

PHARMACOGENETIC TESTS IN BELGIUM



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
6-MMP	6-methylmercaptopurine
6-MTG	6-methylthioguanine
6-TG	6-thioguanine
ABM	Agence de la Biomédecine
ACMG	American College of Medical Genetics and Genomics
ADR	Adverse drug reaction
AGREE	Appraisal of Guidelines Research and Evaluation Enterprise
AHS	Abacavir hypersensitivity
ALL	Acute lymphoblastic leukaemia
ANSM	French national agency for drug security and security of health care products
ATC	Anatomical Therapeutic Chemical
BELAC	Belgian Accreditation Council
BGTD	Belgian Genetic Tests Database
BIA	Budget impact analysis
BSGM	British Society for Genetic Medicine
CBA	Cost-benefit analysis
CCA	Cost-consequence analysis
CDx	Companion diagnostics
CE	Cost-effective
CEA	Cost-effectiveness analysis
CFTR	Cystic fibrosis transmembrane conductance regulator
CHF	Swiss franc
CHG	Centre of human genetics Belgian term for medical genetics centre



CI	Confidence interval
CMA	Cost-minimization analysis
CNV	Copy number variation
COFRAC	Comité français d'accréditation
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPNDS	Canadian Pharmacogenomics Network for Drug Safety
CRD	Centre for Reviews and Dissemination
CS	Cost-saving
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost-utility analysis
CVD	Cardiovascular disease
CYP	Cytochrome P450
DB	Database
DBC	Diagnosis-Treatment Combination
DBS	Dried blood spot
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
DPWG	Dutch Pharmacogenetics Working Group
DTC	Direct-to-consumer
ECCO	European Crohn's and Colitis Organization
EE	Economic evaluation
EFI	European Federation of Immunogenetics
EHR	Electronic Health Records



EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQA	External quality assessment
ESMO	European Society for Medical Oncology
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology and Nutrition
FAMHP	Belgian Federal Agency for Medicines and Health Products
FDA	US Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GDA	Global diversity array
GDPR	General Data Protection Regulation
Genomics CRG	Genomics Clinical Reference Group
GLH	Genomic Laboratory Hub
GP	General practitioner
GSA	Global screening array
GWAS	Genome-wide association analysis
HAS	Haute Autorité de Santé
HCP	Health care payer
HCSC	Health Canada Santé Canada
HIS	In situ hybridisation
HLA	human leukocyte antigen
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRMCA	High Resolution Melting curve analysis
HTA	Health technology assessment



HUG	Hôpitaux Universitaires Genève
ICER	Incremental cost-effectiveness ratio
IMA-AIM	InterMutualistisch Agentschap – Agence InterMutualiste
INAHTA	International Network of Agencies for Health Technology Assessment
INCA	French National Cancer Institute
INDEL	insertions or deletions of bases
IPG	Institut de Pathologie et de Génétique
IVDR	In Vitro Diagnostic Medical Devices Regulation
IVDR	In Vitro Devices Regulation
KNMP	Royal Dutch Pharmacists Association
LAMP	Loop-mediated isothermal amplification
LCAT	Liverpool Causality Assessment Tool
LDT	Laboratory developed tests
LOF	Loss of function
LOH	Loss of heterozygosity
LUMC	Leiden University Medical Centre
LY	Life year
MACE	Major cardiovascular events
mRNA	messenger ribonucleic acid
mtDNA	Mitochondrial DNA
NGS	Next generation sequencing
NHG	Dutch Association of General Practitioners
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database



NICE	National Institute of Care Excellence
NIH	US National Institute of Health
NIPT	Non-invasive prenatal test
NNG	Number needed to genotype
NNT	Number needed to treat
NVKG	Dutch Association of Clinical Chemistry and Laboratory Medicine
PCI	Percutaneous Coronary Intervention
PCR	Polymerase chain reaction
PGRN	Pharmacogenomics Research Network
PGx	Pharmacogenetics
PharmGKB	Pharmacogenomics Knowledgebase
PMDA	Japanese Pharmaceuticals and Medical Devices Agency
POCT	Point-of-care testing
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-adjusted life year
QF-PCR	Quantitative Fluorescence-Polymerase Chain Reaction
QHES	Quality of Health Economic Studies
RCGP	Royal College of General Practitioners
RIHN	Référentiel des actes innovants hors nomenclature
RIZIV – INAMI	National Institute for Health and Disability Insurance
RNPGx	French Network of Pharmacogenetics (Reseau Francophone de Pharmacogénétique)
RR	Relative risk
RT-PCR	Real-time PCR



SmPC	Summary of Product Characteristics
SMRT	Single Molecule Real-Time
SNV	single nucleotide variation
SPT	Swiss Group of Pharmacogenetics and Personalized Therapy
SR	Systematic review
SSCPT	Swiss Society of Clinical Pharmacology and Toxicology
SSOP	Sequence-specific oligonucleotide probes
STR	Short tandem repeats
Swissmedic	Swiss Medicine agency
TAT	Test turnaround time
TDM	Therapeutic drug monitoring
TGN	6-thioguanine nucleotide
TIA	Transient ischemic attack
TPMT	Thiopurine S-methyltransferase
UCL	Université Catholique de Louvain
UKAS	United Kingdom Accreditation Scheme
VAS	Visual Analogue Scale
VUB	Vrije Universiteit Brussel
WES	Whole exome sequencing
WGS	Whole genome sequencing
ZVW	Zorgverzekeringswet



■ SCIENTIFIC REPORT

1 BACKGROUND

1.1 Pharmacogenetic testing in the context of personalised medicine

Why is it that a certain drug works well in one person without causing any side effects, while another patient may experience insufficient efficacy or more side effects when taking the same drug at the same dose?

Multiple variables explain the variation seen in efficacy and side-effects of medicinal products between individuals and over time in the same subject: drug formulation, drug adherence, pharmacokinetics, pharmacodynamics and the pathophysiological system response including the link with patient relevant outcomes.¹

Drugs (and their metabolites) are transported in our body/blood to the place where they need to perform their specific action. Moreover, the body has different enzymes that break down/metabolise the medicine, or sometimes activate the medicine. Furthermore, the drug can trigger the immune system and induce a hypersensitivity reaction. On all these different aspects of a medicine's journey through a human body, variations between people exist. These variations can depend on several factors, including diet, lifestyle, co-medications, renal and hepatic function, environmental factors, disease conditions, and **individual genetic differences**.

Pharmacogenetics is the study of how genetic differences affect the way the body responds to the drug. By testing patients for these genetic variants, the choice of a drug as well as the dose can be adjusted, which helps to increase drug efficacy and safety. Pharmacogenetic testing contributes to the goal of personalised medicine, to have the right therapeutic strategy for the right person at the right time, in contrast to a “one dose fits all” approach.



1.1.1 Which genetic information is tested?

1.1.1.1 DNA as the unique code leading to different gene variants

The typical helix structure of the human DNA harbours the individual code (about 3.2 billion bases expressed as four letters A, C, G and T). Specific parts on this long DNA string code for proteins, and these parts are called 'protein coding genes'. A human has nearly 20 000 protein coding genes.² The remaining segments are referred to as 'non-coding DNA', but these are also important as they play a regulatory role (i.e. regulate which codes are expressed and which not).³ The translation of the DNA code into functioning proteins happens via intermediate steps (transcription to mRNA and translation), and all these steps determine whether or not the gene is expressed. There is DNA in the nucleus of each cell but there is also DNA in the power plants of each cell (i.e. mitochondria), which is called mitochondrial DNA. The mitochondrial DNA has about 37 genes and only contains genetic info from the maternal line. The lengthy DNA string within the nucleus is folded into the structure of chromosomes to fit within the cell's nucleus, while mitochondrial DNA takes on a circular, ring-shaped structure.

When the gene codes for a protein involved in pharmacokinetics, pharmacodynamics or proteins involved with immunological reactions in relation to one or several drugs, it is called a **pharmacogene**. The website of PharmGKB collects information on the relevant pharmacogenes and labels 69 pharmacogenes as very important (i.e. VIP genes – <https://www.pharmgkb.org/vips>).

Changes in DNA are called variations, and can either be harmless, or responsible for a malfunctioning enzyme. Variants may affect DNA at different levels, such as a change in only one base called single nucleotide variations (SNVs), insertions or deletions of bases (INDELs), or more extensive chromosomal structural alterations affecting more than 50 basepairs (copy number variants). The most researched and well-known variants in pharmacogenes are variants affecting one base pair (SNVs). Comparatively less is known about structural, complex rearrangements.³

For some genes there are more than 100 known variants: CYP2D6 gene on chromosome 22 is one of the most variable among all CYP genes, including more complex structural rearrangements (copy number variants).⁴

1.1.1.2 Genetic testing is broader than hereditary information

While genetic testing is commonly associated with examining hereditary traits, the field of genetics encompasses a wider scope, and also includes genetic changes that are not inheritable as these occur during (embryonic) development and are not present in the gametes and can thus not be transmitted to the offspring.

Genetic testing can refer to germline testing that seeks out inherited **germline variants**, as well as testing for somatic variants in tumour tissue. In germline testing the **ethnicity** can play a role in the appearance of certain variants, and therefore influences the need for testing in specific ethnicities.⁵ A characteristic example is testing Asian patients before starting the anti-epileptic carbamazepine treatment because of the association between life-threatening dermatological side effects and the HLA-B*1502 variant, which is seen mainly in people from Asian descent.⁶

1.1.1.3 How are pharmacogenes tested?

The focus is on identifying germline variants, therefore every cell with DNA is a potential source. Often a blood sample or saliva is used. Testing can either be very targeted, for example by detecting a specific variant in one gene, or more comprehensive by detecting multiple variants at multiple genes locations (loci), or even screening the complete genome.

The choice of technique and the available human and laboratory instrument capacity impacts the cost and the time needed to have an answer (turn-around-time), ranging from less than 24 hours in point-of-care testing to more than a month when the whole genome is analysed.⁷ Not every pharmacogene is easy to analyse, for example CYP2D6 and HLA regions are structurally complex and need special attention. Pro's and con's in reference to PGx used techniques are discussed in chapter 3.

**Box 1 – Glossary Definitions**

Gene	Specific part of the genome or chromosome that contains the information to code for a protein.
Genome	Complete set of DNA, including all of its genes, in an individual or cell. The human genome includes DNA in both the nucleus of a cell (nuclear genome) and the mitochondria (while small, the mitochondrial genome has some vital genes and related genetic disorders). The human genome has 23 pairs of chromosomes (diploid organisms) containing 20 000–25 000 genes and 3.2 billion base pairs. A large portion (+/- 99%) of the human genome consists of non-coding DNA, this is DNA that does not code for a protein sequence. Some non-coding DNA sequences may however play important roles in gene transcription and expression.
Exome	The part of the genome that consists only of coding DNA, i.e. genes.
Genetic variation	Differences in the DNA or genomic sequence compared to a reference sequence. A variant can either be pathogenic, likely pathogenic, of uncertain significance, likely benign, or benign.
Germline variant	A variant which is inherited and present in every cell of the body since birth and can be passed on to the next generation.
Somatic variant	A variant which occurs only in a particular cell and its descendants is called a somatic or acquired variant. Often cancers are the result of accumulated somatic mutations and these somatic variants are typically found in tumour tissue.
Nuclear DNA	The DNA in the nucleus of the cell, which is diploid and has two copies (from the mother and from the father). Structurally it is folded into 23 pairs of chromosomes.
Mitochondrial DNA (mtDNA)	The DNA in the mitochondria ‘power plants’ of the cell (encodes 13 proteins). It is inherited via the mother (haploid). Structurally it is folded into 1 circular chromosome. As a cell can have many powerplants the mtDNA can contain 100-1000 copies per cell.
Allele	The DNA sequence in a specific part of a gene. A human has two alleles per gene location, one from the maternal line and one from the paternal line. If the two alleles are the same, the individual is homozygous for that allele. If the alleles are different, the individual is heterozygous.
Pharmacogene	Gene involved in metabolism of, or response to, one or several medicines.
Genotype	A genotype is the notation of the type of variant present at a given location (i.e., a locus) in the genome. It can be represented by symbols (e.g. BB, Bb, bb) or the actual DNA sequence at that specific location (e.g. CC, CT, TT).
Phenotype	An individual’s observable characteristics, such as the response to a drug. It is determined by both their genomic makeup and environmental factors.
Haplotype	A set of DNA variants along a single chromosome that tend to be inherited together due to their proximity to each other in the genome; it can refer to all the chromosomes from one of the parents or to a (minor) part of a chromosome, for example a sequence of 9000 base pairs or a small set of alleles.



