, Gong L, Johnson SG, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for IFNL3 (IL28B) genotype and PEG interferon-α-based regimens. Clin Pharmacol Ther. 2014;95(2):141-146. doi:10.1038/clpt.2013.203

RIBAVIRIN UND PEG PEGINTERPHERON-α

Gentest zur Risikominimierung der Therapie mit Rasburicase und Peginterpheron-α

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Ribavirin und PEG-Interferon-α?

Ribavirin ist ein virostatisches Mittel, das in der Kombinationstherapie mit PEG-Interferon-α 2a und 2b zur Behandlung der chronischen Hepatitis C vom Typ 1 eingesetzt wird. Ribavirin gehört zur Gruppe der Nukleosidanaloga und blockiert als Antimetabolit die virale RNA- und DNA-Synthese. Ribavirin wird nur langsam ausgeschieden und kumuliert intrazellulär.

Die Peginterpheron-α 2a und 2b sind Wirkstoffe aus der Gruppe der Interferone mit antiviralen und antiproliferativen Eigenschaften, die zur Behandlung der viralen chronischen Hepatitis eingesetzt werden. Ihre Wirkung beruht auf der gewebespezifischen Bindung an Interferonrezeptoren auf der Zelloberfläche. Dadurch werden intrazelluläre Signalwege reguliert, die das Zellwachstum und damit auch die Virusreplikation hemmen.

Durch die Bindung des Mittels an Polyethylenglykol (Pegylierung) wird eine signifikant langsamere Freisetzung von Interferonen erreicht und die Wirkung im Vergleich zu nativem Interferon-α 2a um 5 Stunden verlängert.

Gene

Welche Gene beeinflussen die Wirkung von Ribavirin und PEG-Interferon-α?

Der therapeutische Erfolg von Ribavirin und Peginterpheron-α ist signifikant mit dem Genotyp der Variante *c.151-152C> T* (rs12979860) im *Interferon-Lambda-3* (*IFNL3*) - Gen assoziiert. Das IFNL3-Protein wird hauptsächlich in der Leber und in den Epithelzellen gebildet. Anhand der virologischen Ansprechrate (SVR *Sustained Virological Response*), die durch das Fehlen viraler RNA im Blutserum nach 12 bis 24 Wochen Behandlung definiert ist, wird der therapeutische Erfolg prognostiziert.

Test

Was wird getestet?

Das Erbgut des Patienten wird im *IFNL3*-Gen auf die Risikogenvariante *c.151-152C> T* untersucht.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Kombinationstherapie mit Ribavirin und Peginterpheron-α durchgeführt werden, um den Nutzen der Therapie abzuschätzen.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Ribavirin-PEG-Interferon-Therapie mit IFNL3-Genotyp

***IFNL3* Genotyp**	**Therapieerfolgsprognose unter Ribavirin/PEG-Interferon-α**
Wildtyp	Prognose: Therapieerfolg von 70 %, höhere SVR-Rate erwartet
Risikovariante, homozygot oder heterozygot	Prognose: Therapieerfolg von 30 %, niedrigere SVR-Rate erwartet; Nutzen der Therapie fraglich

Nota bene: SVR, anhaltende virologische Reaktion (definiert durch nicht nachweisbare virale Serum-RNA 12–24 Wochen nach Behandlungsende).

Kosten

Die Kosten für die genetische Analyse des *IFNL3*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Muir AJ, Gong L, Johnson SG, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for IFNL3 (IL28B) genotype and PEG interferon-α-based regimens. Clin Pharmacol Ther. 2014;95(2):141-146. doi:10.1038/clpt.2013.203

RIBAVIRIN I PEGINTERFERON α

Genetički test za smanjenje rizika povezanog s primjenom ribavirina i peginterferona α (2a i 2b)

Lijek

Koje su indikacije i mehanizmi djelovanja ribavirina i peginterferona α?

Ribavirin je antivirusni lijek koji se primjenjuje pri liječenju kroničnog hepatitisa C (tip 1) u kombinaciji s peginterferonom α 2a i 2b. Ribavirin pripada skupini nukleozidnih analoga i blokira sintezu virusne RNA i DNA, djelujući kao antimetabolit. Ribavirin se nakuplja u stanicama i izlučuje se vrlo sporo.

Peginterferoni α 2a i 2b imaju antivirusni i antiproliferativni učinak. Njihovo djelovanje temelji se na vezivanju za specifične interferonske receptore na površini stanice. Putem toga se reguliraju unutarstanični signalni putevi koji zaustavljaju rast stanice i samim time i replikaciju virusa. Točan mehanizam djelovanja još nije poznat. Vezivanjem polietilenglikolskih lanaca (pegilacija) postiže se sporije oslobađanje interferona, a djelovanje se u odnosu na prirodni interferon α-2a produžuje za 5 sati.

Geni

Koji geni utječu na djelovanje ribavirina i peginterferona α?

Terapijski učinci ribavirina i peginterferona α značajno su povezani s varijantom *c.151-152C>T* (rs12979860) gena *IFNL3* (interferon lambda 3). Protein IFNL3 se prije svega stvara u jetri kao i u epitelnim stanicama. Uspjeh liječenja se može prognozirati na temelju određivanja održanog virološkog odgovora (eng., sustained virological response, SVR), koji je definiran nepostojanjem virusne RNA u serumu nakon 12-24 tjedana od završetka liječenja.

Analiza

Što se analizira?

Analizira se *IFNL3* genotip na varijantu *c.151-152C>T*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka planirane kombinirane terapije ribavirinom i peginterferonom α u svrhu procjene koristi same terapije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke se temelje na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] i imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje ribavirinom i peginterferonom α ovisno o genotipu IFNL3

***IFNL3* Genotip**	**Prognoza uspješnosti terapije ribavirinom/peginterferonom α**
Divlji tip (wt/wt)	Terapijski učinak 70 % očekivanog, očekivano veći SVR
Rizična varijanta, homozigot ili heterozigot	Terapijski učinak 30 % očekivanog, očekivano niža stopa SVR-a, korist terapije upitna

Napomena: Održivi virološki odgovor (SVR) definiran je nepostojanjem virusne RNA u serumu 12-24 tjedna nakon završetka liječenja.

Troškovi

Troškovi genetičkog testa bit će refundirani pacijentima s državnim i privatnim osiguranjem ukoliko je testiranje indicirano od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Muir AJ, Gong L, Johnson SG, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines for IFNL3 (IL28B) genotype and PEG interferon-α-based regimens. Clin Pharmacol Ther. 2014;95(2):141-146. doi:10.1038/clpt.2013.203

SERTRALINE

Genetic test to minimize the risks related to therapy with sertraline

Drug

What are the indications and mechanism of action of sertraline?

Sertraline belongs to the class of drugs called selective serotonin reuptake inhibitors (SSRIs). They are typically used in the treatment of major depressive disorder and anxiety disorders. SSRIs increase the extracellular level of serotonin, by limiting its reuptake into the presynaptic cell, thus increasing the level of serotonin in the synaptic cleft and its binding to presynaptic and the postsynaptic receptors.

Genes

Which genes influence the effect of sertraline?

Sertraline is extensively metabolized by CYP2C19 to inactive metabolites. *CYP2C19* genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis.

Test

What will be tested?

Commonly reported *CYP2C19* star-alleles are categorized into functional groups (e.g., normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme. To determine the CYP2C19 metabolism type, the patients' *CYP2C19* genotype is tested for the most common activity-variant variants (*1, *2, *17).

Indications

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with sertraline in order to change the active agent, or reduce the starting dose, as required, so that adverse effects can be avoided.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for therapy with sertraline depending on the phenotype of the CYP2C19 gene

CYP2C19 **Genotype / Phenotype (metabolizer status frequencies)**	**Recommended therapy**
*17/*17, *1/*17 / Ultrarapid metabolizer (5-30 %)	Initiate the starting dose. If no therapeutic response is present, the prescription of an alternative agent is recommended
*1/*1 / Rapid metabolizer (35-50 %)	Usage according to the Summary of Product Characteristics
*1/*2, *1/*3, *2/*17 / Intermediate metabolizer (18-45 %)	Usage according to the Summary of Product Characteristics
*2/*2, *2/*3, *3/*3 / Poor metabolizer (2-15 %)	Reduction of starting dose by 50 %, titration is needed for higher target doses, or use an alternative drug

Costs

Costs for the determination of enzymatic status are reimbursed for patients with statutory or private health insurance if testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

SERTRALIN

Gentest zur Risikominimierung der Therapie mit Sertralin

Wirkstoff

Was sind die Indikationen und der Wirkmechanismus von Sertralin?

Sertralin ist ein selektiver Serotonin-Wiederaufnahmehemmer (SSRIs), der als Antidepressiva bei der Behandlung von Depressionen und Angststörungen eingesetzt wird. Der genaue Wirkungsmechanismus von SSRIs ist unbekannt. Es wird angenommen, dass eine Erhöhung des extrazellulären Serotoninspiegel im synaptischen Spalt durch Limitierung der Reabsorption (Wiederaufnahme) in die präsynaptische Zelle erreicht wird. Es sind unterschiedliche Selektivitätsgrade für die anderen Monoamintransporter vorhanden, wobei reine SSRIs nur eine schwache Affinität für die Norepinephrin- und Dopamintransporter aufweisen. Sertralin blockiert selektiv überwiegend den Serotonintransporter (SERT).

Gene

Welche Gene beeinflussen die Wirkung von Sertralin?

Sertralin wird durch CYP2C19 weitgehend zu inaktiven Metaboliten metabolisiert. Genetische *CYP2C19*-Varianten werden typischerweise als Haplotypen angegeben, die durch eine spezifische Kombination von Einzelnukleotidpolymorphismen (SNPs) und/oder anderen Sequenzvarianten definiert sind, einschließlich Insertionen und Deletionen, die während der Genotypisierungsanalyse abgefragt werden.

Test

Was wird getestet?

Häufig berichtete *CYP2C19*-Allele werden basierend auf der vorhergesagten Aktivität des kodierten Enzyms in Phänotypen (ultraschnelle-schnelle-normale-langsame) eingeteilt. Um den CYP2C19-Metabolismustyp zu bestimmen, wird der Genotyp des Patienten im *CYP2C19*-Gen *(*1, *2, *3, *17)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Sertralin durchgeführt werden, um den Wirkstoff zu wechseln oder die Anfangsdosis nach Bedarf zu reduzieren, damit Nebenwirkungen vermieden werden können.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt für *CYP2C19* das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Sertralin-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

***CYP2C19* Genotyp / Phänotyp (Metabolisierungshäufigkeit)**	**Therapieempfehlung**
**17/*17, *1/*17* / Ultraschnelle Metabolisierer (5-30 %)	Therapie mit Startdosis beginnen Wenn keine Reaktion: Wirkstoffwechsel empfohlen
**1/*1* / Schnelle Metabolisierer (35-50 %)	Therapie gemäß Fachinformation
**1/*2, *1/*3, *2/*17* / Intermediäre Metabolisierer (18-45 %)	Therapie gemäß Fachinformation
**2/*2, *2/*3, *3/*3* / Langsame Metabolisierer (2-15 %)	Startdosis um 50 % reduzieren, auf höhere Zieldosis titrieren

Kosten

Die Kosten für die genetische Analyse des *CYP2C19*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

SERTRALIN

Genetički test za smanjenje rizika pri primjeni sertralina

Lijek

Koje su indikacije i mehanizmi djelovanja sertralina?

Sertralin pripada skupini lijekova koji se nazivaju selektivni inhibitori ponovne pohrane serotonina (eng. selective serotonin reuptake inhibitors, SSRI). Sertralin se koristi u lije**če**nju depresivnih i anksioznih poremećaja. Inhibira ponovni povrat serotonina u presinaptički neuron čime se povećava njegova količina u sinaptičkoj pukotini, kao i vezanje za presinaptičke i postsinaptičke receptore.

Geni

Koji geni utječu na djelovanje sertralina?

Sertralin se ekstenzivno metabolizira putem CYP2C19 enzima do inaktivnih metabolita. *CYP2C19* genetičke varijante tipično se opisuju kao haplotipovi, koji su definirani pomoću specifične kombinacije polimorfizma jednog nukleotida (SNP) i drugih varijacija, uključujući insercije i delecije, koje se ispituju tijekom genotipizacije.

Analiza

Što se analizira?

CYP2C19 aleli označeni zvjezdicom kategoriziraju u funkcionalne skupine (npr. pojačana funkcija, normalna funkcija, oslabljena funkcija) prema predviđenoj aktivnosti kodiranog enzima. Za određivanje vrste CYP2C19 metabolizma, pacijentov *CY2C19* genotip se testira za česte varijante (*1, *2, *3, *17).

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka terapije sertralinom kako bi se mogao primijeniti zamjenski lijek, ukoliko je potrebno, da se izbjegnu značajne nuspojave.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za terapiju sertralinom ovisno o CYP2C19 genotipu

***CYP2C19* Genotip / Fenotip (učestalost metabolizatora)**	**Preporučena terapija**
**17/*17, *1/*17* / Ultrabrzi metabolizator (5-30 %)	Započeti s početnom dozom. Ukoliko nema terapijskog odgovora, preporučuje se zamjenski lijek
**1/*1* / Brzi metabolizator (35-50 %)	Terapija sukladno uputama o lijeku
**1/*2, *1/*3, *2/*17* / Intermedijarni metabolizator (18-45 %)	Terapija sukladno uputama o lijeku
**2/*2, *2/*3, *3/*3* / Spori metabolizator (2-15 %)	Smanjiti početnu dozu na 50 % normalne doze. Titracija je potrebna za više doze ili korištenje zamjenskog lijeka

Troškovi

Troškovi za određivanje *CYP2C19* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje ukoliko je testiranje zatraženo od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Hicks JK, Bishop JR, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147

SEVOFLURANE

Genetic test to minimize the risk of malignant hyperthermia (MH) related to the therapy with sevoflurane

Drug

What are the indications and mechanisms of action of sevoflurane?

Sevoflurane is generally a safe volatile inhaled anesthetic used for inducing general anesthesia. Its mechanism of action is complex and includes a reduction in junctional conductance by decreasing gap junction channel opening times and increasing gap junction channel closing times. It also activates calcium-dependent ATPase in the sarcoplasmic reticulum by increasing the fluidity of the lipid membrane. Sevoflurane probably binds to various neurotransmitter receptors (like GABA, glycine, glutamate) and ion channels and interacts with the nerve membranes.

Genes

Which genes influence the effect of sevoflurane?

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the *RYR1* and *CACNA1S* genes under consideration here predispose individuals to a severe and sometimes lethal hypermetabolic reaction whose symptoms include muscle rigidity, high fever, and a fast heart rate. Complications can include rhabdomyolysis and high blood potassium.

Test

What will be tested?

The genotype of the ryanodine receptor isoform 1 protein *(RYR1)* is tested for one of the 48 causative single-nucleotide variants or one deletion that are designated diagnostic MH mutations[1]. The α1S subunit of the dihydropyridine receptor *(CACNA1S)* is tested for the 2 known variants that are MH susceptible. Since MH susceptibility is inherited in an autosomal-dominant pattern, a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as diagnostic for the trait.

Indication

When should a test be performed?

Genetic testing should be carried out before the initiation of the scheduled therapy with sevoflurane in order to predict the risk of MH.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for sevoflurane therapy depending on the phenotype of the RYR1 and CACNA1S genes

RYR1 or CACNA1S Phenotype	Recommended therapy
Malignant hyperthermia susceptible	Sevoflurane is not recommended due to MH susceptibility, use alternative anesthetics
Uncertain susceptibility	Clinical findings, family history, further genetic testing, and other laboratory data should guide the use of sevoflurane

Costs

Costs for the determination of the *RYR1* and *CACNA1S* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

SEVOFLURAN

Gentest zur Risikominimierung der Therapie mit Sevofluran bei maligner Hyperthermie (MH)

Wirkstoff

Was sind die Indikationen und der Wirkmechanismus von Sevofluran?

Sevofluran ist ein weit verbreitetes und allgemein sicheres flüchtiges Inhalationsanästhetikum, das zur Einleitung einer Vollnarkose verwendet wird. Sein Wirkungsmechanismus ist komplex und umfasst eine Verringerung der Verbindungsleitfähigkeit durch verringerte Öffnungszeiten und erhöhte Schließzeiten von *gap junction*-Kanälen. Es aktiviert auch die Calcium-abhängige ATPase im sarkoplasmatischen Retikulum, indem es die Fluidität der Lipidmembran erhöht. Es wird hypothetisiert, dass Sevofluran an verschiedene Neurotransmitter-Rezeptoren und Ionenkanäle (wie GABA, Glycin, Glutamat) bindet und mit Nervenmembranen interagiert.

Gene

Welche Gene beeinflussen die Wirkung von Sevofluran?

Im Gegensatz zu vielen verwertbaren pharmakogenetischen Merkmalen, die den Metabolismus und/oder die Ausscheidung eines Arzneimittels beeinflussen, prädisponieren die hier betrachteten Varianten der Gene *RYR1* und *CACNA1S* zu einer schweren und manchmal tödlichen hypermetabolischen Reaktion, zu deren Symptomen Muskelsteifheit, hohes Fieber und schnelle Herzfrequenz gehören. Weitere Komplikationen können Rhabdomyolyse und hohe Kaliumwerte im Blut darstellen.

Test

Was wird getestet?

Der Genotyp des Ryanodinrezeptor-Isoform-1-Proteins *(RYR1)* wird auf eine der 48 Einzelnukleotidvarianten und eine Deletion getestet, die als diagnostische maligne Hyperthermie (MH)-Mutation[1] bezeichnet werden. Die α1S-Untereinheit des Dihydropyridinrezeptors *(CACNA1S)* wird auf die beiden bekannten Varianten getestet, die für maligne Hyperthermie anfällig sind. Da die Anfälligkeit für maligne Hyperthermie (MHS) in einem autosomal-dominanten Muster vererbt wird, kann ein heterozygoter Genotyp einer pathogenen Variante in *RYR1* als diagnostisch für das Merkmal angesehen werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn der geplanten Therapie mit Desfluran durchgeführt werden, um das Risiko einer bösartigen Hyperthermie zu verringern. Alle nichtdepolarisierenden Muskelrelaxantien außer den Hyperthermie-auslösenden starken, flüchtigen Anästhetika, alle intravenösen Induktionsmittel sowie die verlängerte Inhalationsanästhesie mit nicht auslösenden Mitteln stellen Alternativen dar, die nicht mit bösartiger Hyperthermie assoziiert sind.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Sevofluran-Therapie mit Phänotyp der RYR1- und CACNA1S-Gene

RYR1 oder CACNA1S Phänotyp	Therapieempfehlung
Maligne Hyperthermie Anfälligkeit	Sevofluran kontraindiziert, Anästhetikawechsel empfohlen
Unsichere Anfälligkeit	Klinische Befunde, Familienanamnese, weitere Gentests und andere Labordaten sollten den Einsatz von Sevofluran anleiten

Kosten

Die Kosten für die genetische Analyse der *RYR1 and CACNA1S*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

SEVOFLURAN

Genetički test za smanjenje rizika pojave maligne hipertermije pri primjeni sevoflurana

Lijek

Koje su indikacije i mehanizmi djelovanja sevoflurana?

