OBACH
Privatklinik

1 SYNLAB International GmbH – M. Morris SWISS MEDICAL NETWORK MEMBER

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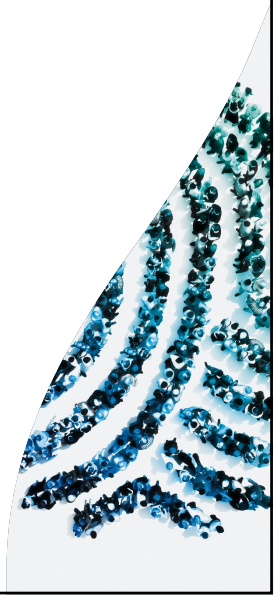
PHARMACOGENETICS FOR THERAPY OPTIMIZATION

A simple genetic test to determine life-long individual drug compatibility

- CASES
- CONCEPTS
- MyPGx

Michael Morris, D.Phil., Head of Genetics, SYNLAB



SYNLAB Switzerland 20.11.12 Obach M. Morris

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CASE REPORT

- POST-OPERATIVE ANALGESIA

10 to 20 %

of hospitalized patients will experience at least one undesirable side effect during their hospital stay

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Mia, 28 years old

- **Personal history**
  - Morphine for pain after caesarean section.
    - Respiratory depression > intensive care > reversal (no serious sequelae).
  - Less severe episode of post-morphine respiratory depression after first delivery.
- **Family history**
  - Father treated with morphine after routine heart surgery.
    - Cardiac arrest, resuscitation.
- → pharmacogenetic screening myPGx®

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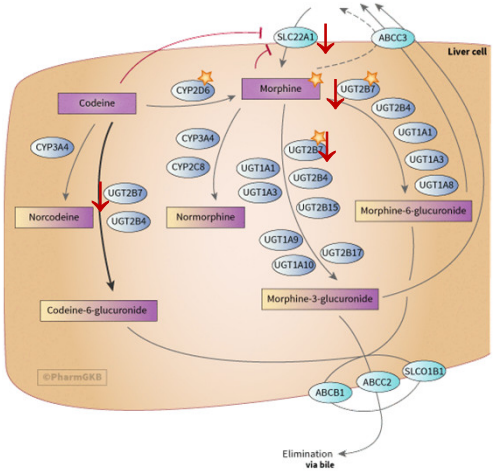
RESULTS

Gene	Genotype-Haplotype	Phenotype
CYP1A1	*1/*4	Intermediate metaboliser
CYP1A2	*1F/*1F	Normal metaboliser
CYP2A6	*1A/*1A	Normal metaboliser
CYP2B6	*1/*10	Normal metaboliser
CYP2C8	*1/*1	Normal metaboliser
CYP2C9	*1/*1	Normal metaboliser
CYP2C19	*1B/*1B	Normal metaboliser
CYP2D6	*1/*36	Intermediate metaboliser
CYP2E1	*1/*7	Normal metaboliser
CYP3A4	*1/*1	Normal metaboliser
CYP3A5	*1A/*3A	Intermediate metaboliser
VKORC1	H1/H7	Intermediate sensitivity to Warfarin
SLC15A2	*1/*1	Normal function
SLC22A1	***420Del/*420Del**	**Low function**
SLC22A2	*270A/*270A	Normal function
SLC22A6	*1/*1	Normal function
SLCO1B1	*1A/*1B	Normal function
SLCO1B3	***112A/*233I**	**Low function**
SLCO2B1	*1/*1	Normal function
ABCB1	*1/*2	Intermediate function
ABCC2	*1/*1324I	Intermediate function
ABCG2	*1/*1	Normal function
SULT1A1	***3/*3**	**Poor metaboliser**
NAT1	*4/*4	Normal acetylator
NAT2	*5A/*12A or *11A/*5C or *5D/*12C or *4/*5B	Normal acetylator
TPMT	*1/*1	Normal metaboliser
GSTM1	*1/*1	Normal metaboliser
GSTP1	***1A/*1C or *1B/*1D**	**Poor metaboliser**
UGT1A1	*1/*60	Intermediate metaboliser
UGT2B7	*2b/*2b	Intermediate metaboliser
UGT2B15	*1/*1	Normal metaboliser
DPYD	*1/*9A	Normal metaboliser