Sequencing	DNA sequencing means determining the order of the four nucleotides (bases) that make up the genetic code of an individual. DNA sequencing can be done for a small part of the genome (e.g. a single gene) up to the whole genome.
Star allele	A classification system for haplotypes relevant for pharmacogenetics, by using numbers based on chronological order of discovery. For example CYP2C19*2. The star allele (or *-allele) refers thus to a specific combination of variants along a pharmacogene.
Star-allele callers	Bioinformatic tools (software) used to identify specific haplotypes (star alleles) from sequencing data. These tools aggregate the data from the existing star-allele databases (examples: Aldy, Astrolabe, Stargazer, Cypiripi, PharmCAT).
Single Nucleotide Polymorphism (SNP)	A mutation/variation at a single base position in the DNA.
Copy Number Variation (CNV)	A mutation where parts of the DNA (more than 50 basepairs) are repeated or lost. It can affect one single gene or more genes.
Insertion	Type of variant involving the addition of one or more nucleotides into a segment of DNA. The inserted fragment can be one nucleotide to an entire piece of a chromosome.
Deletion	Type of variant involving the loss of a part of a chromosome or a DNA sequence during replication.
Indel	Refers to either an insertion or deletion of nucleotides in a segment of DNA. Both of these variant types can result in “frameshift mutations”, which usually have a large impact on transcription of the gene and thus functional impact.
Tandem repeats	A sequence of two or more DNA bases that is repeated numerous times in a chromosome, directly adjacent to each other. Usually, tandem repeats are present in non-coding DNA sections.
Panel testing	A panel genetic test looks for changes in many genes in one test. Genetic testing panels are usually grouped in categories based on different kinds of medical concerns.
Pharmacokinetics	The study of the dynamic changes in the concentration of administered medicines in different compartments (e.g. plasma) of an individual, depending on way of administration, absorption, distribution, metabolism and excretion of the medicine.
Pharmacodynamics	The study of a medicine’s biochemical and physiologic effects on an individual.



1.1.2 Clinical actionability of gene variants – genotype phenotype

Does every change in DNA code impact a drug's behaviour in the body? The answer is no.

First of all, a person has two versions (also called 'alleles') of a gene, one from the maternal and one from the paternal line (except mitochondrial DNA which only has genes from the maternal line, and males have only one copy of genes located on the X or Y chromosomes).

Genotyping is testing the DNA and having the information of both the maternal and paternal version of the gene (two alleles – diplotype). In practice, alleles (maternal and paternal) are not always characterised by the presence of a single variant (SNVs) but rather by the simultaneous presence of several variants present in linkage disequilibrium. This is known as a haplotype and some are defined in the field of PGx by a star allele system. Although all pharmacogenes may be involved, this system is very well described for cytochromes P450 (CYP), for example, and the functionality of the different haplotypes is described in regularly updated databases (PharmVar.org). The genotype (also called diplotype) is defined by the presence of the two haplotypes (e.g. CYP2D6*1/*4, with the *1 allele defined as the wild-type allele). This genotype is used **to predict** how a protein/enzyme will work and how a drug will behave in the body. However, other factors can also have an impact. Co-medications, a person's disease status, the presence of inflammation,⁸ age, smoking status, all influence the true behaviour of a protein/enzyme. The **true behaviour** of a protein/enzyme is called the **phenotype**. The mismatch between the genotype-based prediction and the true behaviour 'phenotype' is called phenoconversion.⁹ Phenoconversion might explain some of the conflicting results from pharmacogenetic studies and difficulties with replication of reported results.¹⁰ In order to elucidate this phenotype, other testing approaches beyond genetic testing are employed. These methods include assessing the enzymatic metabolic activity and measuring the actual drug

concentration in the body (therapeutic drug monitoring, TDM). These tests are often seen in complement to genotyping. In some cases, for some specific medicines and genes it is more opportune to perform these phenotype tests to inform dosing adaptations (for example for the CYP enzymes the impact of co-medication can be significant).¹¹

The website of PharmGKB (Pharmacogenomics Knowledgebase) is a significant source that has compiled a knowledgebase on relevant genetic variants. It also includes clinical guidelines that provide information on what actions to take when a specific variant is detected.¹² The guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) are most renown, but PharmGKB also includes other guidelines.^{13, 14}

1.1.3 What's in a name?

1.1.3.1 Pharmacogenetics versus pharmacogenomics

Pharmacogenetics and pharmacogenomics are frequently used interchangeably, and they both share the abbreviation 'PGx' in literature. The European Medicines Agency distinguishes between them, using PGx for pharmacogenomics and Ptx for pharmacogenetics^{a, 15}.

Pharmacogenomics is a broader concept than pharmacogenetics. While pharmacogenetic testing aims at the detection and interpretation of single to a few variants in one single to a panel of genes, pharmacogenomics moves towards a genome-wide analysis of variants including their associations with pharmacological phenotypes.¹⁶ In this study we will be examining the implementation of tests for known pharmacogenes, rather than delving into the broader and more research-oriented field of pharmacogenomics, therefore we use the term **pharmacogenetic testing along with the commonly used PGx abbreviation**.

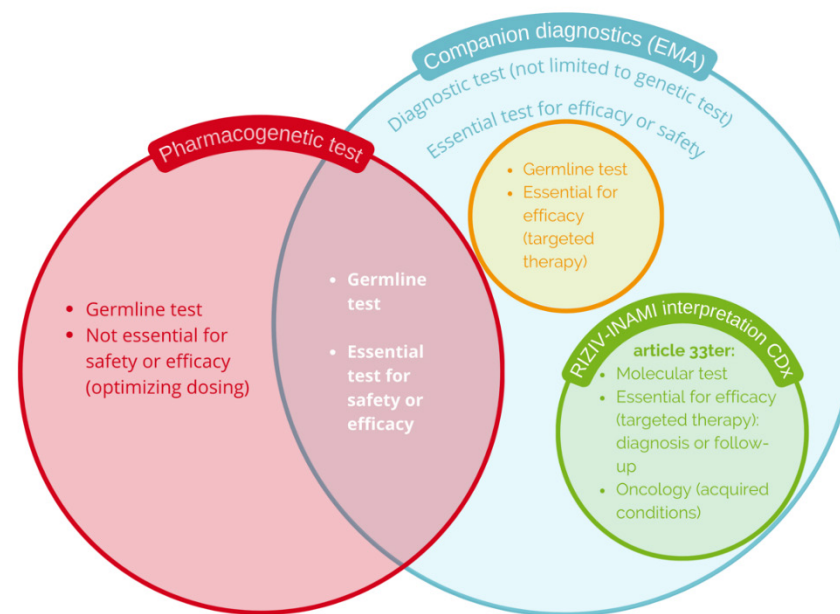
^a EMA definition: Pharmacogenomics is the study of variations of DNA and RNA characteristics as related to drug response. Pharmacogenetics is the study of variations in DNA sequence as related to drug response.

1.1.3.2 Are pharmacogenetic tests companion diagnostics?

Companion diagnostics^b, shortened as CDx, are according to the EMA definition, in vitro medical devices considered **essential** for defining a patient's eligibility for treatment with a medicinal product through quantitative or qualitative determination of biomarkers. The biomarker **may be genetic or non-genetic** and can be used to identify either patient who will most likely benefit (effectiveness) as well as patients most likely at risk (safety).

As illustrated in Figure 1, the blue circle denotes the EMA CDx definition, which broadens the understanding of CDx beyond its typical association with genetic tests for targeted therapy in oncology. This expanded interpretation contrasts with the current reimbursement criteria set by the Belgian national health insurance (RIZIV-INAMI), represented by the green circle, which focuses on molecular tests for targeted therapy in oncology. An example of a CDx in the field of oncology is BRCA1/2 testing before the start of treatment with PARP inhibitors, or testing for HER2 amplification to evaluate if the patient is eligible for treatment with 'trastuzumab'. But targeted medicines and CDx are also used outside of oncology. For example, the identification of a pathogenic variant in the cystic fibrosis transmembrane conductance regulator (CFTR)-gene is necessary for the targeted medicine 'ivacaftor', which is a CFTR gene modulator (see orange circle). The EMA CDx definition also includes non-genetic tests such as immunohistochemistry for CLDN18 for Zolbetuximab.

Figure 1 – Interpretation of PGx



^b The official EU definition of CDx in the In Vitro Diagnostic Regulation 2017/746 states that a 'companion diagnostic' means a device which is **essential** for the safe and effective use of a **corresponding medicinal product** to: (a) identify, before and/or during treatment, patients who are most

likely to benefit from the corresponding medicinal product; or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.



While there is overlap between companion diagnostics and pharmacogenetic testing, the distinction lies in the fact that companion diagnostics are **essential** for a medicine's effectiveness or safety according to the EMA definition. Pharmacogenetic tests are not always considered 'essential', but for example used to inform the dose. However, there are certain PGx tests that have become essential for ensuring safe medicine use and therefore considered CDx. The European Medical Device Coordination Group developed a guidance to know whether it can be considered a CDx or not (see Figure 2). They state that devices identifying CYP2D6 or CYP2C19 genotypes of a patient to determine the appropriate dosage of an already prescribed medication are not considered CDx, while a device intended for the demonstration of dihydropyrimidine dehydrogenase (DPD) deficiency is considered CDx.¹⁷

Figure 2 – Flowchart to help define whether an in-vitro diagnostic is a companion diagnostic according to European commission

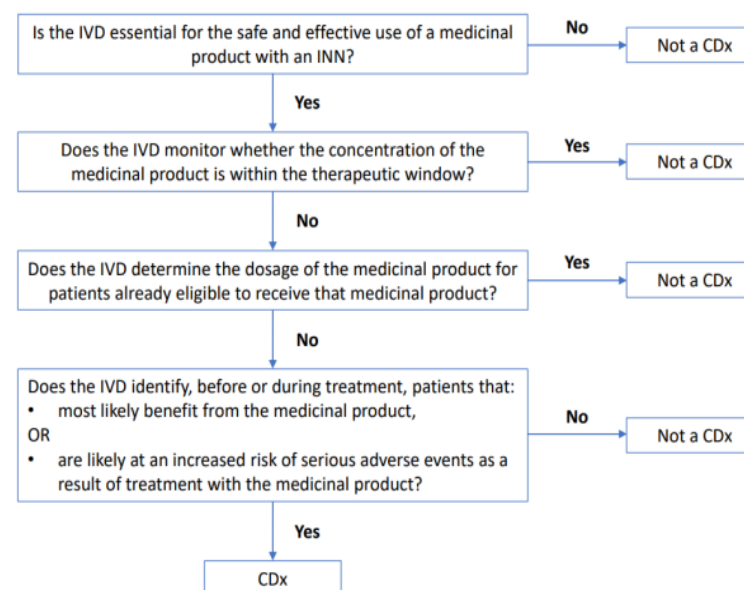
Medical Devices

Medical Device Coordination Group Document

MDCG 2020-16 rev.2

Annex II: Flowchart to help determine whether an IVD is a CDx

This flowchart should be followed for each intended purpose of the device.



Source: The Medical Device Coordination group document: *Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746*.



1.1.3.3 Reactive versus preemptive testing

In clinical practice most of the time PGx testing is requested **reactively**, referring to genotyping performed after a decision to prescribe a drug is made or to explain an unexpected drug response. This form of targeted testing focuses on a limited number of genes relevant for the specific medication or class of medications.¹⁸ For some medicines it is imperative to test before the prescription in order to avoid severe adverse reactions while for other medications it can be during the treatment when experiencing side effects or no effect. Having to wait for the test result can delay initiation of treatment. To address this concern, point-of-care PGx testing is available for certain drug-gene targets (less than 30 minutes,¹⁹ or less than 24 hours²⁰).

In contrast, **preemptive testing** refers to genotyping more as a preventive approach, irrespective of the (future) medicines prescribed. In order to have a clinical impact, this genetic information should be stored, e.g. in medical files, and consulted when new medicines are prescribed.

A **panel test** is typically associated with preemptive testing, because multiple gene targets are analysed at once, even though all this information is not yet needed. However, there are panels with only a limited number of gene targets all relevant to a particular treatment. When this panel is run at the moment of prescription, it is called a reactive panel.²¹

Testing the entire genome (or exome) of a person, **whole genome/exome sequencing**, which is being implemented for specific indications, allows (post-hoc) detection of PGx targets.²² This can be considered as “opportunistic screening” and also classifies as a preemptive testing approach.

Most experience with preemptive testing is panel testing on a hospital basis in the United States.²³ The patient selection to initiate panel testing is either very broad (e.g. all children treated in the St. Jude Children’s Research Hospital - PG4KDS protocol or patients from a the Mayo Clinic biobank – RIGHT protocol) or more focused (e.g. Vanderbilt University Medical Center anticipated cardiac catheterisation – PREDICT).^{24, 25}

Because the patient selection might be too wide in a fully preemptive approach, often PGx panel testing is initiated based on a medication prescription which is actually considered a semi-preemptive approach, including a reactive and a preemptive part of the panel.²³

The experience with preemptive testing is more limited in Europe. However, the European Ubiquitous Pharmacogenomics Consortium finished the first large scale prospective clinical study (PREPARE) in 2023. This study evaluated the semi-preemptive 12-gene pharmacogenetic panel approach across different settings (hospital and primary care).²⁶ The approach was not truly preemptive as they included patients receiving a first prescription for a drug with an actionable drug–gene interaction (part of the panel) to increase efficiency. A truly preemptive approach (without having a first prescription for a relevant drug) would require a 10–20 times larger sample size compared to the 6944 patients included in PREPARE, because many patients would not start a relevant drug within the timeframe of the study.