Sevofluran je siguran hlapljivi inhalacijski anestetik koji se često koristi za indukciju opće anestezije. Njegov mehanizam djelovanja je kompleksan, a uključuje smanjenje provodljivosti skraćivanjem vremena otvaranja kanala na pukotinskim spojevima (gap junctions) i produljujući vrijeme zatvaranja istih. Također aktivira o kalciju ovisnu ATPazu na sarkoplazmatskom retikulumu povećanjem fluidnosti lipidne membrane. Sevofluran se vjerojatno veže na više neurotransmiterskih receptora (poput GABA, glicinskog i glutamatnog), ionskih kanala te ulazi u interakciju s membranama neurona.

Geni

Koji geni utječu na djelovanje sevoflurana?

Za razliku od mnogih drugih lijekova kojima polimorfizmi utječu na metabolizam ili ekskreciju, polimorfizmi *RYR1* i *CACNA1S* gena su predisponirajući za tešku i smrtonosnu hipermetaboličku reakciju, čiji simptomi uključuju: rigidnost mišića, visoku tjelesnu temperaturu, tahikardiju. Komplikacije uključuju rabdomiolizu i hiperkalemiju.

Analiza

Što se analizira?

Genotip rajanodinskog receptora izoforme 1 *(RYR1)* testira se na jedan od 48 nukleotidnih polimorfizama ili jednu deleciju koje su označene kao dijagnostičke mutacije za malignu hipertermiju[1]. α1S podjedinica dihidropiridinskog receptora *(CACNA1S)* se testira za jednu od 2 poznate mutacije koje su dijagnostičke za malignu hipertermiju. Budući da se navedeni geni nasljeđuju autosomno dominantno, heterozigotni genotip navedenih gena smatra se kao dijagnoza sklonosti malignoj hipertermiji.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka primjene sevoflurana kako bi se odredila sklonost ka nastanku maligne hipertermije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortiums (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za primjenu sevoflurana ovisno o fenotipu RYR1 i CACNA1S

RYR1 ili CACNA1S fenotip	Preporučena terapija
Osjetljivost za malignu hipertermiju	Ne preporučuje se primjena sevoflurana Potrebno je korištenje alternativnog anestetika
Neinformativan	Odluka o primjeni sevoflurana trebala bi se voditi kliničkom slikom, obiteljskom anamnezom, daljnjim genskim testiranjem i ostalim laboratorijskim podatcima

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

SIMVASTATIN

Genetic test to minimize the risks related to therapy with simvastatin

Drug

What are the indications and mechanisms of action of simvastatin?

Simvastatin is a lipid lowering medication and is used to treat hypercholesteremia of different origins and is used for the prevention of cardiovascular diseases. Like all statins, simvastatin inhibits the HMG-CoA reductase, the rate-limiting enzyme for the synthesis of cholesterol. This leads to an increased synthesis of LDL receptors and an elevated uptake of LDL in the hepatic cells. The levels of LDL and triglyceride in the blood decrease and the level of HDL increases.

Genes

What genes influence the effect of simvastatin?

Toxic myopathy, a structural and functional change of the skeletal muscles, which may lead to rhabdomyolysis is considered a severe side effect of statins (especially simvastatin). A variant in the *SLCO1B1* gene leading to a deficiency of the SLCO1B1 transport protein markedly increases systemic exposure to simvastatin and the risk of muscle toxicity.

Test

What is tested?

The genotype of patients is tested with regard to the genetic variant *c.521T>C* (p.Val174Ala) in the *SLCO1B1* gene which leads to a OATP1B1 protein deficiency.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with simvastatin in order to reduce the risk of myopathy, as required, by means of an adjustment of the dose or by prescribing an alternative statin (e.g. atorvastatin, rosuvastatin or pitavastatin).

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following procedure is based on the recommendations of the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] and has the highest clinical level of evidence 1A.

Table 1: Dosing recommendations for simvastatin therapy depending on the SLCO1B1 genotype according to the risk of myopathy

SLCO1B1 Genotype (frequency of the polymorphism)	Recommended therapy
Homozygous wild type or normal (55-85 %)	Use in accordance with the Summary of Product Characteristics
Risk variant, heterozygote (11-36 %)	Prescription at lower doses OR an alternative statin is recommended Routine creatine kinase surveillance is recommended
Risk variant, homozygous (0-6 %)	Prescription at lower doses OR an alternative statin is recommended Routine creatine kinase surveillance is recommended

Nota bene: Statin dose is the strongest independent predictor of myopathy risk and is roughly sixfold higher in patients on high-dose than on lower dose statin therapy[2].

Costs

Costs for the *SLCO1B1* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Ramsey LB, Johnson SG, Caudle KE, et al. The *clinical pharmacogenetics implementation consortium* guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014;96(4):423-428. doi:10.1038/clpt.2014.125

[2] McClure DL, Valuck RJ, Glanz M, Murphy JR, Hokanson JE. Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population. J Clin Epidemiol. 2007;60(8):812-818. doi:10.1016/j.jclinepi.2006.11.006

SIMVASTATIN

Gentest zur Risikominimierung der Therapie mit Simvastatin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Simvastatin?

Simvastatin ist ein Lipidsenker und wird zur Behandlung von Hypercholesterinämie verschiedener Genese und zur kardiovaskulären Prävention verordnet. Wie alle Statine hemmt Simvastatin die HMG-CoA-Reduktase, welches die Geschwindigkeit für die Cholesterinsynthese bestimmt. Dies führt zu einer erhöhten Synthese von LDL-Rezeptoren und zu einer erhöhten Aufnahme von LDL in die Leberzellen. Der LDL- und Triglyceridspiegel im Blut nimmt ab und der HDL-Spiegel steigt an.

Gene

Welche Gene beeinflussen die Wirkung von Simvastatin?

Die toxische Myopathie, eine strukturelle und funktionelle Veränderung der Skelettmuskulatur, die zu einer Rhabdomyolyse führen kann, wird als schwerwiegende Nebenwirkung von Statinen (insbesondere Simvastatin) angesehen. Ursächlich für die Muskelschädigung ist eine genetische Variante im *SLCO1B1*-Gen, die zu einem Mangel des SLCO1B1-Transportproteins und damit zu einem erhöhten Simvastatin-Blutspiegel und zu einem verzögerten Abbau von Statinen in der Leber führt. In der europäischen Bevölkerung sind etwa 15 Prozent Träger dieser Genvariante.

Test

Was wird getestet?

Das Erbgut der Patienten wird auf die Genvariante *c.521T> C* (p.Val174Ala) im *SLCO1B1*-Gen getestet, die zum OATP1B1-Proteinmangel führt.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Simvastatin durchgeführt werden, um gegebenfalls durch eine Dosisanpassung oder einen Wirkstoffwechsel (z.B. Atorvastatin, Rosuvastatin, Pitavastatin) das Myopathie-Risiko zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Dosierungsempfehlungen für die Simvastatin-Therapie mit SLCO1B1-Genotyp

***SLCO1B1* Genotyp (Häufigkeit des Polymorphismus)**	**Therapieempfehlung**
Wildtyp (55-85 %)	Anwendung gemäß Fachinformation
Risikovariante, heterozgot (11-36 %)	Niedrigere Dosis bei regelmäßigen CK-Kontrollen Wirkstoffwechsel (alternatives Statin)
Risikovariante, homozygot (0-6 %)	Niedrigere Dosis bei regelmäßigen CK-Kontrollen Wirkstoffwechsel (alternatives Statin)

Nota bene 1:CK, Creatinkinase.
Nota bene 2: Die Statindosis ist der stärkste unabhängige Prädiktor für das Myopathierisiko und bei Patienten mit hoher Dosis etwa sechsmal höher als mit einer Statintherapie mit niedrigerer Dosis[2].

Kosten

Die Kosten für die genetische Analyse des *SLCO1B1* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Ramsey LB, Johnson SG, Caudle KE, et al. The *clinical pharmacogenetics implementation consortium* guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014;96(4):423-428. doi:10.1038/clpt.2014.125

[2] McClure DL, Valuck RJ, Glanz M, Murphy JR, Hokanson JE. Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population. J Clin Epidemiol. 2007;60(8):812-818. doi:10.1016/j.jclinepi.2006.11.006

SIMVASTATIN

Genetički test za smanjenje rizika pri primjeni simvastatina

Lijek

Koje su indikacije i mehanizmi djelovanja lijeka simvastatina?

Simvastatin je lijek koji snižava koncentraciju lipida te se ordinira kod liječenja hiperkolesterolemije različite geneze kao i kod prevencije nastanka kardiovaskularnih bolesti. Poput svih statina, inhibira HMG-CoA reduktazu, enzim važan za sintezu kolesterola, što dovodi do povećane sinteze LDL receptora te povećanog prihvata LDL u stanicama jetre. Posljedično, razina LDL i triglicerida u krvi se snižava, te dolazi do blagog porasta razine HDL.

Geni

Koji geni utječu na djelovanje simvastatina?

Toksična miopatija, koja dovodi do strukturnih i funkcionalnih promjena skeletnih mišića, može dovesti do rabdomiolize i smatra se težom nuspojavom statina (posebno simvastatina). Varijanta u *SLCO1B1* genu koja dovodi do smanjene aktivnosti transportnog proteina OATP1B1 uzrok je povišene sistemske izloženosti simvastatinu te mišićne toksičnosti.

Analiza

Što se analizira?

Analizira se genotip pacijenta, posebice varijanta gena *SLCO1B1 c.521T>C* (p.Val174Ala), što dovodi do smanjene aktivnosti OATP1B1.

Indikacije

U kojem slučaju je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka planirane terapije simvastatinom kako bi se smanjio rizik od miopatija, prilagođavanjem doze ili ordiniranjem alternativnog statina (npr. atorvastatin, rosuvastatin ili pravastatin).

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Sljedeći postupak temelji se preporukama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] i ima najvišu kliničku evidencijsku razinu 1A.

Tablica 1: Preporuke za doziranje simvastatina ovisno o genotipu SLCO1B1 sukladno riziku za razvoj miopatija

***SLCO1B1* Genotip (učestalost polimorfizma)**	**Preporučena terapija**
Homozigot divlji tip ili normalni (55-85 %)	Terapija sukladno uputama o lijeku
Rizična varijanta, heterozigot (11-36 %)	Preporučuje se propisivanje nižih doza ili alternativni statin Uključiti redovitu kontrolu kreatin kinaze (CK)
Rizična varijanta, homozigot (0-6 %)	Preporučuje se propisivanje nižih doza ili alternativni statin Uključiti redovitu kontrolu kreatin kinaze (CK).

Nota bene: Preporučena doza statina najjači je neovisni pokazatelj razvoja statinske miopatije, koja je 6 puta učestalija kod primjene visokih doza statina u odnosu na niže doze[2].

Troškovi

Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize gena *SLCO1B1* bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Ramsey LB, Johnson SG, Caudle KE, et al. The *clinical pharmacogenetics implementation consortium* guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014;96(4):423-428. doi:10.1038/clpt.2014.125

[2] McClure DL, Valuck RJ, Glanz M, Murphy JR, Hokanson JE. Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population. J Clin Epidemiol. 2007;60(8):812-818. doi:10.1016/j.jclinepi.2006.11.006

SIPONIMOD

Genetic test to minimize the risks related to therapy with siponimod

Drug

What are the indications and mechanisms of action of siponimod?

Siponimod is a selective sphingosine-1 phosphate receptor modulator used in secondary progressive multiple sclerosis (SPMS). In patients with active SPMS, siponimod reduces the risk of disabilities and relapses.

Genes

Which genes influence the effect of siponimod?

The metabolism of siponimod via the enzyme CYP2C9 determines the efficiency and duration of action. Several variants of the gene with great variability in the enzymatic activity of CYP2C9 are known in the population.

Test

What is tested?

To determine the CYP2C9 metabolism type, *CYP2C9* genotype is tested for the most common activity-variant variants (*1, *2, *3)

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with siponimod, in order to minimize side effects such as headache, hypertension and damage to the liver if necessary by means of adjusting the dose or changing the active ingredient.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following procedure is based on the recommendations of the *Dutch Pharmacogenetics Working Group Guideline* for siponimod[1,2].

Table 1: Dosage recommendations for siponimod therapy with the CYP2C9 genotype

***CYP2C9* Genotype**	**Therapy recommendation**
**1/*2, *2/*2*	Use in accordance with the Summary of Product Characteristics
**1/*3, *2/*3*	Reduce the recommended maintenance dosage by 50 % If a moderate or strong CYP3A4 inducer is used in combination, reconsider siponimod
**3/*3*	Siponimod contraindicated, choose an alternative medication

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-may-2020.pdf

[2] https://www.pharmgkb.org/labelAnnotation/PA166182738

SIPONIMOD

Gentest zur Risikominimierung der Therapie mit Siponimod

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Siponimod?

Siponimod ist ein selektiver Sphingosin-1-Phosphat-Rezeptor-Modulator, der bei sekundärer progressiver multipler Sklerose (SPMS) eingesetzt wird. Bei aktivem SPMS verringert Siponimod das Risiko von Behinderungen und Rückfällen.

Gene

Welche Gene beeinflussen die Wirkung von Siponimod?

Der Metabolismus von Siponimod über das Enzym CYP2C19 entscheidet über die Effizienz und Wirkdauer. In der Population sind mehrere Varianten des Gens mit großer Variabilität der enzymatischen Wirksamkeit von CYP2C19 bekannt.

Test

Was wird getestet?

Um den CYP2C19-Metabolismustyp zu bestimmen, wird der Genotyp des Patienten im *CYP2C19*-Gen *(*1, *2, *3)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der geplanten Therapie mit Siponimod durchgeführt werden, um gegebenfalls durch eine Dosisanpassung oder einen Wirkstoffwechsel Nebenwirkungen wie Kopfschmerzen, Hypertonie und Leberfunktionsschäden zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen der *Dutch Pharmacogenetics Working Group Guideline for siponimod*[1,2].

Tabelle 1: Dosierungsempfehlungen für die Siponimod-Therapie mit CYP2C9-Genotyp

***CYP2C9* Genotyp**	**Therapieempfehlung**
**1/*2, *2/*2*	Anwendung gemäß Fachinformation
**1/*3, *2/*3*	Dosis um 50 % reduzieren Wenn zusätzlich ein moderater CYP3A4-Induktor (z. B. Modafinil) verwendet wird, überdenken Sie Siponimod
**3/*3*	Siponimod kontraindiziert, Wirkstoffwechsel

Kosten

Die Kosten für die genetische Analyse des *CYP2C9*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-may-2020.pdf

[2] https://www.pharmgkb.org/labelAnnotation/PA166182738

SIPONIMOD

Genetički test za smanjenje rizika pri primjeni siponimoda

Lijek

Koje su indikacije i mehanizmi djelovanja siponimoda?

Siponimod je selektivni modulator receptora za sfingozin-1 fosfat koji se primjenjuje u liječenju sekundarne progresivne multiple skleroze (SPMS). U pacijenata s aktivnim SPMS, siponimod smanjuje rizik relapsa i onesposobljenja.

Geni

Koji geni utječu na djelovanje siponimoda?

Metabolizam siponimoda odvija se preko enzima CYP2C9, što određuje njegovu učinkovitost i trajanje djelovanja. Poznato je nekoliko varijanti gena koji kodiraju za CYP2C9 s bitnim utjecajem na njegovu enzimsku aktivnost.

Analiza

Što se analizira?

Kako bi se odredio tip metabolizatora, analizira se genotip pacijenta za najčešće varijante *CYP2C9* gena *(*1, *2, *3)* koji utječu na aktivnost enzima.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije siponimodom kako bi se smanjio rizik od nuspojava kao što su glavobolja, hipertenzija, oštećenje jetre te, po potrebi, prilagodila doza ili primijenio zamjenski lijek.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Dutch Pharmacogenetics Working Group Guideline for siponimod*[1,2].

Tablica 1: Preporuke za terapiju siponimodom ovisno o genotipu CYP2C9

***CYP2C9* genotip**	**Preporučena terapija**
**1/*2, *2/*2*	Terapija sukladno uputama o lijeku
**1/*3, *2/*3*	Smanjiti preporučenu dozu održavanja za 50 % Ukoliko se istovremeno primjenjuje srednji ili jaki CYP3A4 induktor, potrebno je procijeniti rizik primjene siponimoda
**3/*3*	Siponimod se ne preporučuje, potrebno je primijeniti zamjenski lijek

Troškovi

Troškovi za određivanje *CYP2C9* genotipa bit će priznati i refundirani za pacijente koji imaju obvezno i privatno osiguranje ukoliko je testiranje zatraženo od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-may-2020.pdf

[2] https://www.pharmgkb.org/labelAnnotation/PA166182738

SUCCINYLCHOLINE

Genetic test to minimize the risks related to therapy of succinylcholine

Drug

What are the indications and mechanism of action of succinylcholine?

Succinylcholine (also known as suxamethonium) is a depolarizing muscle relaxant that is used to cause short-term paralysis as part of general anesthesia. The mechanism of action is binding to postsynaptic nicotinic acetylcholine receptors at the neuromuscular junction causing sodium channel opening that leads to sustained depolarization followed by desensitization of the muscle membrane. The result is flaccid skeletal muscle paralysis.

Genes

Which genes influence the effect of succinylcholine?

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the *RYR1* and *CACNA1S* genes under consideration here predisposes individuals to a severe and sometimes lethal hypermetabolic reaction whose symptoms include muscle rigidity, high fever, and a fast heart rate. Complications can include rhabdomyolysis and high blood potassium.

Test

What will be tested?

The genotype of the ryanodine receptor isoform 1 protein *(RYR1)* is tested for one of the 48 causative single-nucleotide variants or one deletion that are designated diagnostic malignant hyperthermia (MH) mutations[1]. The α1S subunit of the dihydropyridine receptor *(CACNA1S)* is tested for the 2 known variants that are MH susceptible. Since MH susceptibility is inherited in an autosomal-dominant pattern, a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as a diagnostic for the trait.

Indication

When should a test be performed?

Genetic testing should be carried out before the initiation of the scheduled usage of succinylcholine in order to reduce the risk of MH.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[2] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for Succinylcholine usage depending on the phenotype of the RYR1 and CACNA1S genes

RYR1 or CACNA1S Phenotype	Recommended therapy
Malignant hyperthermia susceptible	Succinylcholine is not recommended due to MH susceptibility, use non-depolarizing muscle relaxants
Uncertain susceptibility	Clinical findings, family history, further genetic testing, and other laboratory data should guide the use of succinylcholine

Nota bene: A negative or inconclusive genetic test cannot be assumed to indicate normal phenotype and should be interpreted in the context of clinical findings, family history, and other laboratory data.