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Hypothesis:

- Reduced uptake by liver (SLC22A1, SLCO1B3)
- Reduced catabolism/excretion in liver (UGT2B7, SULT1A1)
- Increase in central morphine efficiency (COMT)

→ **Overdose**

Gene	Prediction	Effect
UGT2B7 *2/*2	**Intermediate** activity	Decreased activity may result in increased morphine concentrations with increased effect and risk of serious side effects.
SLC22A1 (OCT1) *420Del/Del	**Low** activity	Important role in hepatocellular absorption of morphine. Significant reduction in morphine clearance
SLCO1B3 *112A/*233I	**Low** activity	? Reduced morphine uptake by hepatocytes, reduced clearance
SULT1A1 *3/*3	**Slow** metabolizer	Reduction of sulfation of certain opiates
COMT 158Met	**Low** activity	May improve the central efficiency of morphine, requires lower doses

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A few numbers

- **United States** :
  - the total cost of adverse drug reactions (ADRs) may be comparable to that of diabetes,
    - Approximately 106'000 deaths per year are caused by ADRs
    - **The fourth-leading cause of death** by disease.
- **EU** :
  - It is estimated that 5% of all hospital admissions are due to ADRs
    - Approximately 197'000 deaths per year in the EU are caused by ADRs.
    - **The fifth-leading cause of hospital death**:
  - The total cost of ADRs to society is approximately €79 billion.

Frueh et al 2008, *J Hum Pharmacol Drug Therapy*, 28(8), 992-998.

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Consequences for individuals - Implications for health systems

Up to **20 %** of **ambulatory** patients have undesirable side effects

Only **~50 %** of patients taking **anti-depressants** will respond to treatment, and **~55 %** have at least one undesirable side effect

It is estimated that **35 %** of those **over 65 years** of age have experienced undesirable side effects

10 to 17 % of **hospitalizations of the elderly** are directly related to adverse side effects due to their medication

Elliott et al, PLOS ONE February 2, 2017

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Individual response to medication
affects all medical specialties

Drugs that should particularly be considered:

- **Analgesics / Antirheumatics**
- **Antibiotics / Antivirals / Antimycotics**
- **Antidepressants / Psychotropics**
- **Antidiabetics**
- **Antihypertensives**
- **Anticoagulants**
- **Cytostatics**
- **Proton pump inhibitors**
- **Statins**

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Same treatment, different people
Inadequacy of a single pharmacological approach

Up to
90 %
of drugs are metabolized by

CYP2D6, **CYP3A4,** CYP3A5,
CYP2C19, CYP1A2, CYP2C9,

More than
85 %
of individuals carry
significant genetic variants
of cytochrome P450 genes

>250
drugs take into account
pharmacogenetic data in
their package inserts (FDA)

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Some important pharmacogenes (after Youssef et al, Pharmaceutical Journal, January 2020, Vol 304, No 7933)

Genes	Examples of clinical impact
Cytochrome P450 genes *CYP2D6*	CYP2D6 metabolises around 25% of medicines in clinical use, including many psychotropics, opioid analgesics and other drug classes. Poor Metabolisers are at increased risk of side effects when taking medicines like venlafaxine, aripiprazole and amitriptyline.
CYP2C19	The CYP2C19 metaboliser state has implications for the antiplatelet drug clopidogrel, many of the proton pump inhibitors and many antidepressants.
CYP2C9	CYP2C9 is important for calculating the starting daily dose for warfarin and is useful for predicting the risk of side effects for several non-steroidal anti-inflammatory drugs.
Drug transporter genes *SLCO1B1*	Drug transporters mediate the active transport of endogenous substrates and xenobiotics. SLCO1B1 encodes the drug transporter responsible for statin uptake into the liver. Carriers of the c.521T>C variant produce a transporter with reduced function, increasing plasma concentration of statins. This is associated with an increased risk of myalgia and myopathy. The association is strongest with simvastatin, for which pharmacogenomic guidelines exist recommending drug/dose changes.
Conversion enzymes *DPYD*	DPD metabolizes at least 80% of administered 5-FU. If DPD has reduced activity, the amount of 5-FU for increases to 5-FU-related ADRs. Patients with partial DPD deficiency in whom the benefit of 5-fluorouracil outweighs the risks should be treated with utmost caution. CPIC provides dosing guidelines (2018).

