medcheck™

Pharmacogenomics

Harnessing the power of personalised prescribing

Nordic Laboratories

dnalife

Pharmacogenomics

Doctors prescribe more than 4 billion drugs annually, and between 38-75% of these drugs don't work.[1] Doctors are overworked and exhausted while patients spend little time with their providers and often report unpleasant side effects or confusion about how to safely use prescription medication.

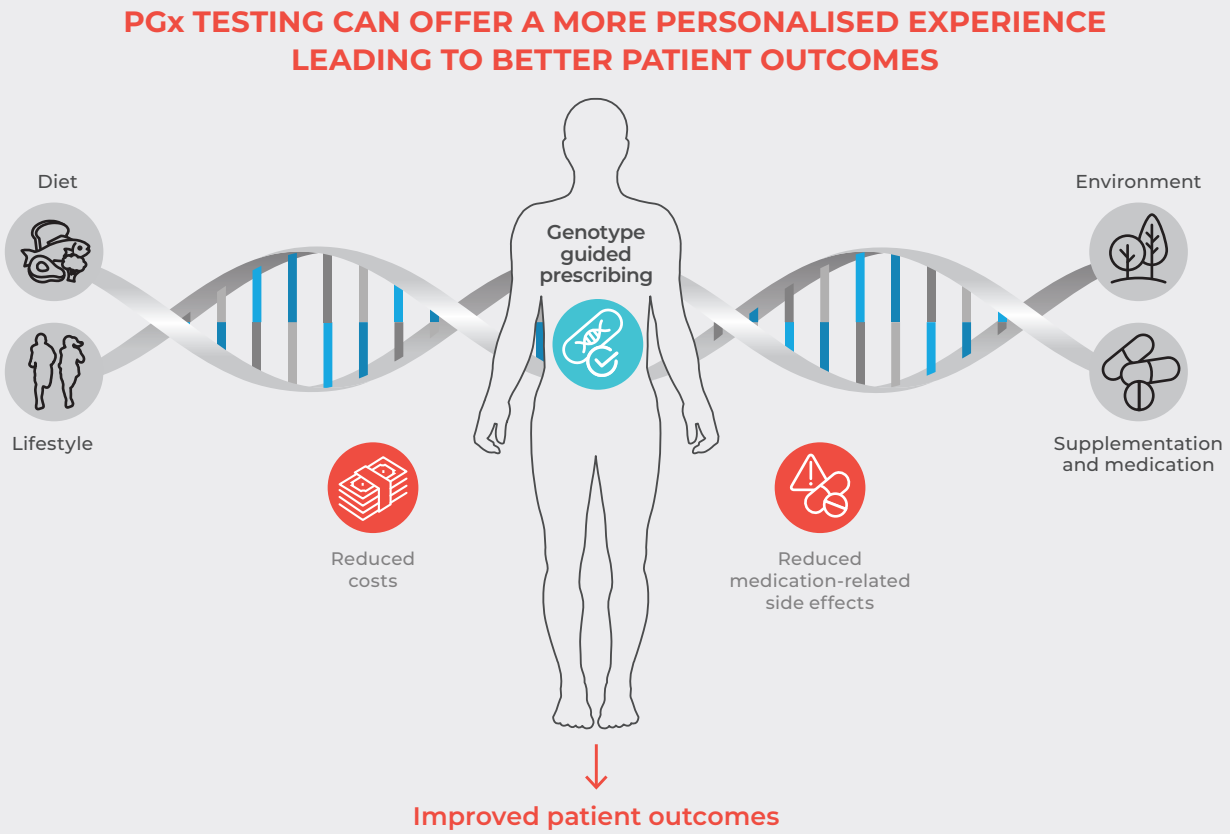
A more personalised approach to medicine can save lives and reduce medication-related side effects. Pharmacogenomics (PGx) is a rapidly growing field which studies how a person's genome affects their response to medication, offering an affordable alternative to trial and error when it comes to prescribing medication.

Laboratories and healthcare providers that embrace PGx testing can offer better outcomes, lower costs, and a more personalised experience. The U.S. Food and Drug Administration has now added2 pharmacogenomic information to more than 200 medications. And with appropriate implementation of PGx into clinical practice, data that's already well-supported and readily available can become part of the standard of care.