Costs

Costs for the determination of the *RYR1* and *CACNA1S* genotype are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

SUCCINYLCHOLIN

Gentest zur Risikominimierung der Therapie mit Succinylcholin

Wirkstoff

Was sind die Indikationen und der Wirkungsmechanismus von Succinylcholin?

Succinylcholin (auch als Suxamethonium bekannt) ist ein depolarisierendes Muskelrelaxans, das im Rahmen einer Vollnarkose eine kurzfristige Lähmung verursacht. Der Wirkungsmechanismus bindet an postsynaptische nikotinische Acetylcholinrezeptoren am neuromuskulären Übergang und verursacht eine Natriumkanalöffnung, die zu einer anhaltenden Depolarisation führt, gefolgt von einer Desensibilisierung der Muskelmembran. Das Ergebnis ist eine schlaffe Skelettmuskelparalyse.

Gene

Welche Gene beeinflussen die Wirkung von Succinylcholin?

Im Gegensatz zu vielen verwertbaren pharmakogenetischen Merkmalen, die den Metabolismus und/oder die Ausscheidung eines Arzneimittels beeinflussen, prädisponieren die hier betrachteten Varianten der Gene *RYR1* und *CACNA1S* zu einer schweren und manchmal tödlichen hypermetabolischen Reaktion, zu deren Symptomen Muskelsteifheit, hohes Fieber und schnelle Herzfrequenz gehören. Weitere Komplikationen können Rhabdomyolyse und hohe Kaliumwerte im Blut darstellen.

Test

Was wird getestet?

Der Genotyp des Ryanodinrezeptor-Isoform-1-Proteins *(RYR1)* wird auf eine der 48 Einzelnukleotidvarianten und eine Deletion getestet, die als diagnostische maligne Hyperthermie (MH)-Mutation[1] bezeichnet werden. Die α1S-Untereinheit des Dihydropyridinrezeptors *(CACNA1S)* wird auf die beiden bekannten Varianten getestet, die für maligne Hyperthermie anfällig sind. Da die Anfälligkeit für maligne Hyperthermie (MHS) in einem autosomal-dominanten Muster vererbt wird, kann ein heterozygoter Genotyp einer pathogenen Variante in *RYR1* als diagnostisch für das Merkmal angesehen werden.

Indikation

Wann sollte ein Test durchgeführt werden?

Gentests sollten vor Beginn dem geplanten Gebrauch von Desfluran durchgeführt werden, um das Risiko einer bösartigen Hyperthermie zu verringern. Alle nichtdepolarisierenden Muskelrelaxantien außer den Hyperthermie-auslösenden starken, flüchtigen Anästhetika, alle intravenösen Induktionsmittel sowie die verlängerte Inhalationsanästhesie mit nicht auslösenden Mitteln stellen Alternativen dar, die nicht mit bösartiger Hyperthermie assoziiert sind.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[2] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für einen Succinylcholin-Einsatz mit Phänotyp der RYR1- und CACNA1S-Gene

RYR1 oder CACNA1S Phänotyp	Therapieempfehlung
Maligne Hyperthermie Anfälligkeit	Succhinylcholin kontraindiziert, Anästhetikawechsel empfohlen
Unsichere Anfälligkeit	Klinische Befunde, Familienanamnese, weitere Gentests und andere Labordaten sollten den Einsatz von Succinylcholin anleiten

Kosten

Die Kosten für die genetische Analyse der *RYR1*- und *CACNA1S*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319

SUKCINILKOLIN

Genetički test za smanjenje rizika pri primjeni sukcinilkolina

Lijek

Koje su indikacije i mehanizmi djelovanja sukcinilkolina?

Sukcinilkolin (također zvan i suksametonij) je depolarizirajući miorelaksans koji se koristi za kratkotrajnu paralizu pri općoj anesteziji. Djeluje vezujući se na postsinaptički nikotinski acetilkolinski receptor na neuromišićnoj spojnici uzrokujući početno otvaranje natrijskih voltažnih kanala, koje vodi do početne depolarizacije (depolarizirajući blok) i kasnije desenzitizacije (desenzitizacijski blok) mišićne membrane, što u konačnici rezultira flakcidnom paralizom skeletnih mišića.

Geni

Koji geni utječu na djelovanje sukcinilkolina?

Za razliku od mnogih drugih lijekova kojima genski polimorfizmi utječu na metabolizam ili ekskreciju, polimorfizmi *RYR1* i *CACNA1S* gena su predisponirajući za tešku i smrtonosnu hipermetaboličku reakciju, čiji simptomi uključuju: rigidnost mišića, visoku tjelesnu temperaturu, tahikardiju. Komplikacije uključuju rabdomiolizu i hiperkalemiju.

Analiza

Što se analizira?

Genotip rajanodinskog receptora izoforme 1 *(RYR1)* testira se na jedan od 48 nukleotidnih polimorfizama ili jednu deleciju koje su označene kao dijagnostičke mutacije za malignu hipertermiju[1]. α1S podjedinica dihidropiridinskog receptora *(CACNA1S)* se testira za jednu od 2 poznate mutacije koje su dijagnostičke za malignu hipertermiju. Budući da se navedeni geni nasljeđuju autosomno dominantno, heterozigotni genotip navedenih gena smatra se kao dijagnoza sklonosti ka malignoj hipertermiji.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije početka primjene sukcinilkolina kako bi se odredila sklonost ka nastanku maligne hipertermije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortiums (CPIC)*[2] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za primjenu sukcinilkolina ovisno o fenotipu RYR1 i CACNA1S

RYR1 ili CACNA1S fenotip	Preporučena terapija
Osjetljivost za malignu hipertermiju	Ne preporučuje se primjena sukcinilkolina. Potrebno je korištenje alternativnog neuromuskularnog blokatora (nedepolarizirajućeg)
Neinformativan	Odluka o primjeni sukcinilkolina trebala bi se voditi kliničkom slikom, obiteljskom anamnezom, daljnjim genskim testiranjem i ostalim laboratorijskim podatcima

Nota bene: negativan ili neinformativan rezultat testa se ne smije uzeti kao indikacija za normalan fenotip te se treba razmotriti u kontekstu kliničkih nalaza, obiteljske anamneze i ostalih laboratorijskih nalaza.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] https://www.emhg.org/diagnostic-mutations

[2] Gonsalves SG, Dirksen RT, Sangkuhl K, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of RYR1 or CACNA1S Genotypes [published correction appears in Clin Pharmacol Ther. 2019 Dec;106(6):1408]. Clin Pharmacol Ther. 2019;105(6):1338-1344. doi:10.1002/cpt.1319.

TACROLIMUS

Genetic test to minimize the risks related to therapy with tacrolimus

Drug

What are the indications and mechanisms of action of tacrolimus?

Tacrolimus is an immunosuppressive agent used after hematopoietic cell and solid organ transplantation, graft versus host reaction and glomerulonephritis treatment. The mechanism of action of tacrolimus is binding to the cytoplasmic protein receptor, FK binding protein 12 in T -lymphocytes thus producing protein complex that binds and inhibits calcineurin and suppresses T- cell lymphocyte activation.

Genes

Which genes influence the effect of tacrolimus?

Several *CYP3A5* gene variants are related to tacrolimus metabolism and define specific metabolic phenotypes: extensive, intermediate and poor metabolizer. Determination of patients *CYP3A5* genotype/phenotype enables individual therapy and dose adjustment related to the patient's individual response.

Test

What will be tested?

The genotype is tested to *CYP3A5* variants. Alleles are defined as a functional *(*1)*, non-functional *(*3)* and unknown significance alleles *(*2, *4, *5)*. Extensive metabolizer has both functional alleles *(*1/*1)*, intermediate metabolizer has one functional and one non-functional allele *(*1/*3, *1/*6, *1/*7)*. Poor metabolizer has both non-functional alleles *(*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7)*.

Indication

When should be a test performed?

The genetic test should be performed in patients before the initiation of tacrolimus therapy.

Consequences and test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium* guidelines[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for tacrolimus therapy depending on the phenotype of the CYP3A5 gene

CYP3A5 Phenotype	Recommended therapy
Extensive metabolizer	Increase starting dose 1.5-2 times recommended starting dose The total starting dose should not exceed 0.3 mg/kg/day
Intermediate metabolizer	Increase starting dose 1.5-2 times recommended starting dose The total starting dose should not exceed 0.3 mg/kg/day
Poor metabolizer	Initiate therapy with the standard recommended dose

Nota bene: Use therapeutic drug monitoring to guide dose adjustment in all metabolizers.

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Birdwell KA, Decker B, Barbarino JM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24. doi:10.1002/cpt.113

TACROLIMUS

Gentest zur Risikominimierung der Therapie mit Tacrolimus

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Tacrolimus?

Tacrolimus ist ein Immunsuppressivum zur Behandlung der Immunantwort nach Transplantation hämatopoetischer Zellen und solider Organe, Transplantat-gegen-Wirt-Reaktion und Glomerulonephritis. Tacrolimus bindet an den zytoplasmatischen Proteinrezeptor (FK-Bindungsprotein 12) in T-Lymphozyten. Dieser Proteinkomplex bindet an Calcineurin, so dass Calcineurin nicht mehr aktiviert werden kann und die Aktivierung von T-Zell-Lymphozyten unterdrückt.

Gene

Welche Gene beeinflussen die Wirkung von Tacrolimus?

Mehrere *CYP3A5*-Genvarianten sind mit verschiedenen Arten des Tacrolimus-Metabolismus verwandt und definieren spezifische metabolische Phänotypen: schnelle, intermediäre und schlechte Metabolisierer. Die Bestimmung des Genotyps *CYP3A5* ermöglicht dem Patienten eine individuelle Therapie und Dosisanpassung. Daneben wird der Tacrolimus-Metabolismus auch von nicht-genetischen Faktoren (Arzneimittelwechselwirkungen, pharmakodynamische Variabilität) beeinflusst.

Test

Was wird getestet?

Der Patientengenotyp wird auf *CYP3A5*-Genvarianten getestet. Allele werden als funktionelle *(*1),* nicht funktionelle *(*3)* und Allele mit unbekannter Signifikanz *(*2, *4, *5)* definiert. Der schnelle Metabolisierer hat beide funktionellen Allele (**1/*1),* der intermediäre Metabolisierer hat ein funktionelles und ein nicht funktionelles Allel *(*1/*3, *1/*6, *1/*7).* Ein schlechter Metabolisierer hat beide nicht funktionierenden Allele *(*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7).*

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Tacrolimus durchgeführt werden, um den Nutzen der Therapie abzuschätzen.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für eine Tacrolimus-Therapie mit CYP3A5 Phänotyp

CYP3A5 Phänotyp	Therapieempfehlung
Schnelle Metabolisierer	Startdosis erhöhen (1,5-2x im Vergleich zur empfohlenen Startdosis), nicht > 0,3mg/kg/Tag
Intermediäre Metabolisierer	Startdosis erhöhen (1,5-2x im Vergleich zur empfohlenen Startdosis), nicht > 0,3mg/kg/Tag
Langsame Metabolisierer	Beginn mit Startdosis

Nota bene: Verwenden Sie *Drug Monitoring*, um die Dosisanpassung bei allen Metabolisierern zu steuern.

Kosten

Die Kosten für die genetische Analyse des *CYP3A5*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Birdwell KA, Decker B, Barbarino JM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24. doi:10.1002/cpt.113.

TAKROLIMUS

Genetički test za smanjenje rizika pri primjeni takrolimusa

Lijek

Koje su indikacije i mehanizmi djelovanja takrolimusa?

Takrolimus je imunosupresivni lijek koji se primjenjuje u sprečavanju imunosne reakcije nakon transplantacije hematopoetskih matičnih stanica i transplantacije solidnih organa, liječenju glomerulonefritisa te reakciji presatka protiv domaćina (eng. graft-versus host disease). Mehanizam djelovanja takrolimusa je vezivanje za citoplazmatski FK protein 12 T limfocita, pri čemu nastaje proteinski kompleks koji se veže za i inhibira kalcineurin i posljedično suprimira aktivaciju T limfocita.

Geni

Koji geni utječu na djelovanje takrolimusa?

Pojedine varijante gena *CYP3A5* povezuju se s različitim metaboliziranjem takrolimusa i određuju tzv. fenotipe metaboliziranja lijeka; ekstenzivni, intermedijarni i spori metabolizatori. Poznavanjem pojedinih varijanti gena *CYP3A5* moguće je individualno doziranje takrolimusa i prilagođavanje doze sukladno pacijentovom genotipu, odnosno metaboličkom fenotipu.

Analiza

Što se analizira?

Analiziraju se varijante gena *CYP3A5*. Analizirani aleli definiraju se kao funkcionalni *(*1)*, nefunkcionalni *(*3)*, odnosno aleli nepoznatog značenja *(*2, *4, *5)*. Osobe koje su ekstenzivni metabolizatori imaju oba funkcionalna alela *(*1/*1)*, intermedijarni metabolizatori imaju jedan funkcionalni i jedan nefunkcionalni alel *(*1/*3, *1/*6, *1/*7)*, dok spori metabolizatori imaju oba nefunkcionalna alela *(*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7)*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije uvođenja terapije takrolimusom.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke se temelje na *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines[1] i imaju najvišu razinu kliničke značajnosti 1A.

Tablica 1: Preporuke za doziranje takrolimusa ovisno o fenotipu CYP3A5

CYP3A5 fenotip	Preporučena terapija
Ekstenzivni metabolizator	Povećati početnu dozu 1,5-2 puta u odnosu na preporučenu početnu dozu Ukupna doza ne smije prijeći 0,3 mg/kg/dan
Intermedijarni metabolizator	Povećati početnu dozu 1,5-2 puta u odnosu na preporučenu početnu dozu Ukupna doza ne smije prijeći 0,3 mg/kg/dan
Spori metabolizator	Uvođenje terapije prema standardnim preporukama za doziranje

Nota bene: Potrebno je pratiti koncentraciju lijeka u plazmi kod svih fenotipa metabolizatora kako bi se optimalno prilagodila doza lijeka.

Troškovi

Troškovi genetičkog testa će biti refundirani pacijentima s državnim i privatnim osiguranjem ukoliko je testiranje indicirano od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Birdwell KA, Decker B, Barbarino JM, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24. doi:10.1002/cpt.113

TAMOXIFEN

Genetic test to minimize the risks related to therapy with tamoxifen

Drug

What are the indications and mechanisms of action of tamoxifen?

Tamoxifen is a prodrug that is used as an anti-estrogen for adjuvant and palliative therapy to treat breast cancer. Tamoxifen has furthermore proven successful as a preventative treatment in high-risk patients. Its active metabolite endoxifen acts as an antagonist in breast tissue, but has an estrogen-like effect in the uterine mucosa, in the bones and on lipid metabolism. Tamoxifen is thus also referred to as SERM (Selective Estrogen Receptor Modulator). Tamoxifen's mechanism of action is based on the competitive blocking of estrogen-receptors in cancer cells. Thus, estrogen-mediated growth signals are suppressed which results in decreased cell propagation.

Genes

What genes influence the effect of tamoxifen?

The conversion of tamoxifen into its active metabolites endoxifen and hydroxytamoxifen is essentially catalysed by the CYP2D6 enzyme. There are many known activity-reducing gene variants that cause a broad fluctuation range of the enzyme activity. Slow CYP2D6 metabolizers produce hardly any endoxifen and hydroxytamoxifen. *CYP2D6* is highly polymorphic, with over 100 known allelic variants and subvariants identified.

Test

What is tested?

In order to determine the CYP2D6 metabolization type, the genotype of patients is examined with regard to the most common *CYP2D6* activity reducing gene variants *(CYP2D6 *3, *4, *5, *6, *9, *10, *17,* and *41)* and also with regard to the number of active genocopies *(* 1XN, * 2XN).*

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with tamoxifen in order to reduce the risk of relapse, as required, by means of an adjustment of the dose or by prescribing an alternative active agent.

Consequences of the test results

How does the therapy need to be adjusted to the test results?

The following recommendations are based on *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] Guideline for CYP2D6 and have the highest clinical level of evidence 1A.

Table 1: Dosing recommendations for tamoxifen depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype	Recommended therapy
Ultrarapid metabolizers	Usage according to the Summary of Product Characteristics Avoid moderate and strong CYP2D6 inhibitors
Normal metabolizers	Usage according to the Summary of Product Characteristics Avoid moderate and strong CYP2D6 inhibitors
Normal to intermediate metabolizers (no *10 allele present)	For those patients the recommendation is optional due to limited data for clinical outcomes and pharmacokinetics Consider aromatase inhibitors for postmenopausal women Consider aromatase inhibitor along with ovarian function suppression in premenopausal women If aromatase inhibitor is contraindicated FDA-approved higher dose of tamoxifen (40 mg/day) Avoid strong / weak CYP2D6 inhibitors
Normal to intermediate metabolizers (*10 allele present)	Consider aromatase inhibitors for postmenopausal women Consider aromatase inhibitor along with ovarian function suppression in premenopausal women If aromatase inhibitor is contraindicated FDA-approved higher dose of tamoxifen (40 mg/day) Avoid strong / weak CYP2D6 inhibitors
Intermediate metabolizers	Consider aromatase inhibitors for postmenopausal women Consider aromatase inhibitor along with ovarian function suppression in premenopausal women If aromatase inhibitor is contraindicated FDA-approved higher dose of tamoxifen (40 mg/day) Avoid strong / weak CYP2D6 inhibitors
Poor metabolizers	Consider aromatase inhibitors for postmenopausal women Consider aromatase inhibitor along with ovarian function suppression in premenopausal women If aromatase inhibitor is contraindicated FDA-approved higher dose of tamoxifen (40 mg/day)

Costs

Costs for the *CYP2D6* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Goetz MP, Sangkuhl K, Guchelaar HJ, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and Tamoxifen Therapy. Clin Pharmacol Ther. 2018;103(5):770-777. doi:10.1002/cpt.1007

TAMOXIFEN

Gentest zur Risikominimierung der Therapie mit Tamoxifen

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Tamoxifen?