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CYP2D6

Pharmacogenomics and Personalized Medicine Dovepress

ORIGINAL RESEARCH

Increased risk of hospitalization for ultrarapid metabolizers of cytochrome P450 2D6

CONCLUSION: Children with CYP2D6 poor or intermediate **metabolizer** phenotypes are at greater risk for risperidone AEs. Pre-prescription genotyping could identify this high-risk subset for an alternate therapy, risperidone dose reduction, and/or increased monitoring for AEs.

PMID: 30661084 DOI: 10.1038/s41390-019-0305-z

Excerpts from the codeine drug label:

Life-threatening respiratory depression and death have occurred in children who received codeine; most cases followed tonsillectomy and/or adenoidectomy and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism.

Nursing Mothers...At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Codeine Sulfate Tablets.

"The pharmacogenomics-guided group had 84% lower health costs than the control group" Olson et al 2017

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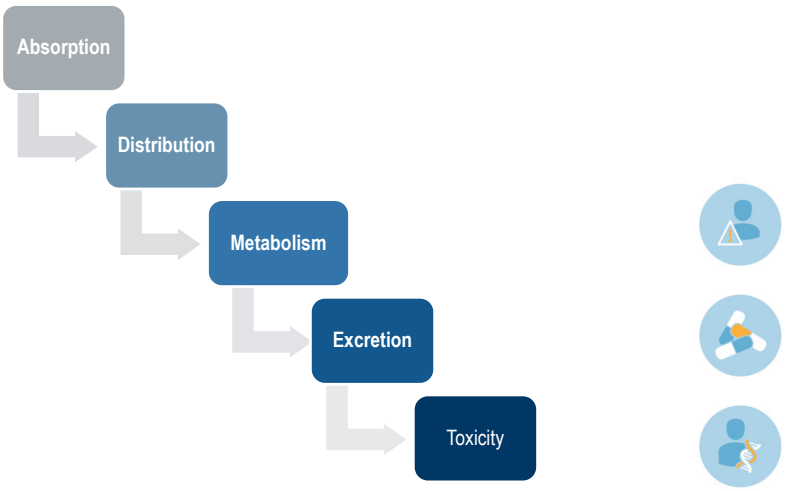
HOW DOES IT WORK? Genetics and ADMET



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Practically...

THE TEST KIT | LOGISTICS | GENETIC TESTING | THE REPORT

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Genetic predictions of phenotypes for 33 genes

Poor metabolizer

Enzyme is inactive

Risk of side effects due to excessive drug concentration in the blood

Prodrugs not activated, no therapeutic effect

Alternative medication should be used

Intermediate metabolizer

Reduced enzymatic activity

Dosage of medication should be adjusted

At risk of becoming slow metabolisers in the presence of inhibitory drugs

Normal metabolizer

Normal activity

Dosage of medications and prodrugs can be prescribed according to standard procedures

Ultra-Rapid metabolizers

Very high activity

If a drug is degraded by the enzyme, actual concentration will be low and therapeutic effect may be diminished

Beware of prodrugs, which are excessively activated with a risk of overdose effects

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Enzymes can activate or inactivate drugs

Codeine → CYP2D6 → **activation** → Morphine

Paroxetine → CYP2D6 → **inactivation** → Catechol

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Predicted phenotype for individual substances
(*caveat*, varying levels of evidence)

PGx Report - Internal Medicine

Type: Drugs Prescribed for the Treatment of Peptic Ulcers and/or Gastro-Esophageal Reflux Disease