Box 2 – Testing approaches

Reactive testing: a targeted testing approach when a specific medication is initiated or being considered. This can either be before the administration of the medication, or during.

(Fully) preemptive testing: a broader testing approach before it is known that a particular drug may be needed.

Semi-preemptive or partially preemptive testing: a panel test for a broad range of genes and possible medications, but initiated based on a specific prescription (for example an index drug), but where the additional genes in the panel provide information for subsequent prescribing. It is a combination of reactive (for the medications for which the panel is launched), and preemptive testing (for the results informing future prescribing).



1.2 Scope and methodology

1.2.1 Rationale

Despite the availability of pharmacogenetic tests for a few decades, the uptake has remained relatively low. In Europe, several implementation studies and initiatives have put PGx on the agenda (EMA Pharmacogenetics working party in 2005,²⁷ the Ubiquitous consortium and study under the Horizon 2020 Programme^{26, 28}). Simultaneously testing of multiple genes for multiple possible medications (panel-testing) has been put forward as the way to implement PGx, therefore putting an emphasis on preventive rather than reactive medicine.^{26, 29} At the same time costs for genetic panel tests are decreasing, and the market of direct-to-consumer tests (over the counter testing) is emerging.^{30, 31} By contrast, the conflicting evidence on clinical utility and the need for cost-effectiveness studies hamper reimbursement and pose a barrier to wider implementation.³²

Interest is also growing in Belgium, as demonstrated by the establishment of a Belgian PGx Interest Group in 2022. This group brings together researchers, (laboratory) clinicians, pharmacists, and policy makers. Various academic centres and hospitals are committed to PGx research and its potential implementation as demonstrated by various master theses,³³⁻³⁷ publications³⁸⁻⁴² and pilot projects (*MyPGx: the fight against medication failure* at the UZ Brussel hospital). However, the situation on PGx testing in Belgium was not well documented at the start of this project.

1.2.2 Aim and Scope

This study has been requested by the National Health Insurance (RIZIV-INAMI). The aim of the project is to inform Belgian decision makers on the use of PGx and to advise on implementation and possible reimbursement by the RIZIV-INAMI of pharmacogenetic testing **in clinical practice**

Confusion on semantics forced us to delineate clearly what we consider pharmacogenetic testing in this study.

In this report, we focus on testing DNA to identify **germline (inheritable) variants** which inform the choice and/or dosing of the medicine (red circle in Figure 1). Testing to identify somatic or tumour mutations, which is more commonly done in the context of oncology and targeted therapies, is out of scope. Testing to identify non-human material like viruses and bacteria is out of scope (e.g. viral resistance testing in HIV). Genetic testing of biomarkers for diagnostic purpose and identify candidates for targeted therapies (e.g. ivacaftor – CFTR), is also out of scope (orange circle in Figure 1). Likewise, the use of genetic testing in research context, e.g. for drug discovery and drug development, is out of scope.⁴³

1.2.3 Research questions and methodology

Table 1 presents the research questions and the methodology applied to provide an answer to each research question.

**Table 1 – Research questions and methodology**

Research Question	Methodology	Chapter in report
What is the current Belgian situation on PGx testing (which gene-targets at what volume)	- Cross sectional (online) survey to 8 centres of human genetics + molecular diagnostic labs with NGS capacity - Individual contact + expert meetings with molecular diagnostic labs (e.g. CHG, HLA labs)	Chapter 2
What are the techniques and methods used for PGx (including quality assurance) - focus on Belgium	- Analysis of the Belgian Genetic Tests Database (BGTD) - Description of commonly used technologies in Belgium (contribution by Belgian experts) - Description of quality assurance (contributed by Sciensano)	Chapter 3
What is the clinical evidence on PGx?	- Narrative review of existing sources and their methodology - Case study on - o Targeted testing in view of clopidogrel - o Preemptive panel approach (PREPARE study) - Explorative analysis of ongoing clinical trials (focus on RCTs)	Chapter 4
What is the cost-effectiveness of PGx testing?	- Pragmatic economic literature search and review of the literature	Chapter 5
What is the potential budget impact of enlarging the public funding of PGx testing in Belgium?	- Development of scenarios to quantify the budget required to finance those tests.	Chapter 6
What can we learn from other countries on the implementation of PGx?	- International comparison: desk research – grey literature – country experts	Chapter 7
What are the current Belgian sources of inspiration for implementation and reimbursement of PGx?	- Describe and analyse the current policy on companion diagnostics (CDx) – grey literature – country expert	Chapter 8



2 BELGIAN SITUATION

2.1 What is known and what remains a mystery?

2.1.1 Is there a legal framework?

Legislation foresees in the establishment of and criteria for **centres for human genetics** (CHG) (Royal Decree of 14 December 1987).⁴⁴ These CHGs must be established and operate within the framework of a university hospital. This certification ('recognition') is granted by the federal minister of Public Health.

Belgium has eight CHGs, one in each of the seven university hospitals and one located in the Institut de Pathologie et de Génétique (IPG), an independent not-for-profit centre (see appendix 1).

The **focus of the 8 CHGs is on diagnosing and analysing germline DNA and the hereditary impact, and communicating this to the patient** (genetic counselling).

The CHGs must also comply with quality requirements stipulated in legislation (Royal Decree of 15 February 1999).^{45, 46} The **Belgian College for Human Genetics and Rare diseases**^c has been established in 2012. This College groups medical experts from each of the eight CHGs and is responsible for the external quality check of the medical activity in the CHGs.

While the legislation on the certification of CHGs does not explicitly limit genetic testing to the 8 CHGs,⁴⁴ the reimbursement legislation is clearer: PGx is only reimbursed by the National Health and Disability Insurance (RIZIV-INAMI) when performed in a certified CHG.⁴⁷ However, molecular diagnostics have become the standard in several medical fields such as microbiology, oncology and equipped laboratories with the technical and intellectual capability to analyze and interpret gene variants. Consequently, certain **germline** genetic tests are commonly performed and **reimbursed^d in clinical biology or anatomopathological labs** having the molecular diagnostic techniques in place and having the accreditation for it: genetic testing of donors and recipients in (stem cell) transplantation (Histocompatibility and Immunogenetics Laboratory – **HLA Lab**), diagnosis of coagulation diseases such as factor V Leiden, prediction of Rhesus antigen problems, or non-invasive prenatal NIPT test (see chapter 8). In the realm of somatic testing for oncology, a growing number of laboratories have the capacity to perform genetic testing to identify somatic mutations to select candidates for targeted medication.

There are no specific laws on genetic testing and PGx in particular, though, some restrictions are in place thanks to more general health care laws.^{30, 48} The 2015 law on the execution of health professions states that practicing medicine, including genetic testing for medical purposes, is reserved for licenced physicians^{e, 49}.

^c This College for Human Genetics and Rare Diseases replaces the High Council of Anthropogenetic.

^d Article 33bis, Article 24 of the RIZIV-INAMI Nomenclature

^e Coordinated law of 10 May 2015 regarding the practice of healthcare professions - Article 3: "No one may practise medicine who does not hold the legal degree of doctor of medicine, surgery and obstetrics, obtained in accordance with the legislation on the awarding of academic degrees and the

programme of university examinations, or who is not legally exempt from it. Shall be deemed to be unlawful practice of medicine, the habitual performance by a person who does not fulfil the whole of the conditions set out in subsection (1), of any act which has as its object, or is proposed to have as its object, in a human being, either the examination of the state of health, or the detection of diseases and infirmities, or the diagnosis, institution or performance of treatment of a physical or psychological, actual or alleged pathological condition, or vaccination."



The 2002 Law on Patient Rights^f specifies the need to be fully informed before giving consent.⁵⁰ The EU General Data Protection Regulation (GDPR) considers health and genetic data as very sensitive.⁹ However, **written consent is not legally mandated** when processing such data within the context of the patient-healthcare provider relationship, as medical confidentiality rules apply.

In the consideration that direct-to-consumer (DTC) genetic tests fall under the practice of medicine, there is the need for the implication/prescription/request of a licensed physician, and the law on Patient Rights applies. However, companies offering DTC tests can have a licensed physician inhouse which can act as the prescriber and counsellor. Furthermore, some DTC companies state in their 'terms of services' that they are not practicing medicine, and that their tests should not be considered medical information, but only serve 'informational purposes'.^{51, 52}

A general legislation which applies to all PGx tests, regardless the context, is the new European Union **In Vitro Diagnostic Medical Devices Regulation** (IVDR).⁵³ Pharmacogenetic tests are in vitro diagnostics, and can either be commercially developed by a company or created in a laboratory (laboratory developed tests LDT in-house). PGx tests are classified in risk class C which means every test needs to have proof of its performance and its quality assurance (though not of its clinical utility per se) (more information see chapter 3.7.4).

^f Patient rights law of 22 August 2002 - Article 8: "The patient has the right to give informed, prior and free consent to any intervention by the professional. Such consent shall be given explicitly except when the practitioner, having adequately informed the patient, can reasonably infer his consent from the patient's conduct. At the request of the patient or the professional and with the consent of the professional or the patient, the consent shall be recorded in writing and added to the patient file."

⁹ EU General Data Protection Regulation (2016/679) - Article 9: processing of special categories of personal data.

2.1.2 The rules of financial accessibility are more stringent

Financial accessibility of genetic testing in terms of reimbursement by the National Health and Disability Insurance (RIZIV-INAMI) is linked to strict conditions. The legal framework is called the nomenclature and the codes available in Article 33 are specific for germline genetic testing including PGx.⁴⁷

For **PGx** there is **only reimbursement** when performed in a **certified CHG**, when the indication and testing is present on a **defined, limitative list** ("*limitatieve lijst – liste exhaustive*"), when it is prescribed by a physician and accepted by the **specialist in medical genetics** who is performing the test in a laboratory with ISO 15189 accreditation or equivalent European or international laboratory standards (for at least 80% of the tests), and participates in internal and external quality controls.

The limitative list contains all the indications for reimbursable genetic testing (around 600), including several indications for PGx. It is updated yearly by the eight CHGs and approved by *Verzekeringscomité – Comité de l'assurance* of the RIZIV-INAMI^h. This list can be consulted on the website of RIZIV-INAMIⁱ. The indications on the limitative list are connected to a specific nomenclature code stipulating the reimbursement rules and specific reimbursement fee (Article 33 of the nomenclature). However, not every gene-target has its own unique code/fee. A form of standardisation has been implemented where the code/fee depends on the complexity of the genetic test. For certain indications there are multiple codes/fees possible,

^h Article 33 of the nomenclature (diagnostic rule 10): This limitative list is updated annually by the College for Human Genetics and Rare diseases (before the Conseil supérieur de Génétique humaine / Hoge Raad voor Antropogenetica), a council with the 8 Centres of Human Genetics. Each year the list is examined by the Clinical Biology Working Group of the Technical Medical Council and submitted for approval by the RIZIV-INAMI Insurance Committee at the latest by 31 January. In case of no receipt of a new list before this date, the previous year's list remains valid.

ⁱ https://www.riziv.fgov.be/SiteCollectionDocuments/liijst_laboratoria_terugbetalings_artikel_33.pdf



depending on the number of genes needed to test and the complexity of the test (e.g. identifying a SNP, testing several genes or large panel tests). Regardless of the complexity of the test, the patient share is fixed at €8.68. The details on reimbursement fees are explained in chapter 2.2.4.

2.1.3 Scale of PGx remains unclear

The Belgian Genetic Tests Database (BGTD), a publicly accessible database^j, curated by the public institution Sciensano, centralises relevant information on the genetic tests offered in the eight CHGs, including the technique used, whether there is external quality assessment, accreditation, the turn-around time, the reimbursement code, and the link to the application form. Importantly, the information on the tests offered is self-reported by the eight CHGs. This database together with the limitative list provides information on available reimbursed PGx tests, although it remains difficult to get a clear overview on which PGx tests for which medicines are available. Moreover, there is no information on the volume of these tests.

As part of the reimbursement rules, the RIZIV-INAMI sets the requirement to receive annual activity reports from the eight CHGs^k. However, it was not possible to extract the volumes of PGx tests directly from those reports, as these reports do not contain information for which of the over 600 indications on the limitative list the tests were performed.

Furthermore, another facet introducing vagueness in the endeavour of grasping an overview is the (technical) possibility of performing PGx outside the CHGs, and outside of specific PGx reimbursement. More specifically, this concerns the histocompatibility and immunogenetics laboratories (HLA Labs) analysing germline variants coding for human leucocyte antigens (HLA) (details see box 3) and the anatomopathological and clinical biology labs performing (panel) tests to identify somatic variations relevant for

oncological diagnosis and targeted medications. Since 2019, there is an ongoing pilot project on introducing NGS panel testing in routine clinical diagnostics for (hemato-)oncology. This pilot offers ten NGS networks, linking more than 100 hospitals to 30 labs, the option to perform reimbursed panel testing in the oncological setting.⁵⁴ It is focused on somatic mutations, though each network must include a CHG to help manage germline findings.