Tamoxifen ist ein Prodrug, welches als Antiöstrogen zur adjuvanten und palliativen Therapie bei Brustkrebs eingesetzt wird. Zudem hat sich Tamoxifen in der Prävention bei Hochrisikopatienten bewährt. Das Medikament wird in der Leber in den aktiven Metaboliten 4-Hydroxy-N-desmethyl-Tamoxifen (Endoxifen) und 4-Hydroxytamoxifen verstoffwechselt. Während Endoxifen im Brustgewebe als Antagonist wirkt, entwickelt der Wirkstoff in der Gebärmutterschleimhaut, im Knochen und im Stoffwechsel der Blutfette eine östrogenähnliche Wirkung. Tamoxifen wird daher auch als SERM (*Selective Estrogen Receptor Modulator*) bezeichnet. Der Wirkprinzip von Tamoxifen beruht auf einer Blockade der intrazellulären Östrogen-Rezeptoren in Krebszellen durch kompetitive Hemmung. Dadurch werden Östrogen-vermittelte Wachstumssignale unterdrückt und das Tumorwachstum reduziert.

Gene

Welche Gene beeinflussen die Wirkung von Tamoxifen?

Die Umwandlung von Tamoxifen in seine aktiven Metaboliten Endoxifen und Hydroxytamoxifen wird maßgeblich durch das CYP2D6-Enzym katalysiert. Ob die beabsichtigte Endoxifenkonzentration am Zielort erreicht wird, hängt entscheidend von der Aktivität des CYP2D6-Enzyms ab. Für das *CYP2D6*-Gen sind eine Vielzahl aktivitätsmindernder und -aktivitätssteigernder Genvarianten bekannt, die eine große Schwankungsbreite der Enzymaktivität bedingen. Langsame CYP2D6-Metabolisierer produzieren kaum Endoxifen und Hydroxytamoxifen. *CYP2D6* ist hoch polymorph, wobei über 100 bekannte Allelvarianten und Subvarianten identifiziert wurden.

Test

Was wird getestet?

Um den CYP2D6-Metabolisierungstyp zu bestimmen, wird das Erbgut der Patienten sowohl auf die häufigsten aktivitätsmindernden Varianten im *CYP2D6*-Gen (*CYP2D6*3, *4, *5, *6, *9, *10, *17, *41*) als auch auf die Anzahl der Genkopien (*CYP2D6*1XN, *2XN*) untersucht.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor einer geplanten Therapie mit Tamoxifen bei Patienten durchgeführt werden, um das Risiko eines therapie versagens durch Dosisanpassung oder Wirkstoffwechsel zu verringern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] für den *CYP2D6*-Genotyp und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Dosierungsempfehlungen für die Tamoxifen-Therapie mit CYP2D6 Phänotyp

CYP2D6 Phänotyp	Therapieempfehlung
Ultraschnelle Metabolisierer	Therapie gemäß Fachinformation (20mg/Tag Tamoxifen) Moderate/starke CYP2D6-Inhibitoren vermeiden
Normale Metabolisierer	Therapie gemäß Fachinformation (20mg/Tag Tamoxifen) Moderate/starke CYP2D6-Inhibitoren vermeiden
Normale-intermediäre Metabolisierer kein *10-Allel präsent	(Empfehlung aufgrund begrenzter Daten zu klinischen Ergebnissen und Pharmakokinetik für diese Gruppe optional) Therapieerwägung Aromatasehemmer (post Menopause) Therapieerwägung Aromatasehemmer plus Suppression Eierstockfunktion (prä Menopause) Aromatasehemmer kontraindiziert: FDA-zugelassene höhere Dosis Tamoxifen (40mg/Tag) erwägen Starke/schwache CYP2D6-Inhibitoren vermeiden
Normale-intermediäre Metabolisierer *10-Allel präsent	Therapieerwägung Aromatasehemmer (post Menopause) Therapieerwägung Aromatasehemmer plus Suppression Eierstockfunktion (prä Menopause) Aromatasehemmer kontraindiziert: FDA-zugelassene höhere Dosis Tamoxifen (40mg/Tag) erwägen Starke/schwache CYP2D6-Inhibitoren vermeiden
Intermediäre Metabolisierer	Therapieerwägung Aromatasehemmer (post Menopause) Therapieerwägung Aromatasehemmer plus Suppression Eierstockfunktion (prä Menopause) Aromatasehemmer kontraindiziert: FDA-zugelassene höhere Dosis Tamoxifen (40mg/Tag) erwägen Starke/schwache CYP2D6-Inhibitoren vermeiden
Langsame Metabolisierer	Therapieerwägung Aromatasehemmer (post Menopause) Therapieerwägung Aromatasehemmer plus Suppression Eierstockfunktion (prä Menopause) Aromatasehemmer kontraindiziert: FDA-zugelassene höhere Dosis Tamoxifen (40mg/Tag) erwägen

Kosten

Die Kosten für die genetische Analyse des *CYP2D6*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Goetz MP, Sangkuhl K, Guchelaar HJ, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and Tamoxifen Therapy. Clin Pharmacol Ther. 2018;103(5):770-777. doi:10.1002/cpt.1007

TAMOKSIFEN

Genetički test za smanjenje rizika pri primjeni tamoksifena

Lijek

Koje su indikacije i mehanizmi djelovanja tamoksifena?

Tamoksifen je prolijek i koristi se kao antiestrogen u adjuvantnoj i palijativnoj terapiji pri liječenju karcinoma dojke. Pokazao se uspješnim kod prevencije visokorizičnih pacijenata. Njegov aktivni metabolit endoksifen djeluje kao antagonist u tkivu dojke, a estrogenu sličan učinak ima u sluznici maternice, kostima i u metabolizmu lipida. Tamoksifen se svrstava u skupinu selektivnih modulatora estrogenskih receptora (SERM). Princip djelovanja tamoksifena bazira se na kompetitivnoj blokadi receptora estrogena unutar stanica karcinoma. Tako se potiskuju estrogenom-posredovani signali i rast tumorskih stanica.

Geni

Koji geni utječu na djelotvornost tamoksifena?

Pretvorba tamoksifena u aktivne metabolite endoksifen i hidroksitamoksifen odvija se prvenstveno putem enzima CYP2D6. Niz je poznatih varijanti gena koji uzrokuju raznoliku enzimsku aktivnost. Spori metabolizatori proizvode jedva i malo endoksifena i hidroksitamoksifena. *CYP2D6* je vrlo polimorfan s preko 100 dosad poznatih alelskih varijanti i podvarijanti.

Analiza

Što se analizira?

Da bi se istražilo u koju skupinu CYP2D6 metabolizatora pacijent pripada, analiziraju se najučestalije varijante gena *(CYP2D6 *3, *4, *5, *6, *9, *10, *17* i *41)* i također s obzirom na broj aktivnih genokopija *(* 1XN, * 2XN).*

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije samoga početka planirane terapije s tamoksifenom da bi se eventualno smanjio rizik recidiva putem prilagođavanja doze ili ordiniranjem alternativne terapije.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke se temelje na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and Tamoxifen Therapy[1] i imaju visoku kliničku razinu dokaza 1A.

Tablica 1: Preporuke za doziranje tamoksifena u ovisnosti o fenotipu CYP2D6 gena

CYP2D6 fenotip	Preporučena terapija
Ultrabrzi metabolizatori	Terapija sukladno uputama o lijeku. Izbjegavati istovremenu primjenu srednjih i jakih CYP2D6 inhibitora
Normalni metabolizatori	Terapija sukladno uputama o lijeku. Izbjegavati istovremenu primjenu srednjih i jakih CYP2D6 inhibitora
Normalni do intermedijarni metabolizatori (*10 alel prisutan)	Razmotriti terapiju inhibitorima aromataze kod postmenopauzalnih žena Razmotriti terapiju inhibitorima aromataze zajedno s ovarijskom supresijom kod premenopauzalnih žena Ako su inhibitori aromataze kontraindicirani, može se dati veća doza tamoksifena (40 mg/dan), odobrena od FDA Izbjegavati istovremenu primjenu CYP2D6 inhibitora (slabih do jakih)
Normalni do intermedijarni metabolizatori (*10 alel nije prisutan)	Preporuke su opcionalne zbog ograničenih kliničkih podataka za taj fenotip Razmotriti terapiju inhibitorima aromataze kod postmenopauzalnih žena Razmotriti terapiju inhibitorima aromataze zajedno s ovarijskom supresijom kod premenopauzalnih žena Ako su inhibitori aromataze kontraindicirani, može se dati veća doza tamoksifena (40 mg/dan), odobrena od FDA Izbjegavati istovremenu primjenu CYP2D6 inhibitora (slabih do jakih)
Intermedijarni metabolizatori	Razmotriti terapiju inhibitorima aromataze kod postmenopauzalnih žena Razmotriti terapiju inhibitorima aromataze zajedno s ovarijskom supresijom kod premenopauzalnih žena Ako su inhibitori aromataze kontraindicirani, može se dati veća doza tamoksifena (40 mg/dan), odobrena od FDA Izbjegavati istovremenu primjenu CYP2D6 inhibitora (slabih do jakih)
Slabi metabolizatori	Razmotriti terapiju inhibitorima aromataze kod postmenopauzalnih žena Razmotriti terapiju inhibitorima aromataze zajedno s ovarijskom supresijom kod premenopauzalnih žena Ako su inhibitori aromataze kontraindicirani, može se dati veća doza tamoksifena (40 mg/dan), odobrena od FDA

Troškovi

Priznavanje i povrat troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize gena *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Goetz MP, Sangkuhl K, Guchelaar HJ, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for CYP2D6 and Tamoxifen Therapy. Clin Pharmacol Ther. 2018;103(5):770-777. doi:10.1002/cpt.1007

TENOXICAM

Genetic test to minimize the risks related to therapy with tenoxicam

Drug

What are the indications and mechanisms of action of tenoxicam?

Tenoxicam is a nonsteroidal drug with analgesic, anti-inflammatory and antipyretic properties. Its therapeutic effects occur via inhibition of prostaglandin biosynthesis from arachidonic acid by cyclooxygenases (COX) isoforms 1 and 2. Tenoxicam is a reversible non-selective inhibitor of both COX isoforms.

Genes

Which genes influence the effect of tenoxicam?

Tenoxicam is metabolized via the enzyme CYP2C9. A decrease in the CYP2C9 function decreases the metabolic clearance of tenoxicam thus prolonging its plasma elimination half-life. Several variants of the gene with great variability in the enzymatic activity of CYP2C9 are known in the population.

Test

What is tested?

To determine the CYP2C9 metabolism type, the testing of *CYP2C9* gene variants *(*2, *3)* associated with significantly reduced CYP2C9 enzyme activity is recommended.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the therapy with tenoxicam, in order to minimize the risk of side effects such as gastrointestinal bleeding, hypertension, myocardial infarction, heart failure, and renal damage through an adjustment of the starting dose or the prescription of alternative therapy.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for tenoxicam therapy according to the CYP2C9 genotype

***CYP2C9* Genotype / Phenotype**	**Recommended therapy**
*CYP2C9*1/*1* / Normal metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*2* / Intermediate metabolizer	Use in accordance with the Summary of Product Characteristics
*CYP2C9*1/*3, *2/*2* / Intermediate metabolizer	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants in vivo or choose a drug metabolized by CYP2C9 but with a shorter half-life
*CYP2C9*2/*3, *3/*3* / Poor metabolizer	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants in vivo or choose a drug metabolized by CYP2C9 but with a shorter half-life

Costs

Costs for the *CYP2C9* gene analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

TENOXICAM

Gentest zur Risikominimierung der Therapie mit Tenoxicam

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Tenoxicam?

Tenoxicam ist ein nichtsteroidales Medikament mit entzündungshemmenden, analgetischen und fiebersenkenden Eigenschaften. Seine therapeutischen Wirkungen treten über die Hemmung der Prostaglandin-Biosynthese aus Arachidonsäure durch die Cyclooxygenasen (COX)-Isoformen 1 und 2 auf. Tenoxicam ist ein reversibler nichtselektiver Inhibitor beider COX-Isoformen.

Gene

Welche Gene beeinflussen die Wirkung von Tenoxicam?

Tenoxicam wird über das Enzym CYP2C9 metabolisiert. Eine Abnahme der CYP2C9-Funktion verringert die metabolische Clearance (Ausscheidung) von Tenoxicam und verlängert so die Halbwertszeit der Plasmaelimination. In der Population sind mehrere Varianten des *CYP2C9*-Gens mit großer Variabilität der enzymatischen Aktivität von CYP2C9 bekannt.

Test

Was wird getestet?

Zur Bestimmung des CYP2C9-Metabolismus wird empfohlen, *CYP2C9*-Genvarianten *(*2,*3)* zu testen, die mit einer signifikant verringerten CYP2C9-Enzymaktivität assoziiert sind.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn der Therapie mit Tenoxicam durchgeführt werden, um das Risiko für Nebenwirkungen wie gastrointestinale Blutungen, Bluthochdruck, Myokardinfarkt, Herzinsuffizienz und Nierenschäden durch Anpassung der Anfangsdosis oder der Verschreibung einer alternativen Behandlung zu minimieren.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Tenoxicam-Therapie in Abhängigkeit vom CYP2C9-Genotyp

***CYP2C9* Genotyp / Phänotyp**	**Therapieempfehlung**
*CYP2C9*1/*1* / Normale Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*2* / Intermediare Metabolisierer	Anwendung gemäß Fachinformation
*CYP2C9*1/*3, *2/*2* / Intermediäre Metabolisierer	Start mit der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder empfohlene maximale Dosis, insbesondere bei Vorliegen von Leberfunktionsstörung oder höherem Alter
*CYP2C9*2/*3, *3/*3* / Langsame Metabolisierer	Start mit 25-50 % der niedrigst empfohlenen Dosis. Vorsichtige Titration auf klinische Wirkung oder 25-50 % der empfohlenen maximalen Dosis Alternativ: Wechsel auf Wirkstoff ohne CYP2C9-Metabolismus

Kosten

Die Kosten für die genetische Analyse des *CYP2C9* -Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

TENOKSIKAM

Genetički test za smanjenje rizika pri primjeni tenoksikama

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja tenoksikama?

Tenoksikam je nesteroidni lijek s analgetskim, protuupalnim i antipiretskim djelovanjem. Njegov mehanizam djelovanja temelji se na inhibiciji biosinteze prostaglandina iz arahidonske kiseline djelovanjem ciklooksigenaze (COX), izoformi 1 i 2. Tenoksikam je reverzibilni ne-selektivni inhibitor obje COX izoforme.

Geni

Koji geni utječu na djelovanje tenoksikama?

Tenoksikam se metabolizira putem enzima CYP2C9. Smanjenje funkcije CYP2C9 usporava eliminaciju tenoksikamom iz organizma i produljuje poluvrijeme eliminacije. Poznato je nekoliko varijanti *CYP2C9* gena s velikom varijabilnošću u enzimskoj aktivnosti CYP2C9 u populaciji.

Test

Što se analizira?

Kako bi se odredio metabolizam s obzirom na CYP2C9, preporučuje se utvrđivanje prisutnosti varijanti *CYP2C9* gena *(*2, *3)* koje su povezane sa značajno reduciranim kapacitetom enzimske aktivnosti.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije započinjanja terapije tenoksikamom kako bi se smanjio rizik neželjenih nuspojava kao što su gastrointestinalno krvarenje, hipertenzija, infarkt miokarda, srčano zatajenje i bubrežno oštećenje na način da se prilagodi početna doza ili propiše druga terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] te imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje tenoksikamom ovisno o CYP2C9 genotipu

***CYP2C9* genotip / fenotip**	**Preporučena terapija**
*CYP2C9*1/*1* / Normalni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*2* / Intermedijarni metabolizator	Terapija sukladno uputama o lijeku
*CYP2C9*1/*3, *2/*2* / Intermedijarni metabolizatori	Potrebno je odabrati lijek koji se ne metabolizira putem CYP2C9 ili čiji metabolizam ne ovisi značajno o *CYP2C9* genotipu, ili lijek s kraćim poluvremenom eliminacije
*CYP2C9*2/*3, *3/*3* / Spori metabolizator	Potrebno je odabrati lijek koji se ne metabolizira putem CYP2C9 ili čiji metabolizam ne ovisi značajno o *CYP2C9* genotipu, ili lijek s kraćim poluvremenom eliminacije

Troškovi

Priznavanje i povrat troškova za određivanje genotipa *CYP2C9* varira od države do države. Ukoliko je analiza ordinirana od strane liječnika, troškovi za određivanje genotipa *CYP2C9* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Theken KN, Lee CR, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs [published online ahead of print, 2020 Mar 19]. Clin Pharmacol Ther. 2020;10.1002/cpt.1830. doi:10.1002/cpt.1830

6-THIOGUANINE

Genetic test to minimize the risks related to therapy with 6-thioguanine

Drug

What are the indications and mechanisms of action of 6-thioguanine?

6-thioguanine is a cytotoxic active agent which is mainly used to treat acute and chronic lymphatic neoplasms and Hodgkin's lymphomas. 6-thioguanine is an analog of the naturally occurring purine base guanine and, as an anti-metabolite, inhibits purine synthesis as well as DNA and RNA synthesis.

Genes

What genes influence the effect of 6-thioguanine?

The enzyme thiopurine methyltransferase (TPMT) is responsible for the inactivation of thioguanine through methylation of the sulfhydryl group. A TPMT deficiency leads to a delayed breakdown of the active agent which can cause severe, life-threatening myelosuppression as a side effect. In the population, there are known activity-reducing gene variants for the *TPMT* gene which require an adjustment of the dose in order to increase the tolerability with regard to 6-thioguanine.

As a nucleoside diphosphatase, NUDT15 catalyzes the conversion of the cytotoxic thioguanine triphosphate (TGTP) metabolites to the less toxic thioguanine monophosphate. Genetic variants in *NUDT15* have been identified that strongly influence thiopurine tolerance in patients with acute lymphoblastic leukemia (ALL) and those with inflammatory bowel disease. In the case of genetically caused NUDT15 defficiency, toxic by-products increasingly accumulate which can lead to myelosuppression with life-threatening side effects.

Test

What is tested?

The genotype of patients is examined with regard to the most common clinically relevant *TPMT* gene variants *(*2, *3A, *3B, *3C, *4)* which, in the compound heterozygous or homozygous state, lead to a complete loss of the TPMT enzyme activity.

The genotype of patients is also examined with regard to the most common clinically relevant *NUDT15* gene variants *(*2, *3)* which, in the compound heterozygous or homozygous state, lead to a partial or complete loss of the NUDT15 enzyme activity.

Indication

When should a test be carried out?

Genetic testing should be carried out before the initiation of the scheduled therapy with 6-thioguanine in order to reduce the risk of myelosuppression (disturbance of hematopoiesis), as required, by means of an adjustment of the initial dose or by prescribing an alternative active agent. Inherited TMPT deficiency is the primary genetic cause of thiopurine intolerance in Europeans and Africans, whereas risk alleles in *NUDT15* explain the majority of thiopurine-related myelosuppression in Asians and are also common in Hispanics.

Consequences and test results

How does the therapy need to be adjusted to the test results?

The following procedure is based on the recommendations of the guidelines of the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] and has the highest clinical level of evidence 1A.