Drug Class	Substance	Primary Mechanism Involved	Other Mechanisms Involved	May Have Decreased Efficacy	Used As Directed	May Have Increased Toxicity
Histamine H2-receptor antagonists	Ranitidine	Renal Excretion	CYP1A2, CYP2C19, CYP3A4, CYP3A5		✓	
Proton-pump inhibitor	Omeprazole	CYP2C19	CYP3A4, CYP2C9, CYP3A5		✓	
	Dexlansoprazole	CYP2C19	CYP3A4, CYP3A5		✓	
	Esomeprazole	CYP2C19	CYP3A4, CYP3A5		✓	
	Lansoprazole	CYP3A4	CYP2C19, CYP3A5			✗
	Rabeprazole	Non Enz	CYP2C19, CYP3A4, CYP3A5		✓	
	Ilaprazole	CYP3A4	CYP3A5			✗
	Pantoprazole	CYP2C19	CYP3A4, CYP2D6, CYP2C9, CYP3A5		✓	

Abbreviations: Non Enz, non-enzymatic metabolism.

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MYPGX OPTIONS

REQUESTED TESTS

- ☐ 8707 MyPGx® (Broad Panel, 33 key genes; personal profile)
- ☐ 8710 MyPSY (Antidepressants, Antipsychotics, Anxiolytics, ADHD)
- ☐ 8711 MyRHUMA (Anti-inflammatories, Analgesics, Antipyretics)
- ☐ 8712 MyCARDIO (Antiarrhythmics, Anticoagulants, Antihypertensives, Antiplatelets)
- ☐ 8751 MyGASTRO (Anti-inflammatories, Analgesics, Proton-pump inhibitors, drugs for Gastrointestinal Disorders, Obesity and Diabetes)
- ☐ Other:

SAMPLE TYPE*:

- ☐1 tube blood / EDTA
- ☐DNA at conc:____
- ☐1 FTA-Card with EDTA drop blood

DRAW DATE:* (day/month/year)

REPORT LANGUAGE*:

☐ English ☐ Italian ☐ French ☐ Turkish

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SUB-PANELS AND ONE-PAGERS FOR SELECTED SPECIALTIES

Pharmacogénétique (PGx)

B MyPSY

une personne sur quatre sera affectée par des troubles mentaux ou neurologiques à un moment a vie. Aujourd'hui, quelques 450 millions de personnes souffrent de tels troubles, ce qui place les parmi les principaux problèmes de santé et de handicap.

MyPSY :

ppé un test pharmacogénétique innovant dans le domaine des psychotropes et des antidépres- ner la variabilité de l'efficacité et de la toxicité des médicaments due aux variations génétiques ariations qui affectent les enzymes de métabolisme des médicaments, les transporteurs ou les leuses.

MyPSY

SYNLAB MyPSY Panel :

Panel	Traitements-clés	Gènes analysés
MyPSY	• antidépresseurs ; • inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) ; • antidépresseurs tricycliques (ATC) ; • antipsychotiques ; • anxiolytiques ; • benzodiazépines.	Voie principale : CYP2D6, CYP2C19 Voies complémentaires : CYP3A4/5, CYP2C8, CYP2C9, CYP1A2 et CYP2B6

Exemple de rapport :

PGx Rapport – Psychiatrie

Type : antidépresseur I

Classe de médicaments	Molécule	Mécanisme primaire impliqué	Peut avoir une efficacité réduite	Utilisation conforme aux recommandations	Peut avoir une toxicité accrue
Antidépresseurs					
ISRS	Citalopram	CYP2C19, CYP2D6			●
	Escitalopram	CYP3A4, CYP2C19			●
	Dapoxétine	CYP2D6			●
	Fluoxétine	CYP2D6			●
	Paroxétine	CYP2D6			●
	Sertraline	CYP2B6		●	
	Fluvoxamine	CYP2D6			●
Modulateur et stimulateur de la sérotonine	Vilazodone	CYP3A4			●
IRSN	Lévomilnacipran	CYP3A4		●	
	Milnacipran	UGT		●	
	Venlafaxine	CYP2D6			●

Définition des symboles, Recommandation :
Peut avoir une efficacité réduite, utiliser un dosage accru.
Utiliser la dose standard.
Peut avoir une toxicité accrue, utiliser une dose réduite.