Box 3 – The particular situation of HLA

Human leukocyte antigens (HLA) are specialized proteins present on the surface of all cells in the body (except red blood cells). They help the body's immune system distinguish between cells that are "self" and cells that are "non-self". Cells that are recognized as "non-self" can trigger an immune response.

In view of transplantation or blood transfusion, it is important to check the compatibility between donor and patient. While originally this was analysed via serology (identifying antibodies), the standard nowadays is via molecular biology technology. The HLA genes that individuals inherit are responsible for the HLA antigens present on their cells. There are 200 genes that can code for HLA proteins. With over 10 000 different HLA alleles identified to date, they are the most polymorphic gene family in the human genome. Due to high polymorphism in various genomic regions, unambiguous HLA genotyping is technically challenging, and expertise lies in the HLA-labs. In Belgium there are seven HLA labs accredited by the European Federation for Immunogenetics. Often, these labs are part of the clinical biology lab of a hospital (see appendix 1.1).

^j <https://gentest.healthdata.be/>

^k Article 33 of the nomenclature: § 7. The recognised CHGs are required to have a uniform annual activity report with an overview of the genetic activities carried out.



The HLA labs are mainly focused on analyses in view of blood transfusion, solid organ and hematopoietic stem cell transplantation. Reimbursement of testing of HLA variants in these contexts is foreseen via nomenclature article 24 and article 33bis. Some HLA variants are linked to specific diseases (coeliac disease) and drug hypersensitivity reactions.⁵⁵ The latter are considered pharmacogenetic tests.

For example:

- the antiviral abacavir is not indicated in patients with the HLA-B*5701-allele due to possible life-threatening hypersensitivity reaction,
- the anti-epileptic carbamazepine can induce life-threatening dermatological side effects in persons with an HLA-B*1502 variant (mostly in Han-Chinese and Thai),
- allopurinol, used for the treatment of gout and hyperuricemia, in patients with an HLA-B*58:01 variant is associated with an increased risk for cutaneous adverse drug effects.

However, for these pharmacogenetic tests on HLA targets there is no reimbursement foreseen when directly requested to the HLA lab (also not in view of abacavir prescription).

A particular, recent case is testing to identify a specific HLA variant (HLA-A*02:01 positive) for the targeted medication tebentafusp in patients with previously untreated metastatic uveal melanoma. As of November 2023, it is reimbursed as a companion diagnostic (Article 33ter of the nomenclature), which means also non-CHGs labs can have access to this reimbursed test.

2.2 Unravelling the Belgian situation

2.2.1 Methodology

By means of a cross-sectional **online survey** we obtained information on which PGx targets were tested, their volume, which technology, and by which labs. Two versions of the survey were distributed: one addressed to the eight CHGs, and one to the non-CHG labs (details in appendix 2.1). Experts from the College of Human Genetics tested the draft version. In order to identify the non-CHG labs with the available technology to carry out PGx, the survey was addressed to the anatomopathological and clinical biology labs in the ten NGS networks (23 labs that are not a CHG and have an agreement with RIZIV-INAMI), as well as the seven HLA labs (which are often part of the clinical biology lab in the NGS network). There was no survey targeted to (commercial) labs which are outside reimbursement options for genetic testing.

The survey ran from January 2023 till March 2023. Laboratoria were contacted when further details were needed. There was a complete response from the eight CHGs. Also from the seven HLA labs we received input on whether or not they perform PGx tests. Of the 23 non-CHG labs in the NGS networks, only seven responded to our survey, of which two were actually HLA labs. Two expert meetings were organized to discuss and interpret the survey results, one for the CHGs and one for the non-CHGs labs.

In addition to the survey, the Belgian Genetic Tests Database was analysed, compared to the limitative list and the survey results.

In order to get an idea on the uptake of PGx for certain drugs, we compared the number of tests performed (obtained via the survey) to the number of patients using the medication. The number of patients was extracted from the number of new drug users (incident users) from the most recent years (2019, 2020, 2021) of the national reimbursement database (InterMutualistisch Agentschap – Agence InterMutualiste, IMA-AIM), using the ATC codes of the corresponding medication (see appendix).



The PGx targets mentioned on the limitative list were compared to prevailing guidelines available in PharmGKB. The most renowned are the guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG).^{13, 14}

2.2.2 The PGx targets on the RIZIV-INAMI limitative list

Twenty indications on the limitative list are labelled 'pharmacogenetics' (see Table 2). However, upon closer examination it becomes clear that not all labelled indications actually pertain to PGx. Two are diagnostic tests (i.e. HLA-DQ2, HLA-DQ8 for coeliac disease and HLA-DQB1*0602 for narcolepsy). Moreover, some indications on the limitative list do not have the label 'pharmacogenetics' but can be considered PGx (e.g. Gilbert Syndrome/Irinotecan sensitivity *homozygous allele - hot spot mutation 1551-G in MT-RNR1* which is used to predict ototoxicity to aminoglycoside exposure, *homocystinuria 2 hot spot mutations in MTHFR* to detect methotrexate toxicity, HLA genotyping for susceptibility to pancreatitis induced by thiopurine immunosuppressants).

Another difficulty in the limitative list is that the clinical indication does **not** usually make any **reference to a specific drug or drug/indication pair**. Only rarely the drug is explicitly mentioned (e.g. *abacavir toxicity HLA-B*57:01 genotyping, clopidogrel resistance*) as usually the designated drug is implicit (e.g. *ABCB1 genotyping (c.3435C>T, c.1199G>A) - Transport protein; CYP2B6*6*11*18 genotyping - drug metabolism*). In order to be able to link the PGx on the limitative list to the relevant medications, the prevailing guidelines in PharmGKB were checked (see Table 2, column 5). This analysis showed that there were **some targets listed on the RIZIV-INAMI list for which no clinical recommendations apply** according to the guidelines consulted (ABCB1, PON1, BCHE, HLA-DQA1-HLA-DRB1).

In Table 2, column 3 lists the variants as they appear on the limitative list, indicating that these are the variants that should be minimally tested. Some PGx indications are mentioned multiple times in the RIZIV-INAMI list as they have multiple testing options, for example, a more targeted approach searching for four variants in the DPYD gene or a more elaborated approach searching all possible variants with a sequencing approach (DPYD sequencing exons).

Table 2, column 5 provides information about the tests offered by each CHG. All eight CHGs offer PGx, although for some, the scope is restricted to only one target. Notably, at the moment there is a concentration of expertise for some PGx targets and the Université Catholique de Louvain (UCL) has the broadest test offer of PGx targets. Often samples are transferred from the facility where the test is initially prescribed to the CHG with the highest expertise in that particular area, such as with CYP enzymes.

Note that some gene targets, which are considered PGx targets according to CPIC guidelines, were identified on the limitative list but without the label PGx. The reason for inclusion on the limitative list was not to optimise drug treatment, but to confirm a diagnosis. For example, the CACNA1S and the related RYR1 gene can assist in identifying patients at high risk of developing malignant hyperthermia when administering potent anaesthetics. On the limitative list a targeted test (hot spot mutations) for the CACNA1S gene is included, though it is used in cardiology to diagnose hypokalemic periodic paralysis. Also several neuromuscular and cardiomyopathy panel tests include de CACNA1S and RYR1 gene.



Table 2 – Pharmacogenetic tests reimbursed by RIZIV - INAMI

Indication (as mentioned on limitative list)*	Gene - target	Variants	Nomenclature	Which CHGs offer? ^s	Medications for which guidelines are available ^e
Pharmacogenetics transportprotein	ABCB1	c.3435C>T, c.1199G>A	565390-565401	UCL	None
Pharmacogenetics Metabolism	CYP2B6	*6,*11,*18	565390-565401	UCL	efavirenz, sertraline
Pharmacogenetics Metabolism	CYP2C19	*2,*3,*17	565390-565401	UCL	amitriptyline, imipramine, clomipramine, imipramine, citalopram, escitalopram, sertraline, clopidogrel, lansoprazole, omeprazole, pantoprazole, voriconazole, mavacantem
Pharmacogenetics Metabolism	CYP2C9	*2,*3	565390-565401	UCL	siponimod, celecoxib, ibuprofen, meloxicam, piroxicam, tenoxicam, warfarine, phenytoin acenocoumarol, phenprocoumon
Pharmacogenetics Metabolism	CYP2D6	*2,*3,*4,*5,*6,*7, *8,*9,*10,*11,*15, *17,*29,*35,*41	565456-565460	UCL	codeine, tamoxifen, amitriptyline, clomipramine, atomoxetine, imipramine, nortriptyline, paroxetine, venlafaxine, ondansetron, tropisetron, aripiprazole, flecainide, haloperidol, metoprolol, pimozide, propafenone, risperidone, zuclopenthixol, eliglustat, tramadol, fluvoxamine, citalopram, escitalopram, sertraline, vortioxetine
Pharmacogenetics Metabolism	CYP3A4	*22	565390-565401	UCL	tacrolimus, quetiapine
Pharmacogenetics Metabolism	CYP3A5	*3,(⁶)	565390-565401	UCL	tacrolimus
Pharmacogenetics transportprotein	SLCO1B1	*1b,*5,*15	565390-565401	UCL	simvastatin, atorvastatine, pravastatine, rosuvastatine
Pharmacogenetics Abacavir hypersensitivity	HLA - B	HLA-B*57:01	565390-565401	VUB, Gent, Liège	abacavir
Pharmacogenetics vit K antagonist sensitivity	VKORC1	-1639G>A + 1173C>T	565390-565401	UCL	warfarine, acenocoumarol, phenprocoumon
Pharmacogenetics vit K antagonist resistance	VKORC1	3 exons and -1639G>A + 1173C>T	565390-565402	UCL, Gent	warfarine, acenocoumarol, phenprocoumon
Pharmacogenetics Clopidogrel resistance	PON1	Q192R	565390-565401	UCL	none



Indication (as mentioned on limitative list)*	Gene - target	Variants	Nomenclature	Which CHGs offer? ^{\$}	Medications for which guidelines are available [£]
Pharmacogenetics Dihydropyrimidine dehydrogenase deficiency/ 5-fluorouracil toxicity	DPYD	exons	565456-565460	UCL	fluorouracil, capecitabine, tegafur
Pharmacogenetics Dihydropyrimidine dehydrogenase deficiency/ 5-fluorouracil toxicity	DPYD	*2A, *13, c.2846A>T, HapB3	565390-565401	UCL, KUL, Liège, Gent, UZA	fluorouracil, capecitabine, tegafur
Pharmacogenetics response to antiviral (Hep C)	IL28B	rs8099917 (T>G) + rs12979860 (C>T)	565390-565401	UCL	PEG-interferon-alpha
Pharmacogenetics Butyrylcholinesterase deficiency	BCHE		565471-565482	Gent	none
Pharmacogenetics Thiopurine S-Methyltransferase deficiency	TPMT		565390-565401	ULB, KUL, Liège, IPG, UCL	azathioprine, mercaptopurine, thioguanine, cisplatin (pediatric)
Pharmacogenetics Thiopurine S-Methyltransferase deficiency	TPMT + NUDT15		565456-565460	UCL	azathioprine, mercaptopurine, thioguanine
Gilbert/Irinotecan sensitivity/ metabolism**	UGT1A1	homozygous A(TA)7TAA allele	565390-565401	KUL, Liège, UCL, ULB, IPG	Irinotecan, atazanavir
Susceptibility to pancreatitis induced by thiopurine immunosuppressants**	HLA-DQA1 HLA-DRB1		565390-565401	Liège	none
Mitochondrial non-syndromic sensorineural deafness with susceptibility to aminoglycoside **	MT-RNR1	hot spot mutation - 1555A-G	565390-565402	IPG, UZA (VUB)	amikacin, gentamicin, paromomycin, tobramycin
Homocystinuria**	MTHFR	hot spot mutation	565331-565342	Liège, UCL	none

* Pharmacogenetics Coeliac disease HLA-DQ2-HLA-DQ8 and Pharmacogenetics Narcolepsy HLA-DQB1 were mentioned as “pharmacogenetics” on the limitative list, but are actually diagnostic tests (sometimes necessary for the reimbursement of medications). They were thus not included in the current table. ** Indicates that in the limitative list this was not explicitly mentioned as ‘pharmacogenetics’ although this is used by some of the CHGs. \$ Offered in CHG as seen on the Belgian Genetic Tests database; £ Manual check for which gene-drug pairs there are recommendations available according to CPIC, DWPG, RNPgX, or CPND. Note that the level of evidence may vary substantially by test/medication/indication triplet and therefore should not be used as a KCE recommendation for testing at drug prescription.



2.2.3 Volume analysis

The largest volume of PGx tests is performed in the eight CHGs. A special case are the HLA targets. The expertise for these targets lies historically in the HLA labs (which are not CHGs). In practice, a lot of the CHGs are transferring the HLA genotyping to a collaborating HLA lab (often in the same hospital).

The volume is on test level, not patients. Some patients need more than one test: a targeted test to check for the most known variants and if further analysis needed, a test to detect a more rare variant (sequencing). Testing for DPYD is such an example (specific reimbursement for targeted testing and sequencing exons).