Personalised healthcare

"We are all unique. Our health is determined by our inherent differences combined with our lifestyles and environment. By combining and analysing information about our genome, with other clinical and diagnostic information, patterns can be identified that can help to determine our individual risk of developing disease; detect illness earlier; and, determine the most effective interventions to help improve our health, be they medicines, lifestyle choices, or even simple changes in diet." NHS*

* Cited from the NHS position paper on personalised medicine, 2020.



An overview of Pharmacogenomic testing

Clinical trials on prescription drugs deduce risk, recommended dosage, and other data based on outcomes in the trial population. This approach is based on a flawed notion: the idea that all, or most, people process drugs at a similar rate and in a similar manner.

The reality is that a significant portion of variation in drug reactions may be due to genetics.

Pharmacogenomics is the study of drug-genome interactions and their clinical implications. This form of precision medicine looks for genetic markers that indicate how a patient might respond to a drug. These biomarkers are present on genes that affect one or more aspects of how the body responds to the drug, including:

- **Pharmacokinetic (PK) biomarkers:**

  PK measures parameters involved in four different processes when a drug is administered: absorption, distribution, metabolism, and elimination. One example of a genome-based difference in PK can be found in variations on cytochrome P450 (CYP) genes. These genes code for enzymes that play a role in the metabolism of at least 70% of prescription drugs.[3] 75% of patients have at least one genetic variant that makes them an atypical drug metabolizer.[4] So variants in drug metabolizing enzymes are the norm amongst the patient population.

NORMAL GENE
Genotype resulting in normal enzyme function and typical drug metabolism

VARIANT GENE
Genotype resulting in altered enzyme function and drug metabolism

- **Pharmacodynamic (PD) biomarkers:**

  PD is the study of how the drug affects the body, including factors such as receptor binding, chemical interactions, and receptor sensitivity.

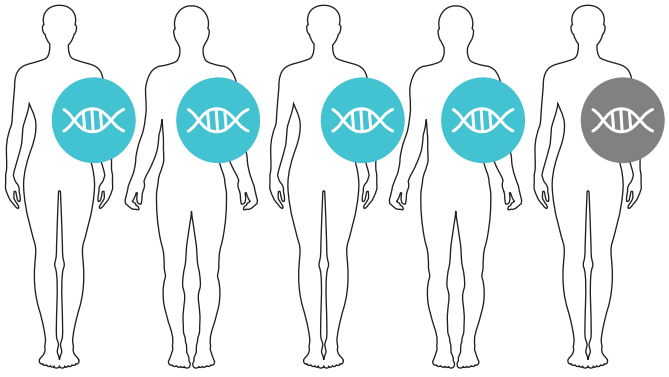
- **Human leukocyte antigen (HLA) biomarkers:**

  HLA is an immune protein located on the surface of white blood cells. HLA can cause off-target binding that causes the immune system to overreact to certain drugs. Several genes that code for HLA are linked to life-threatening drug reactions.[5]

Variations in any genes that affect these three drug response determinants can affect treatment outcomes.

A 2017 study[6] found that **four out of five patients carry at least one genetic variant that may affect targets for commonly prescribed drugs.** Individually, these genetic variants are rare and may not be apparent in clinical trials. But taken together as a group, these genetic variants are common.

Without genetic testing, these variants may go unnoticed, undermining the safety of various prescription drugs.



Improving patient outcomes

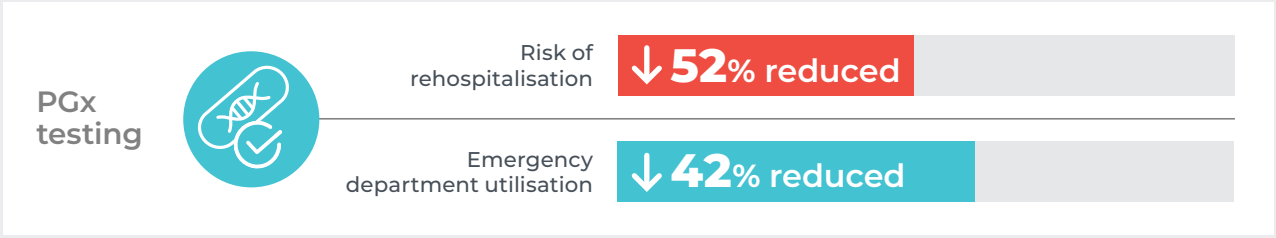
Despite compelling evidence that pharmacogenomics can improve healthcare delivery and patient outcomes, healthcare systems have been slow to adopt genetic testing. A 2016 study[7] suggests that insufficient awareness of the benefits of pharmacogenomics might play a role. Researchers gave 12 physicians a survey that presented queries about their views on pharmacogenomics. Following a one-hour presentation on PGx, physicians took the survey again.