Table 1: Recommendations for 6-thioguanine therapy depending on the TPMT genotype

TPMT Genotype / Phenotype	Recommended therapy
Wild type / Normal metabolizer	Usage according to the Summary of Product Characteristics
Risk variant, heterozygous / Intermediate metabolizer	The initial dose should correspond to 50-80 % of the normal dose in non-malignant conditions; adjust doses based on the degree of myelosuppression
Risk variant, compound heterozygous or homozygous / Poor metabolizer	For malignant conditions: drastic reduction of the initial dose (10-fold reduction and only on 3 days/week), adjust doses based on the degree of myelosuppression For nonmalignant conditions: consider alternative nonthiopurine immunosuppressant therapy

Table 2: Recommendations for 6-thioguanine therapy depending on the NUDT15 genotype

***NUDT15* Genotype / Phenotype**	**Recommended therapy**
Wild type / Normal metabolizer	Usage according to the Summary of Product Characteristics
Risk variant, heterozygous / Intermediate metabolizer	The initial dose should correspond to 50-80 % of the normal dose. Adjust doses based on the degree of myelosuppression
Risk variant, compound heterozygous or homozygous / Poor metabolizer	For malignant conditions: Reduce doses to 25 % of normal dose, adjust doses based on the degree of myelosuppression For nonmalignant conditions: consider alternative nonthiopurine immunosuppressant therapy

Costs

Costs for the *TPMT* and *NUDT15* genes analysis are reimbursed for patients with statutory or private health insurance if the testing is requested by a doctor. The budget of the doctor responsible for the treatment is not affected.

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[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

6-THIOGUANIN

Gentest zur Risikominimierung der Therapie mit 6-Thioguanin

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von 6-Thioguanin?

6-Thioguanin ist ein zytotoxischer Wirkstoff, der hauptsächlich zur Behandlung akuter und chronischer lymphatische Neoplasien und des Hodgkin-Lymphoms eingesetzt wird. 6-Thioguanin ist ein Analogon der natürlich vorkommenden Purinbase Guanin und hemmt als Antimetabolit sowohl die Purinsynthese als auch die DNA- und RNA-Synthese.

Gene

Welche Gene beeinflussen die Wirkung von 6-Thioguanin?

Das Enzym Thiopurinmethyltransferase (TPMT) inaktiviert Thiopurine durch Methylierung der Sulfhydrylgruppe. Ein Mangel an TPMT führt zu einem verzögerten Abbau des Wirkstoffs, wodurch es zu einer schweren, lebensbedrohlichen Myelosuppression kommen kann. Für das *TPMT*-Gen sind in der Bevölkerung aktivitätsrmindernde Genvarianten bekannt, die eine Dosisanpassung erforderlich machen, um die Verträglichkeit von 6-Thioguanin zu erhöhen.

Die Nucleosiddiphosphatase/Nudix-Hydrolase 15 (NUDT15) katalysiert die Umwandlung der zytotoxischen Thioguanintriphosphat (TGTP)-Metaboliten in das weniger toxische Thioguaninmonophosphat (TGMP). Es gibt genetische Varianten von *NUDT15*, die die Thiopurintoleranz bei Patienten mit akuter lymphoblastischer Leukämie (ALL) und bei Patienten mit entzündlichen Darmerkrankungen stark beeinflussen. Bei genetisch bedingtem funktionellem NUDT15-Mangel reichern sich toxische Nebenprodukte an, die zu einer Myelosuppression mit lebensbedrohlichen Nebenwirkungen führen können.

Test

Was wird getestet?

Der Genotyp von Patienten wird auf die häufigsten klinisch relevanten *TPMT*-Genvarianten *(*2, *3A, *3B, *3C, *4)* untersucht, die im compound heterozygoten oder homozygoten Zustand zu einem vollständigen Verlust der TPMT-Enzymaktivität führen. Zudem wird der Genotyp von Patienten auf die häufigsten klinisch relevanten *NUDT15*-Genvarianten *(*2, *3)* untersucht, die im compound heterozygoten oder homozygoten Zustand zu einem partiellen oder vollständigen Verlust der NUDT15-Enzymaktivität führen.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit 6-Thioguanin durchgeführt werden, um gegebenfalls durch eine Anpassung der Startdosis oder die Verordnung eines alternativen Wirkstoffs das Risiko einer Myelosuppression (Störung der Hämatopoese) zu senken.

Bei 30-60 % der Patienten mit einem heterozygoten *TPMT*-Risikogenotyp ist die Standarddosis mit dem Risiko von Nebenwirkungen verbunden. Der angeborene TMPT-Mangel ist die primäre genetische Ursache für die Thiopurin-Intoleranz bei Europäern und Afrikanern, während bei Asiaten und Hispanics Risiko-Allele in *NUDT15* die Mehrheit der Thiopurin-bedingten Myelosuppression erklären.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] und und der letzten Anmerkung zur CPIC-Richtlinie (aktualisiert im Mai 2019) und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die 6-Thioguanin-Therapie in Abhängigkeit vom TPMT-Genotyp

***TPMT* Genotyp / Phänotyp**	**Therapieempfehlung**
Wildtyp / Normale Metabolisierer	Anwendung gemäß der Fachinformation
Risikovariante, heterozygot / Intermediäre Metabolisierer	Startdosis um 50-80 % reduzieren Anpassung der Dosis an Grad der Myelosuppression
Risikovariante, compound heterozygot oder homozygot / Langsame Metabolisierer	Bei nicht malignen Erkrankungen: Wirkstoffwechsel mit nicht-Thiopurin-Immunspressiva empfohlen Bei malignen Erkrankungen: Startdosis drastisch reduzieren (10-fach reduziert und nur an 3 Tagen/Woche), Anpassung der Dosis an Grad der Myelosuppression

Tabelle 2: Empfehlungen für die 6-Thioguanin-Therapie in Abhängigkeit vom NUDT15-Genotyp

***NUDT15* Genotyp / Phänotyp**	**Therapieempfehlung**
Wildtyp / Normale Metabolisierer	Anwendung gemäß der Fachinformation
Risikovariante, heterozygot / Intermediäre Metabolisierer	Startdosis um 50-80 % reduzieren Anpassung der Dosis an Grad der Myelosuppression
Risikovariante, compound heterozygot oder homozygot / Langsame Metabolisierer	Bei nicht malignen Erkrankungen: Wirkstoffwechsel mit nicht-Thiopurin-Immunspressiva empfohlen Bei malignen Erkrankungen: Startdosis drastisch auf 25 % der normalen Dosis reduzieren, Anpassung der Dosis an Grad der Myelosuppression)

Kosten

Die Kosten für die genetische Analyse des *TMPT*-Gens und des *NUDT15*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

6-TIOGVANIN

Genetički test za smanjenje rizika pri primjeni 6-tiogvanina

Lijek

Koje su indikacije i mehanizmi djelovanja 6-tiogvanina?

6-tiogvanin je citostatski lijek koji se uglavnom koristi u liječenju akutnih i kroničnih limfoidnih neoplazmi i Hodgkinovog limfoma. 6-tiogvanin je analog purinske baze gvanina te kao anti-metabolit zaustavlja sintezu purina te posljedično i sintezu DNA i RNA.

Geni

Koji geni utječu na djelovanje 6-tiogvanina?

Enzim tiopurin metiltransferaza (TPMT) inaktivira tiogvanin putem metilacije sulfhidrilne skupine. Nedostatak TPMT dovodi do odgođene razgradnje aktivne tvari, pri čemu može doći do teške, po život opasne supresije koštane srži. U gotovo svim populacijama, poznate su varijante gena *TPMT* koje dovode do smanjene aktivnosti enzima i stoga je potrebno prilagoditi doziranje da bi se povećala podnošljivost 6-tiogvanina.

NUDT15, nukleozidna difosfataza, enzim je koji katalizira konverziju citotoksičnog metabolita tiogvanin trifosfata (TGTP) u manje toksičan tiogvanin monofosfat. Genetske varijante *NUDT15* snažno utječu na toleranciju na tiopurine kod pacijenata koji boluju od akutne limfoblastične leukemije (ALL) i upalnih bolesti crijeva. Smanjena aktivnost NUDT15 također za posljedicu ima akumulaciju toksičnih metabolita koji mogu dovesti do oštećenja funkcije koštane srži (mijelosupresija) s nuspojavama opasnim po život.

Test

Što se analizira?

Analizira se genotip pacijenta na najučestalije klinički relevantne varijante gena *TPMT (*2, *3A, *3B, *3C i *4)* koji u kombiniranih (združenih) heterozigota (eng. compound heterozygous) ili homozigota vode do potpunog gubitka aktivnosti enzima TPMT.

Također se analiziraju najučestalije, klinički relevantne varijante gena *NUDT15 (*2, *3)* koje kombinirane (združene) u heterozigota ili homozigota za posljedicu imaju djelomični ili potpuni gubitak aktivnosti enzima NUDT15.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije sa 6-tiogvaninom da bi se smanjio rizik supresije koštane srži (poremećaj hematopoeze) putem prilagođavanja početne doze ili ordiniranjem alternativnog lijeka. Genski uvjetovana smanjena aktivnost TMPT kao primarni uzrok nepodnošenja tiogvanina češća je u Europljana i Afrikanaca dok rizični aleli u *NUDT15* objašnjavaju većinu supresija koštane srži povezanih s terapijom tiopurinima u Azijata i Hispanoamerikanaca.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Postupak je temeljen na preporukama smjernica the *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2,3] uz najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenjem 6-tiogvaninom ovisno o TPMT genotipu

***TPMT* Genotip / Fenotip**	**Preporučena terapija**
Divlji tip / Normalni metabolizator	Terapija sukladno uputama o lijeku
Rizična varijanta, heterozigot / Intermedijarni metabolizator	Početna doza trebala bi iznositi 50-80 % normalne doze lijeka u nemalignim stanjima. Potrebno je podešavanje doze s obzirom na stupanj mijelosupresije
Rizična varijanta, recipročni/translokacijski heterozigoti ("compound heterozygous") ili homozigot / Spori metabolizator	Za maligna stanja: drastična redukcija inicijalne doze (10-struko reducirana doza i samo 3 dana/tjedno), potrebno je podešavanje doze s obzirom na stupanj mijelosupresije Za nemaligna stanja: razmotriti alternativnu imunosupresivnu terapiju koja nije iz skupine tiopurina

Tablica 2: Preporuke za liječenjem 6-tiogvaninom ovisno o genotipu NUDT15

***NUDT15* Genotip / Fenotip**	**Preporučena terapija**
Divlji tip / Normalni metabolizator	Terapija sukladno uputama o lijeku
Rizična varijanta, heterozigot / Intermedijarni metabolizator	Početna doza trebala bi iznositi 50-80 % prosječne doze lijeka, potrebno je podešavanje doze s obzirom na stupanje mijelosupresije
Rizična varijanta, recipročni/translokacijski heterozigoti ("compound heterozygous") ili homozigot / Spori metabolizator	Za maligna stanja: Smanjenje doze na 25 % od normalne početne doze, potrebno je podešavanje doze s obzirom na stupanj mijelosupresije Za nemaligna stanja: razmotriti alternativnu imunosupresivnu terapiju koja nije iz skupine tiopurina

Troškovi

Priznavanje i povrat troškova za analizu *TPMT i NUDT15* varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical Pharmacogenetics Implementation Consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing [published correction appears in Clin Pharmacol Ther. 2011 Dec;90(6):894]. Clin Pharmacol Ther. 2011;89(3):387-391. doi:10.1038/clpt.2010.320

[2] Relling MV, Gardner EE, Sandborn WJ, et al. *Clinical pharmacogenetics implementation consortium* guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther. 2013;93(4):324-325. doi:10.1038/clpt.2013.4

[3] Relling MV, Schwab M, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304

TRIMIPRAMINE

Genetic test to minimize the risks related to therapy with trimipramine

Drug

What are the indications and mechanisms of action of trimipramine?

Tricyclic antidepressant trimipramine is an inhibitor of both serotonin and norepinephrine reuptake in the presynaptic neuron. It also blocks H1 histamine, 5-HT2A serotonin, α1 adrenergic, D2 dopaminergic and muscarinic receptors. Trimipramine is indicated for the treatment of depression, obsessive-compulsive disorder as well as neuropathic pain and migraine prophylaxis.

Genes

Which genes influence the effect of trimipramine?

Trimipramine, as tertiary amine, is metabolized via the enzyme CYP2C19 to secondary amine. Both are further metabolized via the CYP2D6 enzyme to less-active metabolites. Several variants in the genes of these two enzymes are known in the population. These lead to great variability in the enzymatic efficacy of CYP2C19 and CYP2D6, and can, therefore, be of vital importance for trimipramine therapy.

Test

What will be tested?

In order to determine the CYP2C19 as well as the CYP2D6 metabolism type, the patient's genotype is tested for the most common activity-varying variants in the *CYP2C19* gene *(*2, *3, *17)* and in the *CYP2D6* gene *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41).*

Indication

When should a test be performed?

The genetic test should be performed before the start of planned therapy with trimipramine in order to adjust the dosage or to make a change of active ingredient if necessary.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following recommendations are based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline[1,2] and have the highest clinical level of evidence 1A for *CYP2D6* and clinical level of evidence 2A for *CYP2C19*.

Table 1: Recommendations for trimipramine therapy depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (1-20 %)	Usage of trimipramine is not recommended, the prescription of an alternative agent is recommended. If trimipramine is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Therapeutic drug monitoring is strongly recommended
Normal metabolizer (72-88 %)	Initiate therapy with recommended starting dose
Intermediate metabolizer (1-13 %)	Reduction of starting dose of trimipramine by 25 %
Poor metabolizer (1-10 %)	Usage of trimipramine is not recommended, the prescription of an alternative agent is recommended. If trimipramine is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Table 2: Recommendations for trimipramine therapy depending on the phenotype of the CYP2C19 gene

CYP2C19 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid metabolizer (2-5 %)	Usage of trimipramine is not recommended, the prescription of an alternative agent is recommended. If trimipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Rapid metabolizer (2-30 %)	Usage of trimipramine is not recommended, the prescription of an alternative agent is recommended. If trimipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments
Normal metabolizer (35-50 %)	Initiate therapy with the recommended starting dose
Intermediate metabolizer (18-45 %)	Initiate therapy with the recommended starting dose
Poor metabolizer (2-15 %)	Usage of trimipramine is not recommended, prescription of an alternative agent is recommended. If trimipramine is warranted, consider a 50 % reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments

Nota bene: If a patient is treated with lower doses of trimipramine and is an intermediate or poor CYP2D6/CYP2C19 metabolizer, no dose adjustment is recommended because of a lower prescribed dose initially. Patients should be monitored for potential side effects.

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

TRIMIPRAMIN

Gentest zur Risikominimierung der Therapie mit Trimipramin

Wirkstoff

Was sind die Indikationen und der Wirkmechanismus von Trimipramin?

Das trizyklische Antidepressivum Trimipramin hemmt die Wiederaufnahme von Serotonin und Noradrenalin im präsynaptischen Neuron. Es blockiert auch H1-Histamin-, 5-HT2A-Serotonin-, α1-adrenerge, D2-dopaminerge und muskarinische Rezeptoren. Trimipramin ist zur Behandlung von Depressionen, Zwangsstörungen sowie neuropathischen Schmerzen und Migräneprophylaxe indiziert.

Gene

Welche Gene beeinflussen die Wirkung von Trimipramin?

Trimipramin als tertiäres Amin wird über das Enzym CYP2C19 zu sekundärem Amin metabolisiert. Beide werden über das CYP2D6-Enzym zu weniger aktiven Metaboliten weiter metabolisiert. In der Population sind mehrere Varianten der Gene dieser beiden Enzyme bekannt. Diese führen zu einer großen Variabilität der enzymatischen Wirksamkeit von CYP2C19 und CYP2D6 und können daher für die Trimipramintherapie von entscheidender Bedeutung sein.

Test

Was wird getestet?

Um sowohl den CYP2C19- als auch den CYP2D6-Metabolismustyp zu bestimmen, wird das Erbgut des Patienten im *CYP2C19*-Gen *(*2, *3, *17)* und im *CYP2D6*-Gen *(*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41)* auf die häufigsten aktivitätsvariierenden Genvarianten getestet.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Trimipramin durchgeführt werden, um eine Dosisanpassung vorzunehmen und gegebenfalls einen Wirkstoffwechsel in Erwägung zu ziehen, um schwere Nebenwirkungen zu vermeiden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] und zeigt für *CYP2D6* das höchste klinische Evidenzlevel 1A, für *CYP2C19* ein mittleres klinisches Evidenzlevel 2A.

Tabelle 1: Empfehlungen für die Trimipramin-Therapie in Abhängigkeit vom Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisierungshäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-20 %)	Trimipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Trimipramin: Titration auf höhere Zieldosis (verglichen zu normalen Metabolisierern) mit therapeutischem *Drug Monitoring*
Schnelle Metabolisierer (72-88 %)	Anwendung gemäß Fachinformation
Intermediäre Metabolisierer (1-13 %)	Startdosis um 25 % reduzieren bei therapeutischem *Drug Monitoring*
Langsame Metabolisierer (1-10 %)	Trimipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Trimipramin: Startdosis um 50 % reduzieren bei therapeutischem *Drug Monitoring*

Tabelle 2: Empfehlungen für die Trimipramin-Therapie in Abhängigkeit vom Phänotyp des CYP2C19-Gens

CYP2C19 Phänotyp (Metabolisierungshäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (2-5 %)	Trimipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Trimipramin: therapeutisches *Drug Monitoring*
Schnelle Metabolisierer (2-30 %)	Trimipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Trimipramin: therapeutisches *Drug Monitoring*
Normale Metabolisierer (35-50 %)	Beginn mit Startdosis
Intermediäre Metabolisierer (18-45 %)	Beginn mit Startdosis
Langsame Metabolisierer (2-15 %)	Trimipramin kontraindiziert, Wirkstoffwechsel empfohlen Bei Einsatz Trimipramin: Reduktion Startdosis um 50 % bei therapeutischem *Drug Monitoring*

Nota bene: Wenn ein Patient mit niedrigen Dosen von Trimipramin behandelt wird und ein intermediärer oder langsamer CYP2D6/CYP2C19-Metabolisierer ist, wird aufgrund einer anfänglich niedrigeren verschriebenen Dosis keine Dosisanpassung empfohlen. Die Patienten sollten auf mögliche Nebenwirkungen überwacht werden.

Kosten

Die Kosten für die genetische Analyse der *CYP2D6*- und *CAP2C19*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2.

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597.

TRIMIPRAMIN

Genetički test za smanjenje rizika pri primjeni trimipramina

Lijek

Koje su indikacije i mehanizmi djelovanja trimipramina?