2.2.3.1 Volume of PGx tests in the eight centers of human genetics and in the HLA labs

Figure 3 shows the PGx volume in the eight CHGs and the HLA labs. The eight CHGs and HLA-labs performed a total of **7736 PGx tests in 2021 and 8499 in 2022**. While the majority of tests is reimbursed volume, there are some non-reimbursed (e.g. carbamazepine).

Not all PGx tests offered (as shown in Table 2) have reported volumes. Every CHGs performs PGx, though for some centres the volume is very limited (only 1 target and at low volume).

In the CHGs, the most common PGx involves the **DPYD** gene, with approximately 4000 tests performed annually across five of the eight CHGs. This gene-target is relevant for oncology, most specifically for drugs used in the treatment of digestive oncology (**5-fluorouracil, capecitabine, tegafur**). The test is performed before or close to the start of a prescription. The fact that DPYD is the most prescribed test is coherent with the prevailing recommendations.⁵⁶ In 2020 an EMA recommendation stated that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil or related drugs, capecitabine and tegafur.⁵⁷ In addition, the Belgian Federal Agency for Medicines and Health Products (FAMHP) recommended testing

already in 2019, based on recommendations from the French Medicines Agency.^{58, 59}

The second most performed test is **TPMT** which is relevant for patients with a prescription for the immunosuppressants **azathioprine, mercaptopurine, tioguanine**. This group of thiopurines, with azathioprine as most prevalent, are used in auto-immune diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and in organ transplantation, though not as a first line or frequent agent. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO) recommended in 2014, to test prior to treatment (when available), but stated that cytopenia can still occur despite normal TPMT activity.⁶⁰ The American College of Gastroenterology states that a TPMT test before start of thiopurines should be considered (strong recommendation, low level of evidence).⁶¹ Also the NICE guideline on Crohn's disease recommends to test TPMT activity.⁶² A recent consensus guideline on solid organ transplantation states that despite limited data, routine screening for TPMT is recommended.⁶³ However, **guidelines do not specify whether it should be genotyping or phenotyping**. The survey also showed that most requests come from gastroenterologists (+/-70%) followed by internal medicine and rheumatology, and always before a prescription is issued. One CHG indicated that TPMT genotyping is always combined with the target **NUDT15**.

Another target in oncology is **UGT1A1 for irinotecan**, indicated for colorectal carcinoma. However, the reported numbers (137 in 2021 and 207 in 2022) could be an overestimation as genotyping UGT1A1 is also used for confirming the diagnosis of Gilbert syndrome (when unexpected unconjugated hyperbilirubinemia is noted). The CHGs cannot clearly differentiate in their data whether the test was done for PGx purpose or whether it was done for diagnostic purpose. The survey indicated that this test is often requested during a treatment. The most recent 2022 ESMO guidelines for colorectal cancer do not recommend testing UGT1A1 before prescribing irinotecan.⁵⁶



Testing for variants of the CYP metabolizing enzymes was limited to one CHG to which other centres refer. Figure 4 shows the volumes per gene-target for the CYP enzyme. Testing for **CYP3A4** and **CYP3A5** was most often performed, and these are linked to the prescription of the immunosuppressant **tacrolimus** in view of organ transplantation.⁶⁴ The survey indicated that most often transplant surgeons and nephrologists requested the test before a prescription. Testing for **CYP2C9** has doubled when comparing 2021 to 2022. This is due to the introduction of **siponimod** (Mayzent®) for multiple sclerosis, which specifies in the drug label the requirement to genotype CYP2C9 before starting the treatment: *in patients homozygote CYP2C9 *3*3 siponimod may not be used*. The survey indicated that the requests for CYP2C9 were done by neurologists and before the prescription. Genotyping CYP2D6 and CYP2C19 was mostly requested by psychiatrists in case of abnormal response to antidepressant or antipsychotic treatment. CYP2D6 might also be requested in view of pain therapy, and CYP2C19 by cardiologists in case of non-response to clopidogrel. These last indications consider testing during the treatment, to explain non-effectiveness or side-effects.

Testing variants for the transport protein ABCB1 has been mentioned for tacrolimus dosing in transplant patients, but the survey showed it is limited to one centre.⁶⁴

The **MTRNR1** variants in view of avoiding ototoxicity when administering the **aminoglycosides antibiotics** is offered in three CHGs in a panel test for auditive failure. There are no specific volumes for this target as the CHGs could not distinguish whether the panel was run for the administration of aminoglycosides or to identify possible reasons for auditive failure.

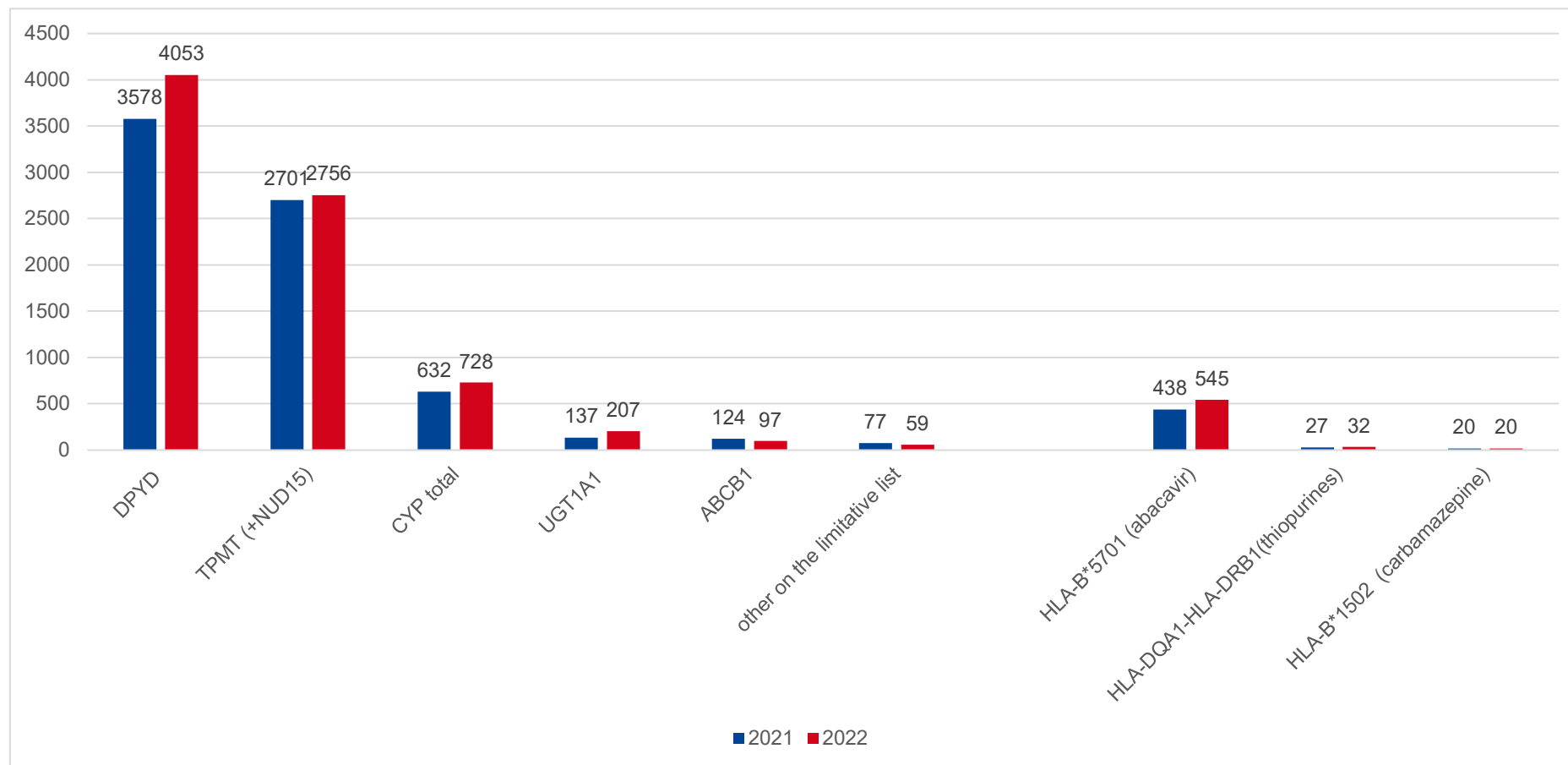
In Figure 3 the group of 'other targets on the limitative list' includes the **MTHFR** for **methotrexate toxicity** (58 in 2021 and 46 in 2022), the transport protein **SLCO1B1** for **muscle toxicity in statins** (only 4 tests per year), **VKORC1** for toxicity or resistance for **vitamin K antagonists** such as warfarin, acenocoumarin (in total 13 test in 2021 and 6 in 2022), and butyrylcholinesterase deficiency which induces prolonged apnea after certain **anesthetic drugs** (2 tests in 2021 and 4 in 2022). For most of these targets the request to test is done after the treatment has been initiated.

There are some targets mentioned on the limitative list for which **no volumes** were reported in 2021 and 2022: PON1 for clopidogrel resistance, and IL28B to predict response to chronic hepatitis C, PEG-IFN antiviral therapy which can be understood given the new class of antivirals that have replaced combination treatment based on PEG-IFN. On the other hand, some new targets are proposed by CHGs: NAT2 to explain isoniazide toxicity (2 tests per year).

One of the most established PGx targets is testing for **HLA-B*5701** when prescribing the antiviral drug '**abacavir**' in HIV positive patients. Due to the risk of fatal hypersensitivity reactions, this requirement for testing has been inserted into the drug label. The numbers are quite low because abacavir for HIV patients is not a first-line treatment.⁶⁵ Before the reform of the nomenclature codes on genetic testing this test was performed in HLA labs, and not in CHGs. Since 2013 this indication entered the limitative list and was therefore only reimbursed for CHGs. In practice, only one CHG is performing the HLA*5701 test in-house, and three CHGs are transferring their samples to that centre. The other four CHGs transfer the sample to an HLA lab, often a lab in the same hospital. Most of them still invoice the nomenclature code via the CHGs as they are receiving the requests, interpret the results and disclose the information to the prescriber. In terms of volume, the CHG collaborating with an HLA lab have the highest number of prescriptions, and the CHGs performing it in-house have volumes less than 50 (see Figure 5). There are at least two HLA labs that are performing the tests outside the reimbursement for a total volume of 83 tests in 2021 and 67 in 2022.

Another HLA target is HLA-DQA1-HLA-DRB1 for identifying susceptibility to thiopurine immunosuppressants. This is only performed in one CHG which outsources the testing to their HLA lab (27 tests in 2021 and 32 in 2022). The other HLA labs can perform these tests, but no volume for 2021 or 2022 was reported.

The HLA labs also have other PGx tests that are performed outside the reimbursement, e.g. HLA-B*1502 and carbamazepine toxicity (around 20 per year) and more recently also HLA-B*5801 for allopurinol (as this is recent, no volumes are available yet).

**Figure 3 – Number of tests per gene target and per year (for 2021 and 2022) in the centres for human genetics and the HLA labs**

Source: survey and contact labs. The volume shown is the total volume of tests (reimbursed + non reimbursed), not patients. The targets DPYD, TPMT (+NUDT15), CYP enzymes, UGT1A1, ABCB1, and the "other", are all gene-targets on the limitative list for which there is reimbursement foreseen when performed in a Centre for Human Genetics. HLA-B 5701 for abacavir is also on the limitative list, but is in reality performed in CHG as well as HLA labs, and for the latter there is no reimbursement foreseen. HLA-B*1502 for carbamazepine is only performed in HLA labs and is not on the limitative list (no reimbursement). NAT2 variants for isoniazide toxicity is performed in CHG but is not on the limitative list (no reimbursement). Note that during 2021 medical activities still suffered from the covid pandemic impact.