Measures of physicians' positive attitudes toward PGx increased following the educational presentation. When clinicians understand the merits of precision medicine, they are more likely to endorse it, and potentially more likely to adopt it.

Although PGx cannot prevent all adverse drug reactions, any reduction in adverse reactions can improve healthcare outcomes. A 2015 study[8] estimates that 7% of FDA-approved drugs have clinically relevant PGx implications. These medications represent 18% of the 4 billion prescriptions written in the United States. More data could eventually increase that number. Even today, with PGx implications for nearly one in five prescription drugs, it's easy to see how widespread implementation could improve outcomes, reduce costs, and save lives.

Risk of rehospitalisation

A 2017 study[9] assessed rehospitalisation risk in 110 patients who were randomised either to PGx testing or a control group of typical care. The study found that patients who were CYP2D6 ultrarapid metabolizers faced an increased risk of rehospitalisation. Pharmacogenomic testing mitigated this risk. At the 60-day mark, PGx testing reduced the risk of rehospitalisation by 52% and of emergency department utilisation by 42%.



Antidepressant efficacy

Depression is the leading worldwide cause of disability. Forty million American adults – 18.1% of the population – experience depression each year. The Center for Workplace Mental Health estimates that major depressive disorder costs the U.S. economy at least $210.5 billion each year.

Despite this, many people with depression struggle to find adequate treatment. Antidepressants take anywhere from 1-6 weeks to achieve full efficacy. For many patients, the **side effects are intolerable**. For many more, **relief is insufficient**. Most patients have to try several drugs before one works or must switch medications when a previously effective drug stops working.[10] Depression remission rates are low, with just 11-30%[11] of patients getting relief after a year of treatment.

PGx offers the potential to disrupt this frustrating phenomenon. A 2017 double-blind study found that **PGx testing significantly increased efficacy of antidepressants** at the 12-week mark. The improvement was most significant among patients who had previously received inadequate relief from 1-3 drugs.

Research published in 2018[12] reached a similar conclusion. In a randomised clinical trial of 685 patients, the PGx-guided treatment group had remission rates much higher (42%) than the control group (27%) at 12 weeks. PGx-guided treatment was also more effective at reducing anxiety.

Lower risk of cardiovascular events

Numerous drugs are linked to adverse cardiovascular events. Even nonsteroidal anti-inflammatory medications, which are well-tolerated in most patients, can trigger cardiovascular issues.[13] Cardiovascular disease is the leading cause of death for most groups in the U.S. and plays a role in one in four deaths. The need to predict drug-related cardiovascular events is an urgent one.

PGx may play a key role in reducing drug-related cardiovascular risk. A 2018 study assessed the role of loss-of-function CYP2C19 alleles in antiplatelet therapy.[14] Researchers followed 1,815 patients after percutaneous coronary intervention for coronary artery disease. Among participants, 572 (31.5%) had a loss-of-function allele.

The risk of a major cardiovascular episode was much higher in the loss-of-function group when prescribed clopidogrel. Those treated with prasugrel or ticagrelor had a much lower risk of a cardiovascular episode. This showcases the role of genetic testing in identifying viable alternatives to first-line treatments.

Warfarin, a blood thinner that is toxic in high doses, accounts for more drug-related emergency room visits by older patients than any other prescription drug.[15] Yet this important anticoagulant can also reduce the risk of life-threatening blood clots, particularly in immobilized patients with cardiovascular risk factors.

A 2017 randomised clinical trial compared outcomes in 1,650 patients who underwent elective knee or hip arthroplasty at one of six medical centers. The mean age was 72.1 years, and patients took warfarin to prevent blood clots. Warfarin dosing guided by PGx, rather than by clinical recommendations, reduced the risk of major bleeding, blood clots, venous thromboembolism, and death.

Lower risk of hematological toxicity

Hematological toxicity is a potentially life-threatening decrease in blood and bone marrow cells.