Triciklički antidepresiv trimipramin je inhibitor ponovne pohrane serotonina i noradrenalina u presinaptičkom neuronu. Također blokira histaminske H1, serotoninergičke 5-HT2A, α-adrenergičke, D2 dopaminergičke i muskarinske receptore. Koristi se za liječenje depresije, anksioznih poremećaja te nesanice.

Geni

Koji geni utječu na djelovanje trimipramina?

Trimipramin se, kao tercijarni amin, metabolizira preko enzima CYP2C19 u sekundarni amin. Oba se dalje metaboliziraju putem enzima CYP2D6 u manje aktivne metabolite. Oba enzima određuju učinkovitost i duljinu djelovanja trimipramina. Nekoliko genskih polimorfizama dovode do velike varijabilnosti u enzimatskoj funkciji CYP2C19 i CYP2D6.

Analiza

Što se analizira?

Kako bi se odredio fenotip enzima CYP2C19 i CYP2D6, analizira se genotip bolesnika na najučestalije polimorfizme *CYP2C19 (*2, *3, *17)* te *CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, 9*, *10, *41)*.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije trimipraminom, kako bi se po potrebi prilagodilo doziranje lijeka ili ordinirala zamjenska terapija.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] te imaju najvišu kliničku razinu dokaza 1A za CYP2D6 te srednju kliničku razinu dokaza 2A za CYP2C19.

Tablica 1: Preporuke za liječenje trimipraminom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizatori (1-20 %)	Ne preporučuje se liječenje trimipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja trimipraminom, potrebno je istitrirati početnu dozu lijeka na veću u odnosu na normalne metabolizatore te se preporučuje terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizatori (77-88 %)	Koristiti lijek prema sažetku opisa svojstava lijeka
Intermedijarni metabolizatori (1-13 %)	Smanjenje početne doze trimipramina za 25 %
Spori metabolizatori (1-10 %)	Ne preporučuje se liječenje trimipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2D6 enzimom. Ukoliko postoji opravdanost liječenja trimipraminom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Tablica 2: Preporuke za liječenje trimipraminom ovisno o fenotipu CYP2C19

CYP2C19 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizatori (2-5 %)	Ne preporučuje se liječenje trimipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja trimipraminom preporučuje se terapijsko praćenje lijeka radi modifikacije doze
Brzi metabolizatori (2-30 %)	Ne preporučuje se liječenje trimipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja trimipraminom preporučuje se terapijsko praćenje lijeka radi modifikacije doze
Normalni metabolizatori (35-50 %)	Započeti terapiju preporučenom početnom dozom
Intermedijarni metabolizatori (18-45 %)	Započeti terapiju preporučenom početnom dozom
Spori metabolizatori (2-15 %)	Ne preporučuje se liječenje trimipraminom. Potrebno je ordinirati zamjensku terapiju lijekovima koji se ne metaboliziraju CYP2C19 enzimom. Ukoliko postoji opravdanost liječenja trimipraminom, potrebno je smanjiti početnu dozu lijeka za 50 % te se preporučuje terapijsko praćenje lijeka radi modifikacije doze

Nota bene: Ukoliko se liječi nesanica, a pacijent je intermedijarni ili spori CYP2D6 / CYP2C19 metabolizator, ne preporučuje se prilagodba doze zbog već inicijalno propisane niže doze. Pacijente treba nadzirati zbog potencijalnih nuspojava.

Troškovi

Priznavanje povrata troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi za određivanje genotipa *CYP2C19* i *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Hicks JK, Swen JJ, Thorn CF, et al. *Clinical Pharmacogenetics Implementation Consortium* guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther. 2013;93(5):402-408. doi:10.1038/clpt.2013.2

[2] Hicks JK, Sangkuhl K, Swen JJ, et al. *Clinical pharmacogenetics implementation consortium* guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597

TROPISETRON

Genetic test to minimize the risks related to therapy with tropisetron

Drug

What are the indications and mechanisms of action of tropisetron?

Tropisetron suppresses nausea and vomiting by selectively blocking 5-HT3 receptors centrally and peripherally, thereby preventing serotonin-mediated emetogenic signaling. Tropisetron is used in the prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting.

Genes

What genes influence the effect of tropisetron?

The 5-HT3 receptor antagonists are generally well tolerated. Tropisetron is extensively metabolized by CYP2D6 to inactive metabolites and further conjugated to glucuronides and sulfates. *CYP2D6* gene is a highly polymorphic gene with over 100 known allelic variants and subvariants. Increased activity of CYP2D6 is associated with a higher clearance of tropisetron and decreased therapeutic response.

Test

What is tested?

Patient's genotype is analyzed for the most common *CYP2D6* variants like *CYP2D6 *1* and **2* that are associated with normal functions, *CYP2D6 *9, *10* and **41* that are associated with reduced functions, *CYP2D6 *3,*4, *5, *6* that are associated with complete lack of functions, while *CYP2D6 *1xN*, where xN represents the copy number of the *CYP2D6* gene, is associated with an increase in function.

Indication

When should a test be carried out?

It is recommended to do pharmacogenetic *CYP2D6* analysis for patients with inadequate therapeutic response to tropisetron, patients suffering side effects, patients which are preparing for chemotherapy, radiotherapy or surgical procedure after which nausea and vomiting are expected.

Consequences and test result

How does the therapy need to be adjusted to the test result?

The following recommendations are based on the guidelines of the *Clinical Pharmacogenetic Implementation Consortium (CPIC)*[1] and have the highest clinical level of evidence 1A.

Table 1: Recommendations for the therapy with tropisetron depending on the phenotype of the CYP2D6 gene

CYP2D6 Phenotype (metabolizer status frequencies)	Recommended therapy
Ultrarapid Metabolizer (1-2 %)	Usage of tropisetron is not recommended, prescription of an alternative agent is recommended (i.e. granisetron)
Normal Metabolizer (77-92 %)	Usage according to the Summary of Product Characteristics
Intermediate Metabolizer (2-11 %)	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Usage according to the Summary of Product Characteristics
Poor Metabolizer (5-10 %)	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Usage according to the Summary of Product Characteristics

Cost

Costs for the *CYP2D6* gene analysis will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Bell GC, Caudle KE, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017;102(2):213-218. doi:10.1002/cpt.598

TROPISETRON

Gentest zur Risikominimierung der Therapie mit Tropisetron

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Tropisetron?

Tropisetron ist ein Antagonist des 5-HT_3-Rezeptors. Der Wirkstoff unterdrückt Übelkeit und Erbrechen, indem er selektiv an 5-HT_3-Rezeptoren bindet und so die Serotonin-vermittelte emetogene Signalübertragung verhindert. Tropisetron wird zur Vorbeugung von durch Chemotherapie induzierter, strahleninduzierter und postoperativer Übelkeit und Erbrechen eingesetzt.

Gene

Welche Gene beeinflussen die Wirkung von Tropisetron?

Die 5-HT_3-Rezeptorantagonisten sind allgemein gut verträglich. Kopfschmerzen, Verstopfung, Durchfall und vorübergehende Erhöhungen der Leberenzyme sind häufige Nebenwirkungen. Tropisetron wird durch CYP2D6 weitgehend zu inaktiven Metaboliten metabolisiert und weiter an Glucuronide und Sulfate konjugiert. Das *CYP2D6*-Gen ist ein hochpolymorphes Gen mit mehr als 100 bekannten Allelvarianten und Subvarianten. Eine erhöhte Aktivität von CYP2D6 ist mit einer höheren Clearance von Tropisetron und einer verminderten therapeutischen Reaktion verbunden.

Test

Was wird getestet?

Das Erbgut des Patienten wird auf die häufigsten *CYP2D6*-Genvarianten überprüft: *CYP2D6*1* und **2* sind mit normalen Funktionen assoziiert; *CYP2D6*9, *10*, **41* sind mit reduzierten Funktionen assoziiert; *CYP2D6*3*, **4*, **5*, **6* sind mit völligem Mangel an Funktionen assoziiert; *CYP2D6*1xN* ist mit einer Funktionssteigerung verbunden.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor einer geplanten Therapie mit Tropisetron bei Patienten, die sich auf eine Chemotherapie, Strahlentherapie oder einen chirurgischen Eingriff vorbereiten, nach denen Übelkeit und Erbrechen zu erwarten sind, durchgeführt werden.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Tropisetron-Therapie nach Phänotyp des CYP2D6-Gens

CYP2D6 Phänotyp (Metabolisierungshäufigkeit)	Therapieempfehlung
Ultraschnelle Metabolisierer (1-2 %)	Wirkstoffwechsel empfohlen
Schnelle Metabolisierer (77-92 %)	Therapie gemäß Fachinformation
Intermediäre Metabolisierer (2-11 %)	Startdosis gemäß Fachinformation, unzureichende klinische Evidenz
Langsame Metabolisierer (5-10 %)	Startdosis gemäß Fachinformation, unzureichende klinische Evidenz

Kosten

Die Kosten für die genetische Analyse des *CYP2D6*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

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[1] Bell GC, Caudle KE, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017;102(2):213-218. doi:10.1002/cpt.598

TROPISETRON

Genetički test za smanjenje rizika pri primjeni tropisetrona

Lijek

Koje su indikacije i mehanizmi djelovanja tropisetrona?

Tropisetron smanjuje mučninu i povraćanje selektivno inhibirajući 5-HT3 receptore središnje i periferno, na taj način prevenira emetogene signale posredovane serotoninom. Tropisetron se koristi u prevenciji mučnina i povraćanja koji nastaju kao posljedica kemoterapije, radioterapije ili postoperativno.

Geni

Koji geni utječu na djelovanje tropisetrona?

Antagonisti 5-HT3 receptora općenito se dobro podnose. Tropisetron se ekstenzivno metabolizira putem CYP2D6 u inaktivne metabolite i dalje konjugira u glukuronide i sulfate. *CYP2D6* je visoko polimorfan gen s preko 100 poznatih alelnih varijanti i subvarijanti. Povećana aktivnost CYP2D6 je povezana s bržim klirensom tropisetrona i smanjenim terapijskim odgovorom.

Analiza

Što se analizira?

Pacijentov genotip se analizira na najčešće varijante *CYP2D6* poput *CYP2D6 *1* i **2* koje su povezane s normalnom funkcijom, *CYP2D6 *9, *10* i **41* koje su povezane sa smanjenom funkcijom, *CYP2D6 *3, *4, *5, *6* koje su povezane s potpunim gubitkom funkcije, dok se *CYP2D6 *1xN*, gdje xN prezentira broj kopija *CYP2D6* gena povezuje s povećanom funkcijom.

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti kod pacijenata koji nemaju odgovarajući terapijski odgovor na tropisetron ili nuspojave te kod pacijenata koji se pripremaju za početak kemoterapije, radioterapije ili operativni zahvat nakon kojeg se očekuje pojava mučnine ili povraćanja.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke su temeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] i imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za liječenje tropisetronom ovisno o fenotipu CYP2D6

CYP2D6 fenotip (učestalost fenotipa)	Preporučena terapija
Ultrabrzi metabolizator (1-2 %)	Nije preporučena upotreba tropisetrona, preporučuje se upotreba alternativnog lijeka poput granisetrona
Normalni metabolizator (77-92 %)	Terapija sukladno uputama o lijeku
Intermedijarni metabolizator (2-11 %)	Započinjanje terapije s preporučenom početnom dozom zbog nedovoljno dokaza o utjecaju genotipa na djelovanje lijeka
Spori metabolizator (2-11 %)	Započinjanje terapije s preporučenom početnom dozom zbog nedovoljno dokaza o utjecaju genotipa na djelovanje lijeka

Troškovi

Priznavanje i povrat troškova za navedenu analizu varira od države do države. Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize *CYP2D6* bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

[1] Bell GC, Caudle KE, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017;102(2):213-218. doi:10.1002/cpt.598

VORICONAZOLE

Genetic test to minimize the risks related to therapy with voriconazole

Drug

What are the indications and mechanisms of action of voriconazole?

Voriconazole is a triazole antifungal agent that inhibits ergosterol synthesis by inhibiting lanosterol 14α-demethylase. Voriconazole is selective for the fungal membrane. It is approved for the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, disseminated Candida infections, esophageal candidiasis, as well as infections caused by *Scedosporium apiospermum* and *Fusarium spp*.

Genes

Which genes influence the effect of voriconazole?

Voriconazole is metabolized predominantly by CYP2C19 with a minor contribution from CYP3A and CYP2C9. There is substantial evidence linking the *CYP2C19* genotype with phenotypic variability in voriconazole concentrations. Adverse effects that have been correlated with voriconazole concentrations include hepatotoxicity, visual disturbances, visual hallucinations, and other neurologic disorders.

Test

What will be tested?

To determine the CYP2C19 metabolism type, the patients' *CYP2C19* genotype is tested for the most common activity-variant variants (*1, *2, *3, *17).

Indication

When should be a test performed?

The genetic test should be performed in patients before the initiation of voriconazole therapy. Knowledge of the *CYP2C19* genotype may prevent the development of serious adverse drug reactions or subtherapeutic concentrations of voriconazole that may lead to treatment failure.

Consequences and test results

How does the therapy have to be adapted to the test results?

The following recommendation is based on the *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines[1] and has the highest clinical level of evidence 1A. In pediatric patients there is insufficient evidence to distinguish a *CYP2C19*1/*17* and **1/*1* and there are separate recommendations for CYP2C19 ultrarapid and rapid metabolizers.

Table 1: Recommendations for voriconazole therapy depending on the phenotype of the CYP2C19 gene in adult patients.

CYP2C19 **Genotype / Phenotype (metabolizer status frequencies)**	**Recommended therapy**
**17/*17* / Ultrarapid metabolizers (2-5 %)	Usage of voriconazole is not recommended, prescription of an alternative agent is recommended
**1/*17* / Rapid metabolizers (2-30 %)	Usage of voriconazole is not recommended, prescription of an alternative agent is recommended
**1/*1* / Normal metabolizers (35-50 %)	Usage according to the Summary of Product Characteristics
**1/*2, *1/*3, *2/*17* / Intermediate metabolizers (18-45 %)	Usage according to the Summary of Product Characteristics
**2/*2, *2/*3, *3/*3* / Poor metabolizers (2-15 %)	Usage of voriconazole is not recommended, prescription of an alternative agent is recommended

Table 2: Recommendations for voriconazole therapy depending on the phenotype of the CYP2C19 gene in pediatric patients (children and adolescents <18 years old)

***CYP2C19* Genotype / Phenotype (metabolizer status frequencies)**	**Recommended therapy**
**17/*17* / Ultrarapid metabolizers	Usage of voriconazole is not recommended, prescription of an alternative agent is recommended
**1/*17* / Rapid metabolizers	Standard dosing recommendations with therapeutic drug monitoring
**1/*1* / Normal metabolizers	Usage according to the Summary of Product Characteristics
**1/*2, *1/*3, *2/*17* / Intermediate metabolizers	Usage according to the Summary of Product Characteristics
**2/*2, *2/*3, *3/*3* / Poor metabolizers	Usage of voriconazole is not recommended, prescription of an alternative agent is recommended

Costs

Costs for genetic analyses will be reimbursed for statutory and privately insured patients if the testing is prescribed by a physician. The attending physician's budget is not burdened as a result.

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[1] Moriyama B, Obeng AO, Barbarino J, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines for CYP2C19 and Voriconazole Therapy [published correction appears in Clin Pharmacol Ther. 2018 Feb;103(2):349]. Clin Pharmacol Ther. 2017;102(1):45-51. doi:10.1002/cpt.583

VORICONAZOL

Gentest zur Risikominimierung der Therapie mit Voriconazol

Wirkstoff

Was sind die Indikationen und Wirkmechanismen von Voriconazol?

Voriconazol ist ein Triazol-Antimykotikum, das die Ergosterolsynthese durch Hemmung der Lanosterol-14α-Demethylase hemmt. Voriconazol ist selektiv für die Pilzmembran. Es ist für die Behandlung von invasiver Aspergillose, Candidämie bei nicht neutropenischen Patienten, disseminierten Candida-Infektionen, Candidiasis der Speiseröhre sowie Infektionen durch *Pseudallescheria boydii* (*Scedosporium apiospermum* anamorph) und *Fusarium spp.* zugelassen.

Gene

Welche Gene beeinflussen die Wirkung von Voriconazol?

Voriconazol wird überwiegend durch CYP2C19 mit geringem Beitrag von CYP3A und CYP2C9 metabolisiert. Es gibt wesentliche Hinweise, die den *CYP2C19*-Genotyp mit der phänotypischen Variabilität der Voriconazol-Konzentrationen in Verbindung bringen. Zu den Nebenwirkungen, die mit den Voriconazol-Konzentrationen korreliert wurden, gehören Hepatotoxizität, Sehstörungen, visuelle Halluzinationen und andere neurologische Störungen.

Test

Was wird getestet?

Um den CYP2C19-Metabolismus-Typ zu bestimmen, wird das Erbgut des Patienten auf die häufigsten aktivitätsvariablen Genvarianten im *CYP2C19*-Gen (**1*, **2*, **3*, **17*) analysiert.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor Beginn einer geplanten Therapie mit Voriconazol durchgeführt werden, um die Dosierung anzupassen oder gegebenenfalls den Wirkstoff zu ändern.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1] und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Voriconazol-Therapie nach Phänotyp des CYP2C19-Gens für erwachsene Patienten

***CYP2C19* Genotyp / Phänotyp (Metabolisiererhäufigkeit)**	**Therapieempfehlung**
**17/*17* / Ultraschnelle Metabolisierer (2-5 %)	Voriconazol kontraindiziert, Wirkstoffwechsel empfohlen
**1/*17* / Schnelle Metabolisierer (2-30 %)	Voriconazol kontraindiziert, Wirkstoffwechsel empfohlen
**1/*1* / Normale Metabolisierer (35-50 %)	Therapie gemäß Fachinformation
**1/*2, *1/*3, *2/*17* / Intermediäre Metabolisierer (18-45 %)	Therapie gemäß Fachinformation
**2/*2, *2/*3, *3/*3* / Langsame Metabolisierer (2-15 %)	Voriconazol kontraindiziert, Wirkstoffwechsel empfohlen

Tabelle 2: Empfehlungen für die Voriconazol-Therapie nach Phänotyp des CYP2C19-Gens für Kinder und Jugendliche <18 Jahre

***CYP2C19* Genotyp / Phänotyp (Metabolisiererhäufigkeit)**	**Therapieempfehlung**
**17/*17* / Ultraschnelle Metabolisierer	Voriconazol kontraindiziert, Wirkstoffwechsel empfohlen
**1/*17* / Schnelle Metabolisierer	Mit normaler Startdosis beginnen, mit therapeutischem *Drug Monitoring* auf therapeutischen Spiegel titrieren
**1/*1* / Normale Metabolisierer	Therapie gemäß Fachinformation
**1/*2, *1/*3, *2/*17* / Intermediäre Metabolisierer	Therapie gemäß Fachinformation
**2/*2, *2/*3, *3/*3* / Langsame Metabolisierer	Voriconazol kontraindiziert, Wirkstoffwechsel empfohlen

Kosten

Die Kosten für die genetische Analyse des *CYP2C19*-Gens werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Moriyama B, Obeng AO, Barbarino J, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines for CYP2C19 and Voriconazole Therapy [published correction appears in Clin Pharmacol Ther. 2018 Feb;103(2):349]. Clin Pharmacol Ther. 2017;102(1):45-51. doi:10.1002/cpt.583

VORIKONAZOL

Genetički test za smanjenje rizika pri primjeni vorikonazola

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja vorikonazola?