Pharmacogenetics (PGx)

SYNLAB MyGASTRO

Proton pump inhibitors (PPIs) are used to treat a wide range of acid-related disorders including peptic ulcer, gastroesophageal reflux disease (GERD), Helicobacter pylori and post-bariatric surgery, among other indications. The degree of acid suppression by PPIs is related to variation in pharmacokinetics, a significant part of which is due to CYP2C19 genetic variants. In addition, patients on PPIs frequently also use antiinflammatory and/or analgesic medication, for example ibuprofen or opioids.

Choose SYNLAB MyGASTRO:

SYNLAB has developed a novel pharmacogenetic test in the area of gastrointestinal disease and post-bariatric surgery, which examines the variability in drug efficacy and toxicity attributed to genetic variation in patients affecting drug-metabolizing enzymes, transporters or drug targets.

SYNLAB MyGASTRO Panel:

Panel	Key medications	Genes analysed
MyGASTRO	• PPIs • Antiemetics • Antiinflammatories • Opioid analgesics • Antiheumatics • Antiobesity drugs • Antidiabetics • Antihistamines	Major genes: CYP2C19, CYP2D6, CYP2C9, CYP3A4 Additionally: UGTs, SLCs, CYP1A2, CYP2B6, CYP2C8, CYP3A5,ABCs

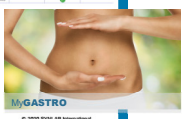
Example report:

PGx Report – Internal Medicine

Type: Drugs Prescribed for the Treatment of Peptic Ulcers and/or GERD

Drug Class	Substance	Primary Mechanism Involved	Other Mechanisms Involved	May Have Increased Efficacy	Used As Directed	May Have Increased Toxicity
Histamine H2-receptor antagonists	Ranitidine	Renal Excretion	CYP1A2, CYP2C19, CYP2D6, CYP3A4		●	
Proton pump inhibitor	Omeprazole	CYP2C19	CYP3A4, CYP2C9, CYP3A5		●	
	Dexlansoprazole	CYP2C19	CYP3A4, CYP3A5		●	
	Esomeprazole	CYP2C19	CYP3A4, CYP3A5		●	
	Lansoprazole	CYP3A4	CYP2C19, CYP3A5		●	
	Rabeprazole	Non-Enz	CYP2C19, CYP3A4, CYP3A5		●	
	Pantoprazole	CYP3A4	CYP3A5		●	
	Pantoprazole	CYP2C19	CYP3A4, CYP1A2, CYP2C9, CYP3A5		●	

- All PPIs are subject to CPIC guidelines and designated CPIC Level B disease: "Prescribing action recommended",
- TheDutch Pharmacogenetics Working Group have specific drug dosage recommendations for PPIs based on CYP2C19 genotype
- PGx helps to plan and implement therapy in a targeted manner.



MyGASTRO

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SUB-PANELS AND ONE-PAGERS FOR SELECTED SPECIALTIES

Pharmakogenetik (PGx)

SYNLAB MyRHUMA

Dem aktuellen Bericht des amerikanischen Nationalen Zentrums für Gesundheitsstatistik zufolge gehören Ar zur Gruppe frei verkäuflicher Medikamente, welche aufgrund von Nebenwirkungen mit besonderer Vorsicht a habt werden müssen.

Eine personalisierte Arzneimittelauswahl und -dosierung für einzelne Patienten mit akuten oder chronischen ist sehr wichtig, um gefährliche Nebenwirkungen zu reduzieren.

Entscheiden Sie sich für SYNLAB MyRHUMA:

SYNLAB hat ein innovatives pharmakogenetisches Testprofil für schmerzlindernde Medikamente entwickelt, rend auf dem genetischen Profil des Patienten untersucht der Test die Variabilität in der Wirksamkeit und To Arzneimitteln. Dies betrifft Arzneimittel-metabolisierende Enzyme, Transporter oder Zielmoleküle (Drug targets).