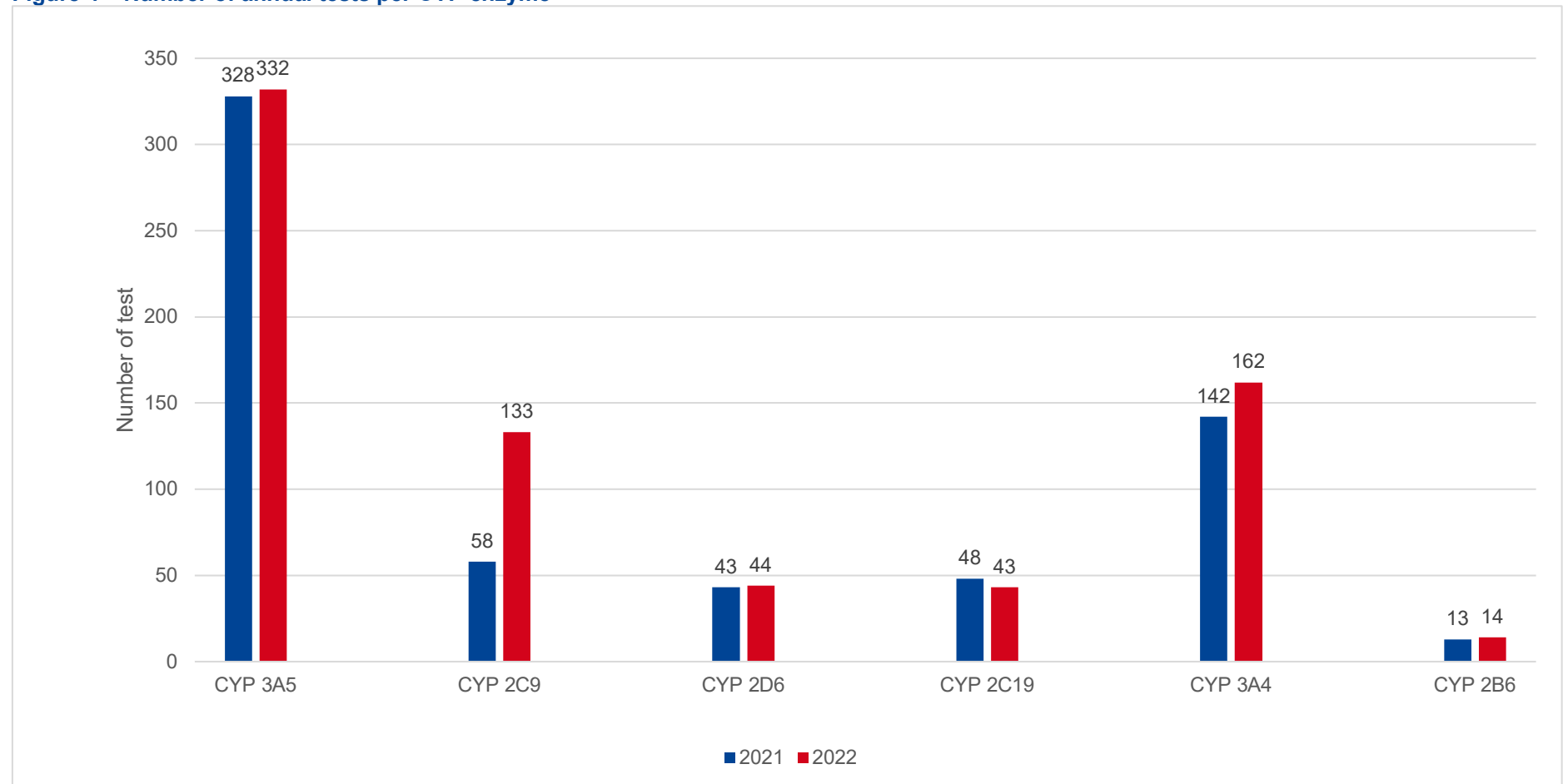
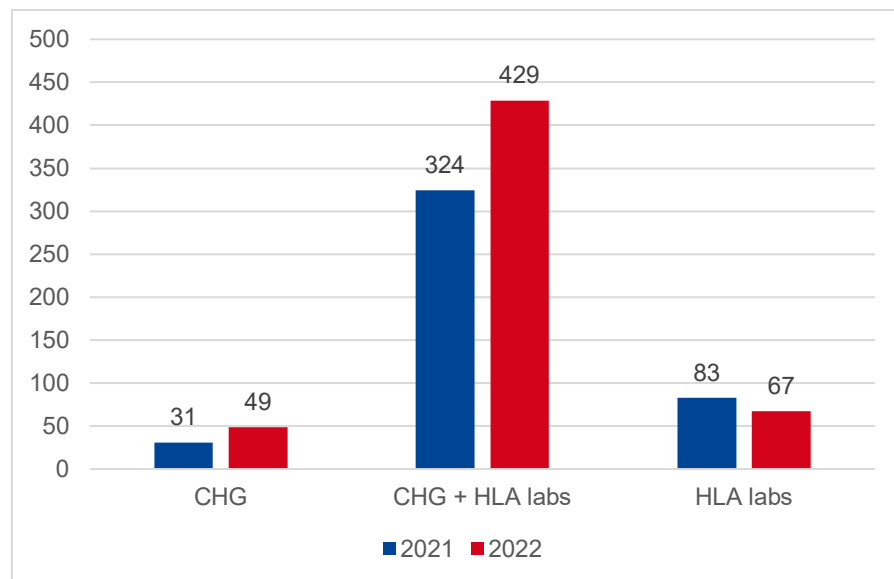
**Figure 4 – Number of annual tests per CYP enzyme**



Figure 5 – PGx testing for HLA*5701 for abacavir, according to where the testing took place



CHG: this means that the request + the analysis has been performed in a Centre for Human Genetics (reimbursed). CHG + HLA labs: the request comes in via the CHG and gets transferred to an HLA lab to perform the analysis (reimbursed). HLA labs: the request is directly targeted towards an HLA lab and performed (no reimbursement).

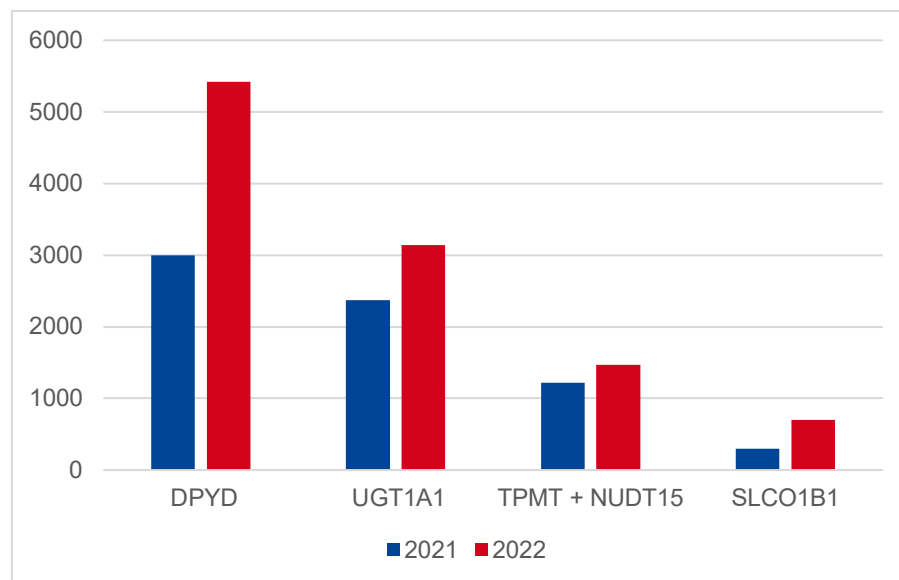
2.2.3.2 PGx volume in non-CHG labs

Some molecular diagnostics labs reported to have PGx targets (DPYD, UGT1A1, TPMT, SLCO1B1) in their oncology (somatic) panels. Somatic gene panels are reimbursed when used for the diagnosis, prognosis or therapy in (hemato-)oncology and performed on tumour tissue or biopsy, through a convention with the health insurance (RIZIV-INAMI) (NGS pilot project). This convention specifies indications and the minimal composition of these panels. DPYD, UGT1A1, TPMT, SLCO1B1 are not required on these panels. There is disagreement among experts on whether PGx germline variants can be reliably detected in cells derived from tumour tissue (see chapter methods 3.3.2). There are different approaches among the labs on how to report variants relevant for PGx. Some report with the disclaimer it is performed on tumour tissue, some do not even report the info on PGx variants included in the oncological panels, while others report the detected mutations and recommend specifically performing the germline testing on blood/saliva if they detect anything aberrant.

Interpreting the volume in labs outside of CHG is challenging. On the one hand there is the risk of underestimation because we did not receive answers from all contacted centres, and PGx testing might be performed outside the contacted NGS-centres. On the other hand, the experts stated that the vast majority of the somatic panel tests which include PGx targets are requested in the context of the NGS-convention and not really requested for the specific PGx target indicating the info on the PGx targets is “nice-to-know”. Consequently, the volume on PGx in these non-CHG labs could be an overestimation. Figure 6 shows the targets and the associated volumes in molecular diagnostic labs that are not CHGs.



Figure 6 – Volume of panel tests which include PGx targets performed on tumour tissue



Source: Based on survey and contact labs. Volume of five non-CHG labs that have the PGx targets in their somatic test panels. Some gene targets are in the haematological panel, while other are in the solid tumour panel.

2.2.4 Current RIZIV expenditure

The reimbursement of PGx is limited to the targets on the limitative list and limited to the CHG setting. Based on the reported volumes, the annual budget for PGx testing was calculated to be €1 359 260 in 2021 and €1 452 399 in 2022 (see Table 4). This budget includes the share of the RIZIV-INAMI and the patient share. As shown in Table 3 most tests are budgeted at around €166 (in 2022) per single gene test (nomenclature code 565390-565401). When more areas need to be checked or when complexity increases, a fee of €383 (in 2022) per test is foreseen (nomenclature code 565456-565460). For some targets such as BCE the fee is even higher – though the survey learned us that this PGx test was rarely performed, with two tests in 2021 and four in 2022. When a PGx target is part of a large panel, up to €1477 (in 2022) can be charged. The survey did not indicate that such complex test was charged for PGx.

Regardless the type of test performed, the patient share is fixed at €8.68 per test, except for hospitalized patients and patients having a preferential status for whom the patient share is €0 and the RIZIV-INAMI pays the total honorarium.

No “genetic counselling consultation” is usually invoiced to explain the results of the tests. The communication of the results is done during a “normal” consultation with the specialist/prescriber.

In general, the total expenditure of genetic testing in article 33 is more than €80 million in 2021 (sum of the 76 nomenclature codes in 2021) and rose to more than €108 million in 2023¹. The total volume for the two most PGx relevant nomenclature codes (565390-565401 and 565456- 565460) was 32 029 in 2021 (numbers in 2022 not available yet). When the volume of PGx (obtained via the survey) is put against the nomenclature volume (obtained via the national database), there is around 23% of those nomenclature codes that are used for PGx.

¹ Personal communication RIZIV-INAMI


Table 3 – Nomenclature codes from Article 33 that can be used for pharmacogenetic testing (as mentioned in the limitative list)

Description	Code	Reimbursement fee		PGx indication in the limitative list linked to the nomenclature code
		In 2022	In 2024	
Simple molecular analysis to search for a constitutional disease, including DNA extraction, maximum three mutations per gene analysed (Diagnostic rule 10, 11, 18)*	565331-565342	€83.14	€92.59	Homocystinuria (hot spot mutation)
Molecular analysis to search for a constitutional disease or to establish an individual genetic profile, for genetic counselling and/or diagnostic purposes, including DNA extraction (diagnostic 10, 11, 18)	565390-565401	€166.29	€185.18	DPYD (4 variants), TPTM, UGT1A1, most metabolizing CYP enzymes, transport protein ABCB1, transport protein SLCO1B1, HLA-B 5701 (abacavir), HLADQA1 and HLA DRB1 (thiopurines), VKORC1, PON1, MT-RNR1 (hot spot mutation)
Complex molecular analysis to search for a constitutional disease (diagnostic rule 6, 10, 18)	Level 1 565456-565460	€382.90	€426.41	TMPT + NUDT 15, DPYD (exons), CYP2D6
	Level 2 565471-565482	€598.41	€666.41	Butyrylcholinesterase deficiency
	Level 3 565493-565504	€1476.89	€1644.71	Not indicated for PGx. But there are some available panel tests that have PGx targets included (e.g. full sequencing of mtDNA for MT RNR1)

* This nomenclature code has only one indication in the whole limitative list. Diagnostic rule 6: the code can be billed only once per diagnostic phase of a constitutional disease per tissue type (max three different tissues); Diagnostic rule 10: the indication of the test is included in the limitative list; Diagnostic rule 11: the code can be billed maximum two times per diagnostic investigation phase; Diagnostic rule 18: in case new clinical elements or new technological possibilities arise, the analysis might be repeated when motivated and in consultation with the medical geneticist.



Table 4 – Expenditure* per PGx target in 2021 and 2022

PGx target / indication	Nomenclature	Invoiced volume tests		Budget 2021 (€)	Budget 2022 (€)
		2021	2022		
DPYD (4 variants)	565390- 565401	3545	3565	573 758	592 824
DPYD (exons)	565456- 565460	29	37	10 807	14 167
TPMT	565390-565401	2061	2118	333 573	352 202
TPMT + NUDT15	565456-565460	637	636	237 391	243 524
HLA-B 5701	565390-565401	256	355	41 434	59 033
UGT1A1	565390-565401	120	153	22 173	34 422
CYP 3A5	565390-565401	328	332	53 087	55 208
CYP 2C9	565390-565401	58	133	9387	22 117
CYP 2C19	565390-565401	48	43	7769	7150
CYP 3A4	565390-565401	142	162	22 983	26 939
CYP 2B4	565390-565401	13	14	2104	2328
CYP 2D6	565456-565460	43	44	16 025	16 848
ABCB1	565390-565401	124	97	20 069	16 130
VKORC1	565390-565401	8	6	1295	998
BCHE	565471-565482	2	4	1165	2514
MTHFR (hot spot)**	565331-565342	7	1	1222	175
HLA-DQA1-HLA-DRB1 (thiopurine)	565390-565401	27	32	4370	5321
Total		7510	8233	1 359 260	1 452 399

* Pertains to the honorarium obtained by the lab (includes the share of the RIZIV-INAMI and the patient share). ** One CHG did perform this test but did not invoice it.