It increases the risk of infection, anemia, bleeding, and other adverse outcomes. Numerous drugs can cause hematological toxicity. Many drugs used in the treatment of cancer have an especially high prevalence of hematological toxicity.

A 2016 analysis compared data on historical controls undergoing treatment with fluoropyrimidines, a group of popular anti-cancer therapies, to treatment data on patients who underwent PGx-guided treatment.[16] **A genetic variant of the enzyme dihydropyrimidine dehydrogenase, which metabolizes fluoropyrimidines, is strongly associated with life-threatening toxicity. The study found a toxicity rate of 73% among historical controls. With the implementation of PGx-guided treatment, toxicity dropped to 28%.**

PGx also saved lives. **The toxicity-related death rate in the control group was 10%. Among those whose treatment was guided by PGx, the death rate dropped to zero.**

The study also found that, even when accounting for the treatment costs of screening, the total treatment costs were lower for patients who underwent PGx screening than for those who did not.

Research published in 2015 highlights the potential of PGx testing to improve safety in patients with inflammatory bowel disease.[17] About 20% of patients with IBD discontinue treatment due to adverse events. Variants in a gene that encodes thiopurine S-methyltransferase (TPMT) are linked to one of the most serious adverse treatment outcomes, leukopenia. Researchers compared 405 patients who underwent PGx testing for variants in this gene to 378 who did not.

Screening did not reduce the proportion of patients who experienced hematologic adverse drug reactions. However, genetic testing reduced the rate of adverse reactions tenfold among patients in the test group who were identified and then given a lower dose. This dose reduction did not reduce treatment efficacy.

A more recent study found that PGx-guided prescription of thiopurines in patients with inflammatory bowel syndrome did not result in additional healthcare costs.[18]

Other possibilities for improved outcomes

Treating chronic diseases is notoriously difficult. About half of patients[19] are noncompliant with medication, often because they feel the medication does not work or they cannot tolerate its side effects. It's reasonable for patients to expect that their medications will work, and that the side effects will be tolerable. But too often, doctors have little to offer patients who are frustrated with inadequate improvements and intolerable side effects.

PGx offers hope for better treatment outcomes, greater patient compliance, and a deeper understanding of how and why prescription drugs work – not to mention a keener understanding of what goes wrong when these drugs fail. Greater clinical acceptance and implementation of these drugs could spur future research. The data on patient outcomes already points clearly to improvements associated with PGx. Wider implementation will further expand our understanding, offering even more opportunities to better serve patients.

A 2016 study of nursing home patients who underwent pharmacogenomic testing suggests the testing could reduce the risk of falling in nursing home patients.[20] This population-level analysis used publicly available data to compare nursing home residents who underwent PGx testing to those who did not. Patients who underwent testing reported a 5.4% reduction in moderate-to-severe pain compared to those who did not undergo testing. Additionally, PGx was linked to a reduction in falls that led to major injuries.

Because the study looked only at population-level correlations, it is unclear why PGx made a difference.

It's likely, however, that the data improved treatment for common conditions while reducing adverse drug reactions. This could reduce the risk of falls while lowering pain levels.

A Lancet article published in 2023 reported on findings from an open-label, multicentre, controlled, cluster-randomised crossover implementation study conducted in seven different European countries encompassing 6944 patients. This study showed that **genotype-guided prescribing using a 12-gene pharmacogenomic panel significantly reduced the incidence of clinically relevant adverse drug reactions by 30%**.

They concluded that this latest study shows the feasibility and benefits of a pharmacogenomic-panel strategy and provides evidence to support large-scale implementation of panel-based pharmacogenomics testing to make drug therapy increasingly safe.[21]

Introducing Medcheck

Medcheck by **dnalife**® is a pharmacogenomic test that reports on responsiveness to over 120 medications and the likelihood of side effects and treatment failure. The test provides insights into how a patient metabolizes, transports and binds specific drugs. This test can be used as a tool to guide physicians with their prescription protocol.

Such a personalised approach to medicine has the power to produce better results, particularly for individuals whose genetic profile puts them at risk of experiencing either treatment failure or an adverse reaction from a given drug.

medcheck™ →

Ideal for:

- A patient on medication*
- Planning to start a new medication*
- Anyone experiencing side-effects to their medication*
- Not responding to their medication*
- Where the prescribing doctor is constantly having to adjust the dose of the medication*

* **It is important to confirm that the medication you are questioning is included in the Medcheck report** as this test does not report on all medications, but only on medications for which there is sufficient scientific evidence and FDA guidelines linking the metabolism of the medication to a genetic variant. **It is also important to note:** Some gene-drug interactions report on efficacy whilst others show evidence on risk of side effects.