Vorikonazol je antimikotik iz skupine triazola koji inhibira sintezu ergosterola, inhibirajući demetilaciju 14-lanosterola. Vorikonazol pokazuje selektivnu osjetljivost prema gljivičnoj membrani. Odobren je za liječenje invazivne aspergiloze, sistemske infekcije Candidom kod bolesnika koji nisu razvili neutropeniju, diseminirane kandidijaze, kandidijaze jednjaka te infekcija uzrokovanih glijivama Scedosporium apiospermum i Fusarium species.

Geni

Koji geni utječu na djelovanje vorikonazola?

Vorikonazol se metabolizira u jetri primarno putem CYP2C19, a manjim dijelom putem CYP3A i CYP2C9. Postoje mnogobrojni dokazi koji povezuju *CYP2C19* genotip s fenotipskom varijabilnošću koncentracija vorikonazola. Neki od neželjenih učinaka koji su u vezi s koncentracijom vorikonazola su: jetrena toksičnost, vizualne smetnje, vizualne halucinacije i druge neurološki poremećaji.

Analiza

Što se analizira?

Kako bi se odredio tip CYP2C19 metabolizatora, kod pacijenta se određuje genotip *CYP2C19 (*1, *2, *3, *17).* Testiraju se varijante gena koje su najčešće povezane s aktivnošću enzima.

Indikacije

U kojim slučajevima je potrebno napraviti test?

Genetički test bi trebalo napraviti prije uvođenja terapije vorikonazolom. Poznavanje genotipa *CYP2C19* omogućuje definiranje metaboličkog fenotipa i odgovarajuće doziranje lijeka čime su izbjegnute opasnosti od subdoziranja ili pak predoziranja i razvoja nuspojava.

Preporuke

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke se temelje na *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines[1] i imaju najvišu razinu kliničke značajnosti 1A. Kod pedijatrijskih pacijenata ne postoji dovoljno dokaza za razlikovanje *CYP2C19*1/*17* od **1/*1* varijante pa stoga postoje odvojene preporuke za CYP2C19 ultra-brze i brze metabolizatore.

Tablica 1: Preporuke za doziranje vorikonazola ovisno o fenotipu CYP2C19 kod odraslih pacijenata

***CYP2C19* genotip / fenotip (učestalost fenotipa)**	**Preporučena terapija**
**17/*17* / Ultrabrzi metabolizator (2-5 %)	Uporaba vorikonazola se ne preporučuje. Izabrati alternativni lijek
**1/*17* / Brzi metabolizator (2-30 %)	Uporaba vorikonazola se ne preporučuje. Izabrati alternativni lijek
**1/*1* / Normalni metabolizator (35-50 %)	Uporaba u skladu s uputama o lijeku
**1/*2, *1/*3, *2/*17* / intermedijarni metabolizator (18-45 %)	Uporaba u skladu s uputama o lijeku
**2/*2, *2/*3, *3/*3* / Spori metabolizator (2-15 %)	Uporaba vorikonazola se ne preporučuje. Izabrati alternativni lijek

Tablica 2: Preporuke za doziranje vorikonazola ovisno o fenotipu CYP2C19 kod pedijatrijskih pacijenata (djeca i adolescenti <18 godina)

***CYP2C19* genotip / fenotip**	**Preporučena terapija**
**17/*17* / Ultrabrzi metabolizator	Uporaba vorikonazola se ne preporučuje. Izabrati alternativni lijek.
**1/*17* / Brzi metabolizator	Standardno doziranje uz praćenje koncentracije lijeka u krvi
**1/*1* / Normalni metabolizator	Uporaba u skladu s uputama o lijeku
**1/*2, *1/*3, *2/*17* / Intermedijarni metabolizator	Uporaba u skladu s uputama o lijeku
**2/*2, *2/*3, *3/*3* / Spori metabolizator	Uporaba vorikonazola se ne preporučuje. Izabrati alternativni lijek

Troškovi

Troškovi genetičkog testa će biti refundirani pacijentima s državnim i privatnim osiguranjem ukoliko je testiranje indicirano od strane liječnika. Troškovi testiranja neće utjecati na proračun nadležnog liječnika ili institucije u kojoj liječnik radi.

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[1] *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guidelines for CYP2C19 and Voriconazole Therapy. Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, Agúndez J, Wingard JR, McLeod HL, Klein TE, Cross SJ, Caudle KE11, Walsh TJ.Clin Pharmacol Ther. 2017, 102(1):45-51 (PMID: 27981672)

WARFARIN

Genetic test to minimize the risks related to therapy with warfarin

Drug

What are the indications and mechanisms of action of warfarin?

Warfarin is a widely used anticoagulant with a narrow therapeutic index prescribed for prophylaxis and treatment of venous thromboembolism (DVT), in the prevention of systematic embolism associated with atrial fibrillation and cardiac valve replacement, stroke, reinfarction or sudden cardiac death in patients with acute myocardial infarction. Large interpatient variability in the warfarin concentrations implicates either lack of anticoagulant effect or serious drug adverse events and complications (bleeding). As a vitamin K antagonist, warfarin suppresses the activation of the coagulation factors II, VII, IX and X as well as the synthesis of the anticoagulant proteins C and S. Along with warfarin, phenprocoumon and acenocoumarol belong to the same group of anticoagulants.

Genes

Which genes influence the effect of warfarin?

VKORC1 and *CYP2C9* genes have the most significant impact on warfarin dosage. *VKORC1* encodes the vitamin K-epoxide reductase complex, the target enzyme of warfarin. A common variant upstream of *VKORC1* on position *1639 G>A* is significantly associated with warfarin sensitivity and patients carrying such polymorphism (*1639 A/A* and *A/G*) require progressively lower warfarin doses than homozygotes (*1639 G/G*). *CYP2C9* encodes for hepatic drug-metabolizing enzyme important for dose variability. Two common gene variants in *CYP2C9*2* and **3* influence the metabolism rate among individuals of European and East Asian ancestry. Additionally, identified gene variants in genes *CYP4F2*3* and *CYP2C cluster* (rs12777823) have a minor contribution to dose requirements.

Test

What will be tested?

To determine the optimal warfarin dose, the most common risk variants of the *VKORC1 1639G>A*, *CYP2C9*2* and **3*, and *CYP4F2*3* are tested.

CYP2C cluster gene variant rs12777823 is associated with a clinically relevant effect on warfarin clearance in the population of African Americans (almost West African ancestry).

Indication

When should a test be performed?

The genetic test should be performed before a planned therapy with warfarin in order to quickly achieve stable INR (international normalized ratio) values through dose adjustment if necessary and to avoid bleeding, specifically in individuals who are carriers of multiple allelic variants. The risk of developing complications is the greatest at warfarin dosing initiation.

Consequences of test results

How does the therapy have to be adapted to the test results?

The following procedure takes place in accordance with *Clinical Pharmacogenetics Implementation Consortium (CPIC)* guidelines[1,2] for warfarin and have the highest clinical level of evidence 1A.

Table 1: Recommendations for Warfarin dosing based on genotype for adult patients

Genotype	Dosing (Non–African Ancestry)	Dosing (African Ancestry)
VKORC1 (1639G>A)	Dosing based on validated published pharmacogenetic algorithms	Dosing based on validated published pharmacogenetic algorithms
*CYP2C9 *2, *3*	Dosing based on validated published pharmacogenetic algorithms	Dosing based on validated published pharmacogenetic algorithms
*CYP2C9 *5, *6, *8, *11*	Decrease calculated dose by 15-30 %	Decrease calculated dose by 15-30 %
*CYP4F2*3*	Increase dose by 5-10 %	/
CYP2C cluster (rs 12777823)	/	Decrease calculated dose by 10-25 %

Nota bene: Using genetic information to guide dosing may lead to false security. In particular, there are risks of using pharmacogenetic dosing in individuals of African ancestry if only *CYP2C9*2* and **3* alleles are included, which is indeed the case in most FDA-approved *CYP2C9* tests. The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group (DPWG) has evaluated therapeutic dose recommendations for phenprocoumon and acenocoumarol based on VKORC1 genotype. The patients with VKORC1 – 1639 AA genotype should receive 50 % of the standard initial dose and more frequent monitoring of INR. There is no recommendation for dose adjustment based on CYP2C9 genotype.

Costs

Costs for the *VKORC1* and *CYP2C9* genetic analyses will be reimbursed for statutory and privately insured patients if the physician prescribes the testing, although most insurance plans do not currently pay for warfarin pharmacogenetic testing.

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[1] Johnson JA, Gong L, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011;90(4):625-629. doi:10.1038/clpt.2011.185

[2] Johnson JA, Caudle KE, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017;102(3):397-404. doi:10.1002/cpt.668

WARFARIN

Gentest zur Risikominimierung der Therapie mit Warfarin

Wirkstoff

Was sind Indikationen und Wirkmechanismen von Warfarin?

Warfarin ist ein weit verbreitetes Antikoagulans mit einem engen therapeutischen Index, das zur Prophylaxe und Behandlung von venösen Thromboembolien (DVT) verschrieben wird, um systematische Embolien im Zusammenhang mit Vorhofflimmern und Herzklappenersatz, Schlaganfall, Reinfarkt oder plötzlichem Herztod bei Patienten mit akutem Myokardinfarkt zu verhindern. Eine große Variabilität der Warfarin-Konzentrationen impliziert entweder einen Mangel an gerinnungshemmender Wirkung oder in den Patienten schwerwiegende unerwünschte Ereignisse und Komplikationen (Blutungen). Als Vitamin-K-Antagonist unterdrückt Warfarin die Aktivierung der Gerinnungsfaktoren II, VII, IX und X sowie die Synthese der Antikoagulansproteine C und S. Phenprocoumon und Acenocoumarol gehören neben Warfarin zur gleichen Gruppe von Antikoagulantien.

Gene

Welche Gene beeinflussen die Wirkung von Warfarin?

Die *VKORC1*- und *CYP2C9*-Gene beeinflussen maßgeblich die Warfarin-Dosierung. VKORC1 codiert den Vitamin K-Epoxid-Reduktase-Komplex, das Zielenzym von Warfarin. Eine häufige Variante stromaufwärts von *VKORC1* an Position *1639 G>A* ist signifikant mit der Warfarinsensitivität assoziiert, und Patienten mit einem solchen Polymorphismus (*1639 A/A* und *A/G*) benötigen im weiteren Verlauf niedrigere Warfarin-Dosen als Homozygote (*1639 G/G*). *CYP2C9* kodiert für ein für die Dosisvariabilität wichtiges hepatisches Arzneimittel metabolisierendes Enzym. Zwei häufige Genvarianten in *CYP2C9*2*, **3* beeinflussen die Stoffwechselrate bei Personen europäischer und ostasiatischer Abstammung. Additiv leisten identifizierte Genvarianten in den Genen *CYP4F2*3* und im *CYP2C-Cluster* (rs12777823) einen geringen Beitrag zum Dosisbedarf.

Test

Was wird getestet?

Um die am besten geeignete Warfarin-Dosis zu bestimmen, werden die häufigsten Risikovarianten von *VKORC1 1639G>A*, *CYP2C9*2*, **3*, und *CYP4F2*3* im Erbgut der Patienten getestet. Die *CYP2C-Cluster*-Genvariante rs12777823 ist mit einer klinisch relevanten Auswirkung auf die Warfarin-Clearance in der Bevölkerung von Afroamerikanern verbunden.

Indikation

Wann sollte ein Test durchgeführt werden?

Der Gentest sollte vor einer geplanten Therapie mit Warfarin durchgeführt werden, um bei Bedarf durch Dosisanpassung schnell konstante INR-Werte (International Normalized Ratio) zu erreichen und Nebenwirkungen (Blutungen) zu vermeiden. Das Risiko, Komplikationen zu entwickeln, ist bei Beginn der Warfarin-Dosierung am größten. Beachtet werden sollte eine Einführung von Warfarin in die Therapie und eine Titration seiner stabilen Dosis sowie einige individuelle Faktoren: Alter, Geschlecht, Körpergewicht, Rasse, interagierende Medikamente (insbesondere Amiodaron), Vitamin-K-Aufnahme (Lebensmittel, insbesondere Zitrusfrüchte (Grapefruit), grünes Gemüse), Rauchen und Komorbiditäten.

Konsequenzen der Testergebnisse

Wie muss die Therapie an die Testergebnisse angepasst werden?

Folgendes Vorgehen basiert auf Empfehlungen des *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] für Warfarin und zeigt das höchste klinische Evidenzlevel 1A.

Tabelle 1: Empfehlungen für die Warfarin-Dosierung mit VKORC1-CYP2C9-CYP4F2-CYP2C-cluster-Genotyp für erwachsene Patienten

Genotyp	Dosierung (Nicht-afrikanische Abstammung)	Dosierung (Afrikanische Abstammung)
VKORC1 (1639G>A)	Dosierung basierend auf validierten veröffentlichten pharmakogenetischen Algorithmen	Dosierung basierend auf validierten veröffentlichten pharmakogenetischen Algorithmen
*CYP2C9 *2, *3*	Dosierung basierend auf validierten veröffentlichten pharmakogenetischen Algorithmen	Dosierung basierend auf validierten veröffentlichten pharmakogenetischen Algorithmen
*CYP2C9 *5,*6, *8, *11*	Verringerung der berechneten Dosis um 15-30 %	Verringerung der berechneten Dosis um 15-30 %
*CYP4F2*3*	Erhöhung der berechneten Dosis um 5-10 %	/
CYP2C-cluster (rs 12777823)	/	Verringerung der Dosis um 10-25 %

Nota bene: Die Verwendung genetischer Informationen in Algorithmen zur Berechnung der Dosierung kann zu falscher Sicherheit verleiten. Insbesondere besteht das Risiko einer fehlerhaften pharmakogenetischen Dosierung bei Personen afrikanischer Herkunft, wenn nur *CYP2C9*2*- und **3*-Allele enthalten sind wie es in vielen FDA-zugelassenen *CYP2C9*-Testkits der Fall ist. Die *Royal Dutch Pharmacists Association - Pharmacogenetics Working Group* (DPWG) hat Empfehlungen zur therapeutischen Dosis von Phenprocoumon und Acenocoumarol basierend auf dem *VKORC1*-Genotyp bewertet. Die Patienten mit dem *VKORC1 - 1639 AA*-Genotyp sollten 50 % der Standard-Anfangsdosis und eine häufigere Überwachung der INR erhalten. Es gibt keine Empfehlung für eine Dosisanpassung basierend auf dem *CYP2C9*-Genotyp.

Kosten

Die Kosten für die genetische Analyse der *VKORC1*- und *CYP2C9*-Gene werden für gesetzlich und privat versicherte Patienten erstattet, wenn die Testung durch einen Arzt angeordnet wird, obwohl die meisten Versicherungspläne derzeit nicht für pharmakogenetische Warfarin-Tests bezahlen. Das Budget des behandelnden Arztes wird dadurch nicht belastet.

[1] Johnson JA, Gong L, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011;90(4):625-629. doi:10.1038/clpt.2011.185

[2] Johnson JA, Caudle KE, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017;102(3):397-404. doi:10.1002/cpt.668

VARFARIN

Genetički test za smanjenje rizika pri primjeni varfarina

Lijek

Koje su indikacije za primjenu i mehanizmi djelovanja varfarina?

Varfarin je široko primjenjivani oralni antikoagulans uske terapijske širine u liječenju i prevenciji duboke venske tromboze (DVT) i plućne embolije, u prevenciji sustavne embolije kod pacijenata s atrijskom fibrilacijom i umjetnim srčanim zaliscima, prevenciji moždanog udara, ponovnog infarkta ili iznenadne smrti u pacijenata s akutnim infarktom miokarda. Velika interindividualna varijabilnost u odgovoru na terapiju varfarinom može utjecati ili na izostanak antikoagulacijskog učinka ili često potencira niz nuspojava, kao i opasnost od krvarenja. Kao antagonist vitamina K, varfarin smanjuje aktivaciju faktora zgrušavanja II, VII, IX i X, ali i sintezu antikoagulacijskih proteina C i S. Zajedno s varfarinom, fenprokumon i acenokumarol pripadaju istoj skupini lijekova.

Geni

Koji geni utječu na djelovanje varfarina?

Na doziranje varfarina najznačajnije utječu geni *VKORC1* i *CYP2C9*. Enzim vitamin K-epoksid reduktaza kompleks ciljno je mjesto djelovanja varfarina kojeg kodira *VKORC1*. Jednonukleotidni polimorfizam na poziciji 1639 je supstitucija aminokiseline gvanin u adenin *(1639G>A)* koji je povezan s povećanom osjetljivošću na varfarin pa nositelji ovog polimorfizma *(1639 A/A i A/G)* zahtjevaju niže doze varfarina u odnosu na pojedince koji su homozigoti (1639 G/G). *CYP2C9* kodira za jetreni enzim koji metabolizira varfarin. Na učinkovitost razgradnje lijeka značajno utječu polimorfizmi gena *CYP2C9* 2* i 3* koji su najčešće zastupljeni kod populacije europskog i istočno-azijskog porijekla. Utvrđene su genske varijante u genima *CYP4F2*3* i *CYP2C* klastera (rs12777823) koje imaju slabiji utjecaj na doziranje varfarina.

Analiza

Što se analizira?

Da bi se ustanovila optimalna doza lijeka, analiziraju se najučestalije rizične varijante gena *VKORC1* 1639G>A, *CYP2C9 2** i *3** i *CYP4F2 *3*.

Genska varijanta *CYP2C* klastera (rs12777823) je povezana s klinički značajnim učinkom na klirens varfarina u populaciji Afroamerikanaca (uglavnom zapadno-afričkog porijekla).

Indikacije

U kojim je slučajevima potrebno napraviti test?

Genetički test bi trebalo napraviti prije planirane terapije varfarinom kako bi se prilagodilo doziranje i postigao terapijski INR (međunarodno normalizirani omjer) 2-3 te izbjegle nuspojave krvarenja, osobito kod nositelja višestrukih alelnih varijanti. Rizik razvoja komplikacija najveći je u samom početku primjene varfarina.

Posljedice rezultata testova

Na koji način se terapija mora prilagoditi rezultatima testa?