2.2.5 Uptake of PGx in Belgium

The numbers computed here offer a general approximation of the PGx uptake. Foremost, the data on testing volume is on test level (not patient level) and the data on drug users is on patient level. Moreover, we focused on incident users.

Table 5 shows the uptake for several medications for which we know PGx is implemented and for which there was no ambiguity with regard to linking the test to the medication (for example for CYP enzyme tests there is a very large group of drugs that potentially qualifies for a PGx test, and therefore not included). As the COVID pandemic impacted health care provision, the numbers of 2020 and 2021 are not always representative. Therefore the numbers of 2019 were also shown.

For fluoropyrimidines, in 2021 there were around 8126 incident users (6466 fluorouracil, 1650 capecitabin, 10 tegafur), and 3549 DPYD targeted genotyping tests were conducted. This results to a PGx implementation of 44% in 2021 knowing the EMA and FAGG-AFMPS recommendations are recent, issued in respectively 2020 and 2019.^{57, 58} The Belgian guidelines put forward the option to phenotype,⁶⁶ and the survey indicated that there were 2797 phenotype tests performed in 2022. If we simply add the phenotyping tests to the genotyping, 6346 tests were performed ($\approx 78\%$). However, simply adding the numbers is not correct as they are not from the same year, and for some patients both genotyping and phenotyping is performed. Moreover, we know clinical biology laboratories have included

DPYD targeted tests in the somatic panels, though, quantification is difficult as these panels are not specifically prescribed for PGx.

For thiopurines, in 2021, there were 1117 incident users (174 mercaptopurine, 62 thioguanine, 881 azathioprine), but surprisingly the number of tests was larger, i.e. 2678. Possible explanations are that also patients already on the drug (prevalent users) get the testing to either explain myelosuppression, or because a test was not possible in the COVID pandemic year. The number of incident users is higher in 2019 (1600). However a main reason why the number of tests is higher is because requesting the PGx test is part of a standard care pathway regardless of the actual prescription of the drug, to keep therapy options open, and because there is a large turn-around-time (several weeks). It is also possible that because of the test result, patients did not receive the medication. However, only 10% of Caucasians carry a genetic variant in the TPMT gene.⁶⁷

For abacavir, a similar result was noted, with 89 incident users in 2021 (125 in 2019), the number of reimbursed HLA-B*5701 tests was reported to be 355. For abacavir the recommendation to test is not that recent compared to the one for DPYD. An explanation is that ordering the PGx test is part of a standard care pathway, regardless of the actual prescription of the drug.

Another possible explanation for the higher number of tests compared to incident users, is that tests might be repeated as the PGx test result is not readily available in the EHR.

Table 5 – Examples of PGx uptake

Medication (ATC)	Incident users in 2019	Incident users in 2020	Incident user in 2021	Number of reimbursed PGx tests in 2021
Abacavir (J05AF06, J05AR02, J05AR04, J05AR13)	125	142	89	HLA-B*5701 → 355
Fluoropyrimidines (L01BC02, L01BC03, L01BC06, L01BC52, L01BC53)	8 542	7 701	8 126	DPYD 4 variants → 3549 DPYD exon sequencing* → 29
Thiopurines (L01BB02, L01BB03, L04AX01)	1 600	1 190	1 117	TPMT (+ NUDT15) → 2701
Irinotecan (L01CE02)	2 286	2 283	2 429	UGT1A1 → 137

* DPYD Exon sequencing is done in a second line, when the targeted test for the 4 variants does not explain the poor results. Source: IMA-AIM data (KCE calculation).



Comprehensive volume data together with details on the indication to test are key for a solid interpretation of PGx implementation. France is the only country where the national volumes of PGx are systematically collected and publicly disclosed (see chapter 7.3 and appendix 5.3). If we roughly calculate the number of PGx tests performed per million inhabitants, more PGx tests are performed in Belgium compared to France (In France in 2022, 24 245 tests on a population of 67.93 million $\approx$ 357 tests per million, and in Belgium 8499 tests on a 11.58 million population $\approx$ 733.9 tests per million inhabitants). When not taking DPYD testing into account as there is a clear HAS recommendation to perform phenotyping,⁶⁸ still proportionally more PGx tests are performed in Belgium: for France excl. DPYD in 2021 = 279 tests/million inhabitants, in Belgium excl. DPYD in 2021 = 361 tests/million inhabitants)

Key points on the Belgian volume of PGx tests

- In Belgium, only the 8 certified Centres for Human Genetics are entitled to reimbursement for around 20 PGx indications, mentioned on a limitative list.
 - The limitative list does not consistently include the names of the specific drugs. It is thus not possible to accurately state for which drugs the tests are performed.
 - The process of selecting PGx targets for inclusion in the limitative list is not clear. For example, HLA for carbamazepine is not included, while other targets have no clinical recommendations (PON1) or became obsolete (IL28B).
 - There are discrepancies in the indications (some HLA targets are diagnostic, mix between diagnostic and PGx indication) which hampers capturing the exact volume.
- All eight CHGs offer PGx, although for some the scope is restricted to only one target. One CHG offers the broadest range of PGx.

- Overall around 7736 in 2021 and 8499 in 2022 PGx tests were reported by the 8 CHG and 7 HLA laboratories. For these centres the testing is done on a specific request, when a specific drug is/will be prescribed (reactive testing).
 - More than half of the PGx tests is for oncological indications with DPYD testing being the most frequently performed test.
 - Around 2700 tests to detect variants of TPMT for immunosuppressive drugs (e.g. azathioprine, mercaptopurine) in the field of auto-immune diseases and organ transplantation were performed.
 - Testing for HLA-targets (such as abacavir, carbamazepine) is most often performed in HLA laboratories.
 - The volume of non-reimbursed PGx in CHGs and HLA labs seems small: NAT2 for isoniazide toxicity and HLA-1502 for carbamazepine toxicity are performed without reimbursement as these targets are not included on the limitative list. The volume for abacavir HLA-5701 is split in a reimbursed and non-reimbursed part. The non reimbursed part is situated in HLA labs that are not affiliated to a CHG.
 - Most of the time the CHGs have an agreement with the HLA lab (when located in the same hospital) in order to have the test reimbursed.
 - However, around 100 HLA tests for abacavir and carbamazepine are performed without specific reimbursement.
- In other centres (not CHGs or HLA), PGx targets for oncology are included in panels for solid tumours or haematological cancers.
 - These tests are performed on tumour samples.
 - It is difficult to interpret the volumes as these tests were not specifically prescribed for the specific prescription of a drug, but rather seen as “nice-to know”



- Based on the reported volumes, the annual reimbursed expenses for PGx testing was calculated to be €1 359 260 in 2021 and €1 452 399 in 2022.
 - Most tests cost around €166 (in 2022) per single gene test. When more areas need to be checked or when complexity increases, a fee of €383 (in 2022) per test is foreseen.
- For some patients a combination of tests is needed: a targeted test to detect known variants + sequencing to identify rare variants (sometimes in combination with a phenotyping test): DPYD.

3 TECHNOLOGIES FOR PHARMACOGENETIC TESTS

This chapter was developed by clinical experts prof. dr. Kathleen Claes, prof. dr. Vincent Haufroid, prof. dr. Freya Vaeyens and prof. dr. Sonia Van Dooren

3.1 Methodology

The techniques covered in this chapter were selected based on the current information in the Belgian Genetic Tests Database, and on the expertise of the clinical experts in medical genetics, performing PGx tests on a daily basis (cited above). The focus is on the clinical setting and detection of clinically relevant actionable germline variants. However, some technologies are able to discover new variants and are situated in both the clinical and research setting.

3.2 Testing techniques

Accurate clinical PGx profiling remains a challenge as it ideally requires accurate single nucleotide variations (SNV) calling and haplotyping, copy number variation (CNV) detection, short tandem repeats (STR, i.e. regions where a certain number of nucleotides are repeated a variable number of times) and structural variant assessment (e.g. CYP2D6) of a growing number of genes. Table 6 gives an example of pharmacogenes and their challenges, which render them difficult to genotype.

An up-to-date overview of relevant pharmacogenes and their variants can be found on the websites of PharmGKB^m or the Clinical Pharmacogenetics Implementation Consortium (CPIC)ⁿ. Some of these variants are described as “star*-alleles”; a list of these alleles can be found on the Pharmacogene Variation Consortium website^o.

^m <https://www.pharmgkb.org>

ⁿ <https://cpicpgx.org/guidelines/>

^o <https://www.pharmvar.org/>



Techniques are either focused on specific regions in the DNA/RNA (targeted testing), or analyse the entire genome.

Table 6 – Example of Pharmacogenes with technological challenges

Gene	Challenges
CYP2D6	1. Structural variants and gene rearrangements 2. Pseudogenes 3. Copy number variations 4. Presence of novel variants 5. Highly polymorphic region 6. Substrate-specific effects of some alleles
UGT1A1	1. Rare population-specific variants 2. Variants in non-coding parts of the gene 3. Independent haplotypes with less linkage disequilibrium
HLA	1. Rare population-specific variants 2. Highly polymorphic regions
VKORC1	1. Important variants in non-coding parts of the gene

Based on the table by Tafazoli et al.⁶⁹

3.2.1 PCR based techniques

If only a single or a few SNVs or local genome variations are the focus of analysis, PCR, and modifications thereof, are used, as DNA amplification can be restricted to the regions of the genome that include the variant(s) of interest by the use of sequence-specific primer sets. Subsequent selection of a molecular platform for testing the PGx variants is based on:

1. technical feasibility for analysing the regions of interest – for adequate primer design possible interference of pseudogenes has to be considered and primer design in highly polymorphic regions or for the detection of large structural rearrangements can be challenging; and
2. practical considerations such as instrument availability, cost, laboratory workflows available, test volume, and desired test turn-around-time.

A wide range of molecular biology techniques are available for genotyping. In the following paragraphs, some PCR-based methods applied in Belgium and used for genotype determination in the context of PGx are presented.

Quantitative Fluorescence-Polymerase Chain Reaction (QF-PCR)

Quantitative Fluorescence-Polymerase Chain Reaction (QF-PCR) is a technique used for **detection of loss of heterozygosity (LOH), aneuploidy and large chromosomal deletions** using microsatellites or **SNVs**. QF-PCR consists of a multiplex PCR followed by capillary electrophoresis. Selection of appropriate PCR primers enables amplification and detection of specific normal or mutant DNA sequences. The amplified sequences (amplicons) are separated by capillary electrophoresis using a genetic analyser (e.g. Applied Biosystems). Analysis software is used to identify and label the amplicons according to their size and fluorochrome colour (e.g. GeneMapper™ or GeneMarker® software). This technique can for example be applied for the detection of 6 different SNVs in DPYD (e.g. Elucigene Diagnostics (Yourgene health)).

Genotyping by sequence-specific oligonucleotides probes (PCR-SSOP)

The procedure relies on the locus-specific amplification of the genomic DNA segment comprising the polymorphic sites to be investigated. Amplified DNA is then immobilized on a solid support, usually a nylon membrane, and then hybridized with a battery of **sequence-specific oligonucleotide probes (SSOP)** (direct hybridization). Fluorochromes are linked with the probes to allow their detection by chemiluminescence.

Alternatively, SSO probes can be immobilized on a solid support, for example color-coded microspheres (e.g. Luminex® technology), and hybridized with labeled PCR product (reverse hybridization).

The higher the number of probes the better the resolution level. Usually 50-100 probes per locus are used for intermediate/high resolution typing, however, only the probe completely matched with the target sequence amplified will hybridize and give a positive signal.⁷⁰ This approach has been widely applied for HLA genotyping.



Real-time PCR genotyping assay (RT-PCR)

Real-time PCR genotyping assays involve PCR primers to amplify specific DNA fragments and probes to detect specific SNVs. One end of the probe has a fluorescent label, and the other end has a quencher. The probe binds to the target sequence of the template DNA. During amplification hydrolysis of the probe takes place by the polymerase when it reaches the location of the probe. This leads to release of the fluorescent group and emission of a fluorescent signal as this group is no longer near the quenching group. The emitted signal is proportionate to the amount in the PCR product. **Both SNVs and indels** can be determined. It has also been applied for the detection of **CNVs** in *CYP2D6*.⁷¹ Thermofisher® has predesigned Taqman assays available for a large number of PGx targets.