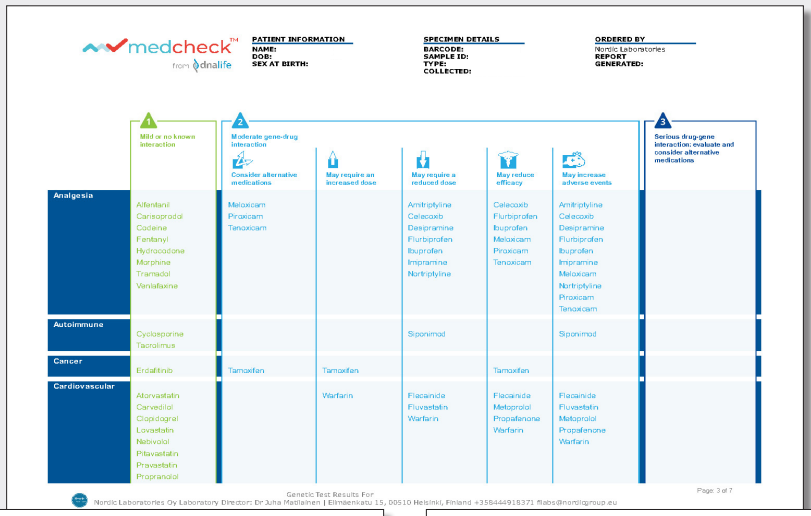
The benefits of the Medcheck pharmacogenomics test include:

- Improving drug efficacy
- Decreasing length of treatment time
- Minimising adverse side effects
- Reducing money spent on ineffective medications or time in hospital

Medcheck training:

Scan the QR code to sign up for Medcheck training.

Sample extracts of the Medcheck report



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	1 Mild or no known interaction	2 Moderate gene-drug interaction: Consider alternative medications	2 Moderate gene-drug interaction: May require an increased dose	2 Moderate gene-drug interaction: May require a reduced dose	2 Moderate gene-drug interaction: May reduce efficacy	2 Moderate gene-drug interaction: May increase adverse events	3 Serious drug-gene interaction: evaluate and consider alternative medications
Analgesia	Alfentanil Carisoprodol Codeine Fentanyl Hydrocodone Morphine Tramadol Venlafaxine	Meloxicam Piroxicam Tenoxicam		Amitriptyline Celecoxib Desipramine Flurbiprofen Ibuprofen Imipramine Nortriptyline	Celecoxib Flurbiprofen Ibuprofen Meloxicam Piroxicam Tenoxicam	Amitriptyline Celecoxib Desipramine Flurbiprofen Ibuprofen Imipramine Meloxicam Nortriptyline Piroxicam Tenoxicam	
Autoimmune	Cyclosporine Tacrolimus			Siponimod		Siponimod	
Cancer	Erdafitinib	Tamoxifen	Tamoxifen		Tamoxifen		
Cardiovascular	Atorvastatin Carvedilol Clopidogrel Lovastatin Nebivolol Pitavastatin Pravastatin Propranolol		Warfarin	Flecainide Fluvastatin Warfarin	Flecainide Metoprolol Propafenone Warfarin	Flecainide Fluvastatin Metoprolol Propafenone Warfarin	