Preporuke za doziranje varfarina su utemeljene na smjernicama *Clinical Pharmacogenetics Implementation Consortium (CPIC)*[1,2] imaju najvišu kliničku razinu dokaza 1A.

Tablica 1: Preporuke za doziranje varfarina bazirane prema genotipu za odrasle

Nositelji genske varijante	Doziranje (populacija neafričkog podrijetla)	Doziranje (populacija afričkog podrijetla)
VKORC1 (1639G>A)	Doziranje prema farmakogenomskim smjernicama	Doziranje prema farmakogenomskim smjernicama
*CYP2C9 *2 *3*	Doziranje prema farmakogenomskim smjernicama	Doziranje prema farmakogenomskim smjernicama
*CYP2C9 *5*6 *8 *11*	Smanjiti dozu za 15-30 %	Smanjiti dozu za 15-30 %
*CYP4F2*3*	Povećati dozu za 5-10 %	/
CYP2C klastera (rs 12777823)	/	Smanjiti dozu za 10-25 %

Nota bene: Primjena genetičkih podataka pri vođenju doziranja može dovesti do lažne sigurnosti. Posebno, doziranje varfarina temeljeno na farmakogenomskom testiranju je visokorizično kod pojedinaca afričkog podrijetla ukoliko su uključene samo genske varijante *CYP2C9*2* i **3*, što je i doista slučaj u većini *CYP2C9* testova odobrenih od FDA.

Troškovi

Ukoliko je testiranje ordinirano od strane liječnika, troškovi analize gena bit će priznati i refundirani za bolesnike koji imaju obvezno i privatno osiguranje, iako većina osiguranja za sada ne plaća farmakogenomsko testiranje varfarina.

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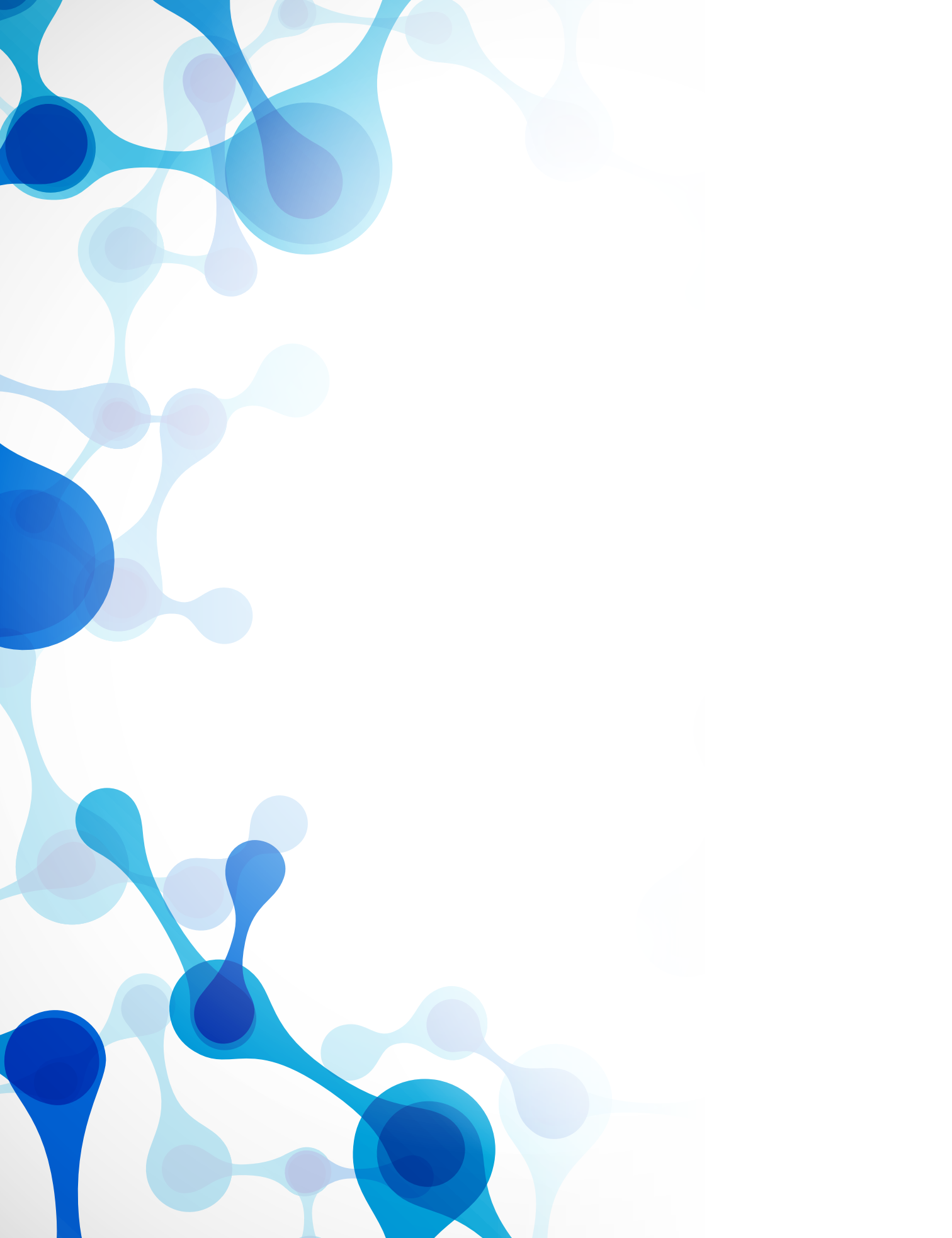
[1] Johnson JA, Gong L, Whirl-Carrillo M, et al. *Clinical Pharmacogenetics Implementation Consortium* Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011;90(4):625-629. doi:10.1038/clpt.2011.185

[2] Johnson JA, Caudle KE, Gong L, et al. *Clinical Pharmacogenetics Implementation Consortium (CPIC)* Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017;102(3):397-404. doi:10.1002/cpt.668



Glossary

Glossar

Rječnik

Allele: Different versions of the same gene.

Allel: Alternative Versionen des gleichen Gens.

Alel: Različita varijanta (modalitet) istog gena.

Chromosome: The biological packaging system for storing and regulating DNA. Each chromosome is made up of DNA tightly coiled many times around proteins called histones that support its structure.

Chromosom: Die biologische Verpackungsform zur Speicherung und Regulation der DNA. Jedes Chromosom besteht aus einem DNA Molekül, das kompakt um Proteinpartikel, sogenannte Histone, gewickelt ist.

Kromosom: Biološka struktura za pohranu i regulaciju DNA molekule. Svaki kromosom je građen od DNA molekule koja obavija bjelančevine zvane histoni, koji daju potporu cijeloj strukturi.

Compound heterozygote: The presence of two different mutant alleles at a particular gene locus, one on each chromosome of a pair (trans).

Compound heterozygot: Das Vorhandensein von zwei verschiedenen mutierten Allele an einem bestimmten Genlocus, eines auf jedem Chromosom eines Paares (trans).

Kombinirani (združeni) heterozigot: Prisustvo dva različita alela na određenom genskom lokusu od kojih se svaki nalazi na različitom kromosomu (trans).

Cytochromes P450 (CYPs): The superfamily of proteins. Cytochrome P450 enzymes account for 70 percent to 80 percent of enzymes involved in drug metabolism. Each cytochrome P450 gene is named with CYP, indicating that it is part of the cytochrome P450 gene family.

Cytochrom P450 (CYPs): Eine Protein Superfamilie, deren Mitglieder enzymatisch aktiv sind. Cytochrom P450 Enzyme sind für 70 % bis 80 % des Stoffwechsels von Medikamenten verantwortlich. Die Bezeichnung der Gene für diese Enzyme beginnt mit „CYP", wodurch sie als Mitglied der Cytochrom P450 Genfamilie erkennbar sind.

Citokrom P450 (CYP): Superobitelj bjelančevina. Enzimi superobitelji citokroma P450 predstavljaju 70-80 % svih enzima uključenih u metabolizam lijekova. Svaki gen koji kodira enzime iz superobitelji P450 označen je kao CYP, što istodobno upućuje da je dio obitelji gena citokroma P450.

DNA: (Deoxyribonucleic acid) is organized into structures called chromosomes and housed within the nucleus of our cells. DNA is also found in cell mitochondria. It is the carrier of genetic information.

DNA: Deoxyribonukleinsäure ist Träger der genetischen Information. Sie ist in Strukturen organisiert, die als Chromosomen bezeichnet werden und in den Kernen unserer menschlichen Zellen untergebracht sind. Ein Teil der DNA ist auch in den Mitochondrien zu finden.

DNA (DNK-deoksiribonukleinska kiselina): smještena je u kromosomima koji se nalaze u jezgri naših stanica. DNA se isto tako nalazi i u mitohondrijima. Prenosi genske informacije.

Drug: A medicine or other substance which has a physiological effect when ingested or otherwise introduced into the body.

Medikament, Arzneiwirkstoff: Eine künstliche oder natürliche Substanz, die aus therapeutischem Anlass geschluckt oder auf andere Weise in den Körper gebracht wird

Lijek: Svaka tvar ili kombinacija tvari koja nakon unosa u organizam utječe na odvijanje fizioloških funkcija, a ima svojstva liječenja ili sprječavanja bolesti.

Enzymes: Proteins that act as catalysts within living cells.

Enzyme: Katalytisch wirksame Proteine, die Stoffwechselreaktionen in lebenden Zellen ermöglichen.

Enzimi: Stanične bjelančevine s katalitičkim svojstvima.

Gene: A working subunit of DNA and a unit of heredity which is transferred from a parent to offspring and is held to determine some characteristic of the offspring. National Human Genome Research Institute estimates there are anywhere from 20,000 to 25,000 genes in the average human genome.

Gen: Eine funktionelle Einheit der DNA, die genetische Information von Eltern auf die Nachkommen übertragen. Das amerikanische National Human Genome Research Institute schätzt das menschliche Genom auf 20.000 bis 25.000 Gene.

Gen: Funkcionalna podjedinica DNA molekule i jedinica nasljeđivanja koja se prenosi s roditelja na potomstvo te time određuje neke značajke potomstva. Američki Nacionalni institut za istraživanje ljudskog genoma procjenjuje da unutar genoma čovjeka postoji 20,000 – 25,000 gena.

Genome: The complete set of genes and genetic material present in a cell or organism.

Genom: Die Gesamtheit der Gene und des genetischen Materials in den Zellen eines Organismus.

Genom: Svi geni i genski materijal prisutan u stanici ili organizmu.

Genotyping: is the process of determining differences in the genetic make-up (genotype) of an individual by examining the individual's DNA sequence using biological assays and comparing it to another individual's sequence or a reference sequence.

Genotypisierung: Die Methoden zum Nachweis von Unterschieden im genetischen Aufbau (Genotyp) eines Individuums im Vergleich zu anderen Personen durch DNA-Sequenzierung und Vergleich mit einer Referenzsequenz.

Genotipizacija: proces određivanja raznolikosti genotipa (DNA sekvencije pojedinca) u odnosu na DNA sekvenciju drugog pojedinca ili referentnu sekvenciju.

HLA: The HLA gene family provides instructions for making a group of related proteins known as the human leukocyte antigen (HLA) complex. These cell-surface proteins are responsible for the regulation of the immune system in humans.

HLA: Die HLA Genfamilie enthält die Informationen zum Aufbau einer Gruppe von Proteinen, die als Human Leukozyten Antigen (HLA) Komplex bezeichnet werden. Diese Zelloberflächenproteine spielen eine Schlüsselrolle bei der Regulation des Immunsystems.

HLA: Genski sustav ljudskih leukocitnih antigena ili genski sustav tkivne podudarnosti, u čovjeka osigurava informacije za proizvodnju bjelančevina zvanih ljudski leukocitni antigenski kompleks (HLA). Ovi proteini smješteni na površini stanice odgovorni su za funkcioniranje imunološkog sustava čovjeka.

Homozygous: Describes a genotype consisting of two identical alleles at a given locus

Homozygot: Bezeichnet den Genotyp mit zwei identischen Allelen am gleichen Genort.

Homozigot: Opisuje genotip sastavljen od dva identična alela na određenom lokusu.

Heterozygous: Describes a genotype consisting of two different alleles at a locus

Heterozygot: Bezeichnet den Genotyp mit zwei unterschiedlichen Allelen am gleichen Genort.

Heterozigot: Opisuje genotip sastavljen od dva različita alela na određenom lokusu.

Individualized medicine: Also known as personalized medicine or precision medicine is the medicine with personalization and customization of health care, with decisions and treatments tailored to each individual patient in every way possible.

Individuelle Medizin: Auch als personalisierte Medizin oder Präzisionsmedizin bezeichnet. Hierbei richten sich medizinische Behandlungen soweit irgend möglich maßgeschneidert nach den individuellen Gegebenheiten eines Patienten.

Individualizirana medicina: Poznata još kao personalizirana ili precizna medicina kojoj je temeljni cilj omogućiti specifičnu terapiju "skrojenu" prema potrebama pojedinca.

Mitochondria: Are often referred to as the powerhouses of the cells converting oxygen and nutrients into adenosine triphosphate.

Mitochondrium: Häufig als Kraftwerke der Zellen bezeichnet. Diese Zellorganellen können als Generatoren der Zellen angesehen werden. In ihnen wird aus Nährstoffen unter Beteiligung von Sauerstoff der Energieträger Adenosin Triphosphat (ATP) gebildet.

Mitohondrij: Često zvan energetskom centralom stanice u kojem se tijekom postupka oksidacijske fosforilacije stvara adenozin trifosfat (ATP).

Mitochondrial DNA: DNA located in mitochondria.

Mitochondriale DNA: DNA, die in den Mitochondrien lokalisiert ist.

Mitohondrijska DNA: DNA smještena u mitohondrijima.

Mutation: Is genetic change, resulting in a variant form which may be transmitted to subsequent generations, caused by the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes.

Mutation: Eine genetische Veränderung, die an die nachfolgende Generation weitergegeben werden kann. Sie beruht entweder auf dem Austausch eines einzelnen genetischen Bausteins (Base) oder auf Deletionen, Insertionen oder Umlagerungen von Teilen von Genen, Genen- oder Chromosomenabschnitten.

Mutacija: Nasumična promjena genskog materijala kojom nastaje varijanta koja se može prenijeti na slijedeće generacije. Najčešće su promjene jedne baze unutar DNA molekule, ali mogu biti i promjene poput delecije, insercije ili preraspodjela većeg segmenta gena ili čak kromosoma.

Pharmacogenomics: Is the study of how genes affect a person's response to drugs

Pharmakogenomik: Befasst sich damit, wie bei einer bestimmten Person Gene die Wirkung von Medikamenten beeinflussen.

Farmakogenomika: Proučava vezu između genske predispozicije pojedinca i njegove sposobnosti da metabolizira neki lijek ili tvar.

Single nucleotide polymorphism (SNP): Are the most common type of genetic variation among people and represent a variation in a single nucleotide that occurs at a specific position in the genome.

Single nucleotide polymorphism (SNP): Der häufigste Typ der genetischen Variationen von Mensch zu Mensch. SNPs basieren auf dem Austausch einer einzelnen Base in einem Gen.

Polimorfizam jednog nukleotida (SNP): Najčešći oblik genske varijacije u populaciji i predstavlja varijaciju jednog nukleotida koja se događa na specifičnoj poziciji unutar genoma.

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Personalized medicine is an important topic in today's health care. Adjusting the dose of frequently prescribes medicines to the genetic profile of patients is a tool which is nowadays available: pharmacogenetics. Yet, it is not always clear how this genetic information can be used in health care settings. Or for which drugs this information can be helpful. The current book "Pharmacogenetics in Clinical Practice" by Dragan Primorac and Wolfgang Höppner excellently provides this information in a clear and accessible manner. In 210 pages, an overview of 55 drugs, their important gene-drug interactions are presented, including background, genes involved, test descriptions, indications for using pharmacogenetic testing, and the consequences of test results. It is especially the included tables with specific dose recommendations based on genotype that make this book an essential tool for every health care practisioner who want to achieve optimal and safe drug treatment of their patients. Highly recommended.

Professor Ron van Schaik, Ph.D.
Erasmus University Medical Center, The Netherlands

Modern medicine is unthinkable without modern drugs. Pharmacogenetics is lifting their clinical use to new levels of efficacy and safety. This book delivers the basis of personalized medicine for them – it has been of great significance for me personally. Clinical medicine of the future will strongly depend on knowledgable physicians capable of applying pharmacogenetics to the benefit of their patients. This book serves as an outstanding tool to, provide the essentials of pharmacogenomics for all clinicians.

Prof. Johannes Brachmann, M.D., Ph.D.,
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For those keen on bringing pharmacogenomics into their daily clinical practice, this book is sure to serve as a reliable and informative resource. I highly recommend this publication to physicians, pharmacists, nurses, and other healthcare providers who are committed to bringing personalized medicine to their patients' bedside. It quickly became one of the most frequent resources to consult in my pharmacogenomics practice because it is easy to use, quick to reference, and relevant to practice.

Dr. Adrijana Kekić, Pharm. D.,
Mayo Clinic, Phoenix, Arizona, United States

This compendium on "Pharmacogenetics in clinical practice" by Primorac and Höppner has compiled clinically highly relevant contemporary information on the pharmacogenetics of 55 often prescribed drugs for physicians and other health care professionals. The great value of this work lies in the efficient communication of the essential information on how the specific genetic makeup determines drug actions and adverse reactions. Physicians and health care professionals can immediately come up with sound decisions on the use of these drugs. Primorac and Höppner give the state of the art knowledge and advice that enables personalized medicine to harvest the latest progress in the fields of molecular biology and genetics for the practice of drug treatment.

Prof. Burkhard Poeggeler, Ph.D.,
Georg-August-University of Göttingen, Gütersloh, Germany

The book "Pharmacogenetics in Clinical Practice" by Dragan Primorac and Wolfgang Höppner, which is available in 3 languages, deals with the pharmacokinetics of 55 frequently used drugs against the background of pharmacogenetics. It takes up in a clear form the difficulties that the practicing physician experiences in his everyday life when he repeatedly finds that the same drug in apparently identical patients (age, size, gender) has a completely different effect and thus potentially one has an adverse effect. The work shows that the way to personalized medicine, as we would like it to be in the future, is through understanding pharmacogenetics.

Dr. Jan Oliver Schönfeldt, M.D.,
Institut für Kinderneurologie, Hamburg, Germany

The second edition of this book, written in English, German and Croatian, presents a systematic approach to patient pharmacogenetics. The recommendations are based on the CPIC ones and have the highest clinical level of evidence. This book certainly represents a contribution to safer treatment with minimal or no side effects, along with its role in the current and future efforts to develop fully personalized medicine.

Prof. Elizabeta Topić, Ph.D.,
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This text is excerpted from original summary statements by reviewers.

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