MyRHUMA

SYNLAB MyRHUMA Profil:

Profil	Schlüsselmedikamente	Untersuchte Gene
MyRHUMA	• Analgetika • Entzündungshemmer • Antipyretika	Hauptwege: CYP2C9, CYP2C8, UGTs Zusätzlich: CYP1A2, CYP3A4, CYP3A5, CYP2C8, CYP2C19, CYP2E1

Beispiel:

PGx Bericht – Schmerzmanagement

Typ: Entzündungshemmender Wirkstoff, Analgetikum, Antipyretikum

Arzneimittelklasse	Generikum	Beteiligter Primärmechanismus	Könnte eine vermiderte Wirksamkeit aufweisen	Kann nach Anweisung genutzt werden	Könnte eine erhöhte Toxizität aufweisen
Essigsäure-derivate	Diclofenac	UGT2B7		●	
	Nabumeton	CYP1 A2		●	
	Indomethacin	CYP2C9			●
	Ibuprofen	CYP2C9			●
	Flurbiprofen	CYP2C9			●
Propionsäure-derivate	Ketoprofen	CYP3A4		●	
	Fenoprofen	CYP2C9			●
	Vicoprofen	CYP2D6			●

Definition der Symbole, Empfehlung:
Wirksamkeit kann verringert sein, die Medikamentendosierung sollte angepasst werden.
Verwenden Sie die Standarddosis.
Toxizität kann erhöht sein, die Medikamentendosierung sollte angepasst werden.

Farmacogenetica (PGx)

SYNLAB MyCARDIO

Secondo i dati dell'Organizzazione mondiale per la Salute (OMS), le malattie cardiovascolari (MCV) sono una delle maggiori sfide in campo medico a livello mondiale. Le MCV sono malattie del cuore e dei vasi sanguigni, tra cui coronaropatie, patologie cerebrovascolari, reumatismo cardiaco e altri disturbi.

Oltre alle abitudini legate alla salute (per es. dieta, fumo, attività fisica), il profilo genetico di un individuo ha un ruolo determinante sia per la probabilità di contrarre una patologia cardiovascolare sia per gli esiti della terapia.

Perché scegliere MyCARDIO SYNLAB:

SYNLAB ha sviluppato un innovativo test farmacogenetico applicato a patologie cardiovascolari, allo scopo di esaminare la variabilità dell'efficacia e tossicità di un farmaco sul singolo paziente, correlata a una variazione genetica, che influisce sugli enzimi metabolizzanti, sui trasportatori o sul target del farmaco stesso.

Pannello SYNLAB MyCARDIO:

Pannello	Farmaci chiave		Geni analizzati
MyCARDIO	• Antiaritmici • Anticoagulanti • Antipertensivi • Antipiastrinici	• Stimolanti cardiaci • Ipolipidemizzanti • Vasodilatatori	Principali pathway metabolici: CYP2C19, CYP2C9, CYP3A4, VKORC1, UGTs Indine: ABCs, CYP1A2, CYP2B6, CYP2C8/9/19, CYP2D6, CYP3A5

Esempio di report:

Report PGx – Funzione cardiovascolare

Tipologia: Anticoagulante, antipiastrinico

Categoria farmaco	Generico	Meccanismo primario interessato	Può avere efficacia ridotta	Utilizzato secondo prescrizione	Può incrementare la tossicità
Coagulazione sanguigna e anticoagulanti, farmaci antipiastrinici					
Antagonista della vitamina K	Warfarin	CYP2C9, VKORC1	●		
	Acenocumarolo	CYP2C9, VKORC1	●		
	Fenprocumone	CYP2C9, VKORC1	●		
Farmaci diretti del fattore Xa	Rivaroxaban	CYP3A4		●	
	Apixaban	CYP3A4		●	
Farmaci antipiastrinici					
Agenti inibitori del recettore P (P2Y12)/ analoghi di ADP	Ticagrelor	CYP3A4		●	
Tienopiridine inibitrici del recettore ADP (P2Y12)	Clopidogrel	CYP2C19		●	
	Prasugrel	CYP3A4		●	
Farmaci inibitori della cicloossigenasi	Aspirina	UGTs, Escrezione renale		●	
Inibitori della fosfodiesterasi	Cilostazolo	CYP3A4		●	
Antagonisti del recettore trombina 1	Vorapaxar	CYP3A4		●	
Inibitori da proteasi (PAR 1)					

MyCARDIO

simboli, Raccomandazione:
ere una diminuzione dell'efficacia, usare un dosaggio maggiore.
are la dose standard. Può avere una maggiore tossicità, usare una dose ridotta.