Genetic Test Results For
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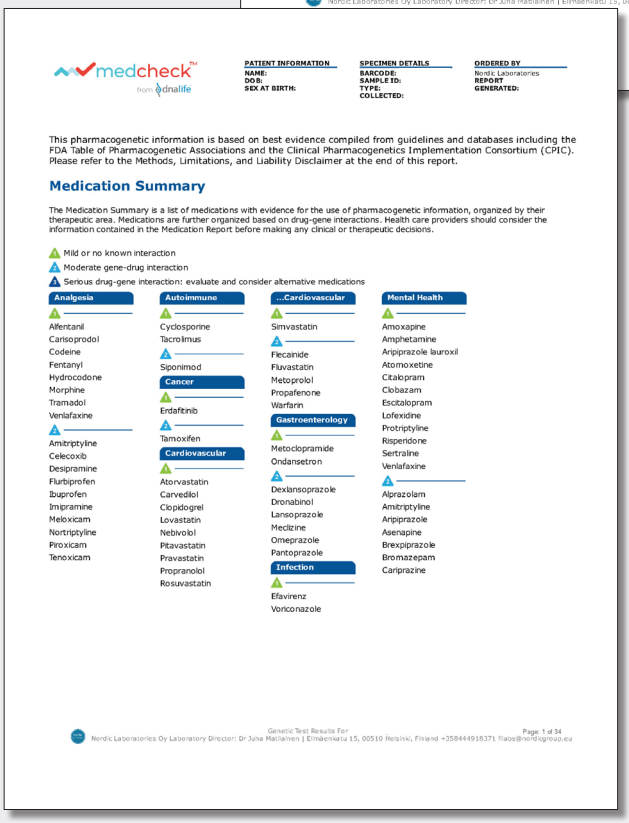

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This pharmacogenetic information is based on best evidence compiled from guidelines and databases including the FDA Table of Pharmacogenetic Associations and the Clinical Pharmacogenetics Implementation Consortium (CPIC). Please refer to the Methods, Limitations, and Liability Disclaimer at the end of this report.

Medication Summary

The Medication Summary is a list of medications with evidence for the use of pharmacogenetic information, organized by their therapeutic area. Medications are further organized based on drug-gene interactions. Health care providers should consider the information contained in the Medication Report before making any clinical or therapeutic decisions.

- Mild or no known interaction
- Moderate gene-drug interaction
- Serious drug-gene interaction: evaluate and consider alternative medications

Analgesia
- Mild or no known interaction: Alfentanil, Carisoprodol, Codeine, Fentanyl, Hydrocodone, Morphine, Tramadol, Venlafaxine
- Moderate gene-drug interaction: Amitriptyline, Celecoxib, Desipramine, Flurbiprofen, Ibuprofen, Imipramine, Meloxicam, Nortriptyline, Piroxicam, Tenoxicam

Autoimmune
- Mild or no known interaction: Cyclosporine, Tacrolimus
- Moderate gene-drug interaction: Siponimod

Cancer
- Mild or no known interaction: Erdafitinib
- Moderate gene-drug interaction: Tamoxifen

Cardiovascular
- Mild or no known interaction: Atorvastatin, Carvedilol, Clopidogrel, Lovastatin, Nebivolol, Pitavastatin, Pravastatin, Propranolol, Rosuvastatin

...Cardiovascular
- Moderate gene-drug interaction: Simvastatin
- Serious drug-gene interaction: evaluate and consider alternative medications: Flecainide, Fluvastatin, Metoprolol, Propafenone, Warfarin

Gastroenterology
- Mild or no known interaction: Metoclopramide, Ondansetron
- Moderate gene-drug interaction: Dexlansoprazole, Dronabinol, Lansoprazole, Meclizine, Omeprazole, Pantoprazole

Infection
- Moderate gene-drug interaction: Efavirenz, Voriconazole

Mental Health
- Mild or no known interaction: Amoxapine, Amphetamine, Aripiprazole lauroxil, Atomoxetine, Citalopram, Clobazam, Escitalopram, Lofexidine, Protriptyline, Risperidone, Sertraline, Venlafaxine
- Moderate gene-drug interaction: Alprazolam, Amitriptyline, Aripiprazole, Asenapine, Brexpiprazole, Bromazepam, Cariprazine

Genetic Test Results For
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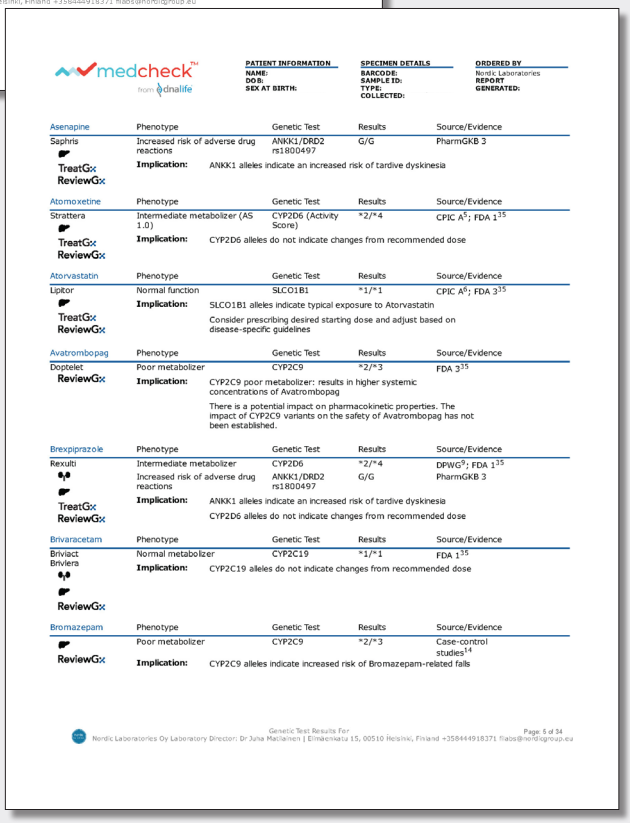

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Asenapine	**Phenotype**	**Genetic Test**	**Results**	**Source/Evidence**
Saphris TreatGx ReviewGx	Increased risk of adverse drug reactions	ANKK1/DRD2 rs1800497	G/G	PharmGKB 3
	Implication: ANKK1 alleles indicate an increased risk of tardive dyskinesia			
Atomoxetine	**Phenotype**	**Genetic Test**	**Results**	**Source/Evidence**
Strattera TreatGx ReviewGx	Intermediate metabolizer (AS 1.0)	CYP2D6 (Activity Score)	*2/*4	CPIC A[5]; FDA 1[35]
	Implication: CYP2D6 alleles do not indicate changes from recommended dose			
Atorvastatin	**Phenotype**	**Genetic Test**	**Results**	**Source/Evidence**
Lipitor TreatGx ReviewGx	Normal function	SLCO1B1	*1/*1	CPIC A[5]; FDA 3[35]
	Implication: SLCO1B1 alleles indicate typical exposure to Atorvastatin Consider prescribing desired starting dose and adjust based on disease-specific guidelines			
Avatrombopag	**Phenotype**	**Genetic Test**	**Results**	**Source/Evidence**
Doptelet ReviewGx	Poor metabolizer	CYP2C9	*2/*3	FDA 3[35]
	Implication: CYP2C9 poor metabolizer: results in higher systemic concentrations of Avatrombopag There is a potential impact on pharmacokinetic properties. The impact of CYP2C9 variants on the safety of Avatrombopag has not been established.			
Brexpiprazole	**Phenotype**	**Genetic Test**	**Results**	**Source/Evidence**
Rexulti TreatGx ReviewGx	Intermediate metabolizer	CYP2D6	*2/*4	DPWG[9]; FDA 1[35]
	Increased risk of adverse drug reactions	ANKK1/DRD2 rs1800497	G/G	PharmGKB 3
	Implication: ANKK1 alleles indicate an increased risk of tardive dyskinesia CYP2D6 alleles do not indicate changes from recommended dose			
Brivaracetam	**Phenotype**	**Genetic Test**	**Results**	**Source/Evidence**
Briviact Briviera ReviewGx	Normal metabolizer	CYP2C19	*1/*1	FDA 1[35]
	Implication: CYP2C19 alleles do not indicate changes from recommended dose			
Bromazepam	**Phenotype**	**Genetic Test**	**Results**	**Source/Evidence**
ReviewGx	Poor metabolizer	CYP2C9	*2/*3	Case-control studies[14]
	Implication: CYP2C9 alleles indicate increased risk of Bromazepam-related falls			

Genetic Test Results For
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Medications covered in Medcheck

Analgesia | Pain

Opioids
- Alfentanil
- Codeine
- Fentanyl
- Hydrocodone
- Morphine
- Tramadol

NSAIDs
- Celecoxib
- Ibuprofen
- Flurbiprofen
- Meloxicam
- Piroxicam
- Tenoxicam

Pain and Antidepressants
- Amitriptyline
- Desipramine
- Imipramine
- Nortriptyline
- Venlafaxine

Muscle Relaxants
- Carisoprodol

Autoimmune

Immunosuppressants
- Cyclosporine
- Siponimod
- Tacrolimus

Cancer

Anti-Estrogens
- Tamoxifen

Protein Kinase Inhibitors
- Erdafitinib

Cardiovascular

Antiarrhythmics
- Flecainide
- Propafenone

Anticoagulants
- Warfarin

Antiplatelets
- Clopidogrel

Beta Blockers
- Carvedilol
- Metoprolol
- Nebivolol
- Propranolol

Statins
- Atorvastatin
- Fluvastatin
- Lovastatin
- Pitavastatin
- Pravastatin
- Rosuvastatin
- Simvastatin