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MYPGX® REPORT

EUROPE'S NUMBER ONE
MEDICAL DIAGNOSTICS PROVIDER

Quick and effective medical decisions

Summary of key pharmacogenetic results (predicted Poor or Ultrarapid activity):

Gene	Prediction
CYP2A6	Poor metabolizer
CYP2C19	Ultrarapid metabolizer
CYP2D6	Poor metabolizer
CYP3A5	Poor metabolizer
SLC22A1	Low function
SLCO1B3	Low function
ABCB1	Low function
SULT1A1	Poor metabolizer
NAT2	Poor acetylator
GSTP1	Poor metabolizer

The detailed pharmacogenetic results are presented on the following pages.

Technical comments and limitations:

Coverage 99.5%. Haplotypes not determined (failed SNPs): None

PGx is a rapidly-evolving field primarily providing evidence-based predictions of how the tested individual's genetic profile may affect reaction to certain drugs. Factors such as drug-drug interaction and also age, diet, ethnicity, family and personal health history, can also impact the likelihood of exhibiting certain drug reactions, independently of genotype-based predictions.

This report is intended for use by a healthcare professional. Based on PGx results, **patients should make no changes to medical care without the prior advice of and consultation with a healthcare professional** [including, but not limited to, changes in dosage or frequency of medication, diet and/or exercise regimens, or pregnancy planning].

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Fast and effective medical decisions

PGx Report - Internal Medicine

Type: Drugs Prescribed for the Treatment of Peptic Ulcers and/or Gastro-Esophageal Reflux Disease

Drug Class	Substance	Primary Mechanism Involved	Other Mechanisms Involved	May Have Decreased Efficacy	Used As Directed	May Have Increased Toxicity
Histamine H2-receptor antagonists	Ranitidine	Renal Excretion	CYP1A2, CYP2C19, CYP3A4, CYP3A5		✓	
Proton-pump inhibitor	Omeprazole	CYP2C19	CYP3A4, CYP2C9, CYP3A5		✓	
	Dexlansoprazole	CYP2C19	CYP3A4, CYP3A5		✓	
	Esomeprazole	CYP2C19	CYP3A4, CYP3A5		✓	
	Lansoprazole	CYP3A4	CYP2C19, CYP3A5			✗
	Rabeprazole	Non Enz	CYP2C19, CYP3A4, CYP3A5		✓	
	Ilaprazole	CYP3A4	CYP3A5			✗
	Pantoprazole	CYP2C19	CYP3A4, CYP2D6, CYP2C9, CYP3A5		✓	

Abbreviations: Non Enz, non-enzymatic metabolism.

To Drugbank Canada

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SYNLAB

EUROPE'S NUMBER ONE
MEDICAL DIAGNOSTICS PROVIDER

MYPGX

Who can benefit from MyPGx?

- Patients
  - with a history of side-effects
  - who do not get positive benefit from their medication
  - on long-term mediation
  - on polypharmacy
  - you suspect are non-compliant
  - for whom surgery is programmed
- Adults
  - who choose to invest (financially and/or intellectually) in their health

Analgesics
Antidepressants, antipsychotics
Statins
PPI

The right drug, at the right dose, from the start.

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SYNLAB

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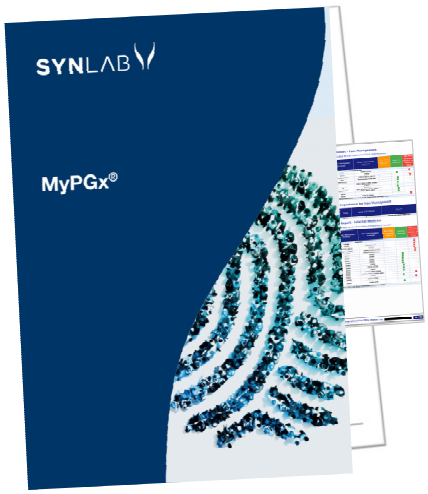

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