Gastroentorology

Antiemetics
- Dronabinol
- Metoclopramide
- Ondansetron

Antihistamine
- Meclizine

Proton Pump Inhibitors
- Dexlansoprazole
- Lansoprazole
- Omeprazole
- Pantoprazole

Infection

Antifungals
- Voriconazole

Anti-HIV Agents
- Efavirenz

Mental Health

Antiaddictives
- Lofexidine

Anti-ADHD Agents
- Amphetamine
- Atomoxetine

Antidepressants
- Amitriptyline
- Amoxapine
- Citalopram
- Clomipramine
- Desipramine
- Doxepin
- Escitalopram
- Fluvoxamine
- Imipramine
- Nortriptyline
- Paroxetine
- Protriptyline
- Sertraline
- Trimipramine
- Venlafaxine
- Vortioxetine

Antipsychotics
- Aripiprazole
- Aripiprazole lauroxil
- Asenapine
- Brexpiprazole
- Cariprazine
- Chlorpromazine
- Clozapine
- Flupentixol
- Fluphenazine
- Haloperidol
- Iloperidone
- Loxapine
- Lurasidone
- Methotrimeprazine
- Molindone
- Olanzapine
- Paliperidone
- Perphenazine
- Pimozide
- Prochlorperazine
- Promethazine
- Quetiapine
- Risperidone
- Thioridazine
- Trifluoperazine
- Ziprasidone
- Zuclopenthixol

Benzodiazepines
- Alprazolam
- Bromazepam
- Chlordiazepoxide
- Clobazam
- Clonazepam
- Clorazepate
- Diazepam
- Flurazepam
- Lorazepam
- Nitrazepam
- Oxazepam
- Temazepam
- Triazolam

Medications covered in Medcheck

Neurology

Anticonvulsants
- Brivaracetam
- Fosphenytoin
- Phenytoin

Antidementia Agents
- Donepezil
- Galantamine

Antidepressants
- Amitriptyline
- Desipramine
- Nortriptyline
- Venlafaxine

Benzodiazepines
- Clobazam
- Clonazepam
- Diazepam

Beta Blockers
- Metoprolol
- Propranolol

Other Neurological Agents
- Deutetrabenazine
- Tetrabenazine
- Valbenazine

Rheumatology

NSAIDs
- Celecoxib
- Flurbiprofen
- Ibuprofen
- Meloxicam
- Piroxicam
- Tenoxicam

Urology

Alpha-Blockers
- Tamsulosin

Antispasmodics
- Darifenacin
- Fesoterodine
- Mirabegron
- Tolterodine

Other

Gaucher Disease
- Eliglustat

Gynaecology
- Elagolix
- Flibanserin
- Oral Contraceptives

Hematology
- Avatrombopag
- Eltrombopag

Sjogren's Syndrome
- Cevimeline

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Together we change healthcare

Nordic Laboratories® was founded over 25 years ago with the goal of providing patients and practitioners with clear, reliable laboratory test results. We set about to become the right hand of the practitioner by ascertaining which laboratory offers the best methodology, the most reproducible results, with the most clinically relevant analytes.

dnalife® was established by two independent companies, **Nordic Laboratories®** and **DNAlysis Biotechnology**, who together have more than 40 years experience in providing cutting edge laboratory tests to clinicians across the globe.

For more than a decade **dnalife®** has been at the forefront of genetic testing. As one of the premier genetic testing laboratories, **dnalife®** offers an innovative approach to personalised medicine; offering a suite of nutrigenomic and pharmacogenomic tests that have been developed by our team of geneticists. We differentiate ourselves in the market through our extensive knowledge base, our selective test panels and our practical and user-friendly reports. We are committed to continually developing tests, and updating our reports, which truly help and guide practitioners and patients in optimising health and create longevity through personalised healthcare.

Our Commitment

dnalife® is continuously developing new tests with the highest standards of scientific rigour. Our commitment to ensuring the ethical and appropriate use of genetic tests in practice means that gene variants are only included in panels once there is sound motivation for their clinical utility and their impact on health outcomes.

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