High Resolution Melting curve analysis (HRMCA)

High Resolution Melting curve analysis (HRMCA) is a Real time (RT)-PCR-based technique for the detection of SNVs and epigenetic differences through analysis of RT-PCR melting curves. PCR primers are used to amplify specific DNA fragments. The HRMCA consists in a precise warming of the amplicon from around 50 °C up to around 95 °C. At some point during this process, the melting temperature of the amplicon is reached and the two strands of DNA dissociate. **The melting temperature of the amplicon at which the two DNA strands dissociate is predictable and is dependent on the sequence of the DNA.** The separation of strands is monitored by using a fluorescent intercalating dye (e.g. SYBR Green from Roche) in a RT-PCR device that has the ability to monitor the process in “high resolution”. For example, this technique can be applied for the detection of SNVs in *UGT1A1* and is used to identify the genotypes *1/*1, *1/*28 or *28/*28.⁷²

Loop-mediated isothermal amplification (LAMP)

The LAMP method was first described in 2000.⁷³ It enables rapid reaction times from the exponential accumulation of amplicons. Subsequently, there is a big diversity of methods to detect LAMP amplicons, of which high resolution melting curve analysis (HRMCA) on real-time qPCR instruments is popular. For instance, CE-IVD kits for genotyping SNVs in *TPMT*, *DPYD*, *CYP2C9* and *CYP2C19* using the LAMP technology in combination with HRMCA were commercialized via the Belgian company LaCAR (website consulted 1/09/2023). The technology has also been applied to determine *CYP2D6* copy numbers by combining a DNA chip and LAMP.⁷⁴

3.2.2 Sequencing

PCR amplification followed by **Sanger sequencing** remains a widely used and trusted method in molecular biology and genetics, especially for targeted analysis of specific regions of interest. It is still considered as the “gold standard” for detection of homozygous or heterozygous variants. It is highly specific and very flexible. Therefore, novel targets can be quickly implemented. However, one of the major drawbacks of PCR-Sanger sequencing is its limited throughput, inability to detect structural variants and limited read lengths.

It is expected that the field of PGx is moving from reactive testing of a single gene towards preemptive genotyping by scanning a broad panel of genes. **Next-generation sequencing (NGS) platforms** allow such broad testing, by sequencing either specifically targeted regions or the entire exome or genome (see 3.3.3).⁷⁵

It is important to note that some non-coding parts and complex structural variants including CNVs are relevant in several pharmacogenes (*CYP2D6* and *HLA* locus) and accurate detection is challenging and **requires computational resources (bio-informatics) for adequate data interpretation.**



Short read sequencing (often referred to as second generation sequencing) allows reliable detection of SNVs and several algorithms have become available allowing detection of CNVs based on sequencing reads. While the approach is less suitable for the identification of all significant PGx variants in complex genes (the CYP2D6 superfamily and HLA), these limitations can be overcome by complementing short read DNA sequencing with RNA sequencing of the complete transcriptome or of a targeted PGx gene panel (e.g. TruSeq targeted RNA expression P450) or bioinformatics.

Short read sequencing instruments are mainly offered by Illumina® (San Diego, USA) with current NextSeq (for exome) and NovaSeq (for exome and whole genome) instrument series in combination with, targeted PGx gene panel, whole exome or whole genome NGS library kits offered by a large variety of companies. Other platforms (Aviti, MGI, ...) are emerging.

Long read sequencing (often referred to as third generation sequencing) offers a new opportunity to better characterize clinically relevant PGx variants and haplotypes. The longer reads allow sequencing through repeat regions, a better mapping of pseudogene regions and accurate structural variant detection. Furthermore, it allows phasing of alleles in order to resolve haplotypes of complex pharmacogenes.

Currently there are two providers of long read sequencing: Oxford Nanopore Technologies® and Pacific Biosciences® (PacBio). Specifically PacBio sequencing currently allows the combination of long read sequencing while maintaining a very high sequencing quality and variant calling accuracy,^{76, 77} but the field is constantly evolving.

Long read sequencing technologies remain **expensive and the assembly challenging** to currently allow implementation in a clinical routine. Therefore some laboratories have focused on enrichment based methodologies. Oxford nanopore developed **adaptive sampling** and other techniques in order to enrich specific regions of the genome.⁷⁸ This methodology could be used for PGx sequencing, however, regions with a low sequencing coverage might suffer from poor SNV calling as nanopore sequencing remains relatively error prone. In this regard targeted PacBio sequencing using long fragment capturing with probes (panel based approach) costs a fraction of

the price and has a shorter turnaround time compared to WGS, making it more accessible for PGx testing in routine diagnostics.^{77, 79}

An important aspect of all NGS sequencing is the possibility to find **new variants of unknown significance**. However, it can be difficult to match new variants and completely resolved haplotypes with existing star*-alleles. This matching will require **more research** and adjustment of existing star*-allele callers.^{22, 80}

3.2.3 Microarray

The microarray technology enables the simultaneous analysis of thousands to millions of SNVs in a single experiment. This technique by itself is mainly capable of detecting SNV's and no structural variants like CNVs, inversions, deletions and insertions. The arrays contain a preselected set of SNVs, which, depending on the array and platform, can range from a few variants in a single gene to thousands of variants genome wide.

A microarray is a small solid support (a glass slide or a silicon/bead chip), coated with thousands to millions known DNA probes, which are strategically arranged in a grid-like pattern. Labelled individual's DNA will specifically bind to the complementary probe sequences immobilized on the array. Following hybridization, array processing involves washing non-specific binding DNA and scanning the microarray plate to detect the fluorescence or chemiluminescence signals emitted by the labelled DNA bound to the probes. The acquired images are processed using specific software tools and algorithms.⁸¹

The targeted sequences may represent PGx variants, which can be included in custom-designed arrays or commercially available genotyping arrays.^{75, 82} There are many arrays available, some of them are small (VeraCode ADME core panel (Illumina), VeriDose core panel (Agena BioScience), OpenArray (ThermoFisher scientific)); others may consist of more extensive panels (Pharmacoscan and Pharmacofocus (ThermoFisher Scientific)). Note that the inclusion of several PGx variants in a commercial panel is not necessarily based on evidence of the clinical utility of these variants.



Besides the above-mentioned arrays developed specifically for PGx, multiple **arrays with genome-wide coverage** are also available and allow for genome-wide association analysis (GWAS) in addition to providing PGx information (Illumina GSA (Global Screening Array), Illumina GDA (Global Diversity Array) with Enhanced PGx and Axiom arrays (ThermoFisher scientific)). These genome-wide arrays are intended for **research purposes** and require computational resources for adequate data interpretation.

Some points of attention need to be made when using the microarray approach for PGx testing.

- Interpretation of variants leading to star*-haplotypes of unknown function may be challenging with microarray technology.
- Only variants included in the array can be detected; therefore, rare and novel variant detection may not be possible.^{75, 83} Moreover, as each array contains its own set of detected variants, assigned haplotypes can differ when the same sample is tested in different laboratories.⁸⁴
- Not all arrays contain probes that can accurately detect **CNVs**, which are important in a sizeable proportion of clinically important pharmacovariants.^{85, 86} Several software tools (e.g. PennCNV,⁸⁷ QuantiSNP⁸⁸...) are available to extract CNV data from microarrays, but full validation of these tools for PGx is needed.
- **Highly polymorphic genes** like CYP2D6, HLA-A, HLA-B, CYP2B6, and TPMT can make it difficult to obtain reliable data.⁸⁵ Some arrays offer adjusted workflows that incorporate targeted gene amplification to address this issue (Illumina GDA (Global Diversity Array) with Enhanced PGx).

3.3 Testing approaches

3.3.1 Single gene testing

Single-gene tests imply a practice model in which genes are contemplated one at a time, if new medication is considered for the patient. For some medications it is opportune to test two or three genes (e.g. thiopurine medications and the genes TPMT and NUDT15).

The techniques used to interrogate a single or two/three genes can vary, from interrogating only a handful of variants in that gene by PCR-based techniques to complete gene sequencing.

For some medications, harm may come to the patient because of either drug toxicity or a lack of efficacy while the test result is still pending, and the patient could be receiving inappropriate therapy. Therefore, the turn-around-time should be as short as possible as it may be difficult to revise the prescription in a timely fashion if the test results require a change in pharmacotherapy, especially in ambulatory settings. **Point-of-care testing (POCT)** is performed at or near the patient. In some acute care settings, it may be important to physically perform the test using an instrument that is in the clinic or inpatient unit to guarantee a quick turn-around-time. For such tests there is a clear need to develop equipment with completely disposable devices to avoid maintenance.⁸⁹ Recently, a prospective implementation trial in UK evaluated a POCT genotyping platform in neonatal setting to predict aminoglycoside-induced ototoxicity (Genedrive®).¹⁹ This is a rapid thermocycling instrument programmed to perform loop-mediated isothermal amplification followed by fluorescent hybridization probe-based melting analysis to enable allelic discrimination. The assay was designed to genotype the mitochondrial SNV m.1555A>G from a buccal swab to differentiate wild-type and variant alleles by melting peak analysis. There are a few other examples of POCT, such as anticipating the need for clopidogrel antiplatelet therapy after percutaneous coronary intervention, when the availability of quick turn-around-times in or near the coronary procedure room could facilitate prescribing decisions needed the same day as the procedure.^{90, 91}



POCT has also been employed for warfarin (analyzing variants in CYP2C9 and VKORC1), when the decision to prescribe and dose the medication is urgent,⁹² for HLA-B*57:01 with abacavir,⁹³ and for TPMT with thiopurines. To our knowledge POCT for PGx has not (yet) been implemented in Belgium.

3.3.2 Gene panel testing = multiple gene testing

Germline gene panel testing

Simultaneous analysis of variants across multiple genes is a potentially cost-effective approach in the field of PGx, where DNA extracted from a single sample (usually blood or saliva) is used to interrogate multiple genes at once (in contrast to a single gene test where there is the possibility that over a patient's lifetime multiple samples are needed).²¹

A first challenge relates to the **standardisation concerning the genes and variants which need to be tested** in a clinical setting. Keeping in mind that the aim of PGx is to personalise treatments through pharmacological advice (choice of the drug and its dosing), the clinical implementation of a PGx gene panel should be guided by **existing actionable therapeutic recommendations**. Therefore, actionable pharmacogenes and variants should be selected when designing a routine PGx gene panel (e.g. RNPGx will update in 2024 its recommendation for PGx panel design at the request of French authorities) and only those should be reported. Such recommendations are found on the PharmGKB website^P (see section 4.1.4). Such information is sometimes referred to as PGx-passport.⁹⁴

A second challenge relates to the **clinical utility** of using a multiple-compared to a single-gene testing approach. While the benefit of PGx testing before starting drug therapy has been documented for several single gene–drug combinations, the clinical utility of a preemptive genotyping strategy using a PGx gene panel has yet to be evaluated.

A third challenge in the use of PGx gene panels will be to regularly **update the composition of the variants included in the panel**, in line with **new actionable** therapeutic recommendations. An example in this case is that normally for DPYD there are 4 variants that are considered actionable. However, recent studies suggest that in Caucasian cohorts some of the investigated DPYD variants (in particular HapB3 variant) may not significantly alter the enzyme activity of DPD, and may be less relevant to check.⁹⁵

Panels can be set up using conventional **PCR-based, NGS** and **array** technologies.

The PREPARE study used a 12-gene PGx panel (*CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1 and VKORC1*) with a PCR-based genotyping solution (SNPline™ workflow) including 50 germline actionable variants.²⁶

A working group within the French-speaking Network of Pharmacogenetics (RNPGx) proposed to use a 41-gene PGx panel (*ABCB1, ABCC2, ABCC4, ABCG2, ACE, ADRB1, ADRB2, BCHE, CDA, COMT, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, DPYD, DRD2, G6PD, HTR2A, ITPA, MTHFR, NAT2, NR1I2, NR1I3, NUDT15, OPRM1, P2RY12, POR, RYR1, SLCO1B1, TPMT, TYMS, UGT1A1, UGT1A4, UGT2B7 and VKORC1*) with NGS technology.⁹⁶

Example of targeted micro-array panels are VeraCode ADME core panel (Illumina), VeriDose core panel (Agena BioScience), OpenArray (ThermoFisher scientific); others may consist of more extensive panels (Pharmacoscan and Pharmacofocus (ThermoFisher Scientific)), but also arrays with genome-wide coverage are used (Illumina Global Diversity Array with Enhanced PGx, and Axiom arrays from ThermoFisher scientific).

As expected, the selected pharmacogenes and their variants overlap in the many existing panels. For example, 10 of the genes included in the 12-gene PREPARE panel are included in the 41-gene PGx panel, validated by RNPGx (bearing in mind that *F5* has not to be considered *stricto sensu* as a

^P <https://www.pharmgkb.org/>



pharmacogene). The vast majority of actionable pharmacogenes according to CPIC and DPWG are found in the 41-gene PGx panel, with only 6 exceptions: *HLA-A* and *HLA-B* (also related to transplantation HLA activities), *MT-RNR1* (mitochondrial gene), *CACNA1S* (related to anaesthetics mainly used in USA), *CFTR* (also related to cystic fibrosis diagnostic), and *IFNL3* (in relation to the medicine PEG-interferon-alfa for which prescription has fallen sharply).

From a technical point of view, the use of “x-gene PGx panels” poses no additional specific problems (e.g. in term of sensitivity/specificity) to those described specifically for each technique. In particular, “x-gene PGx panels” based on NGS technology allows to cover all the variations encountered in PGx (SNVs (including SNVs and indels), CNVs, gene conversion and structural rearrangements) with a very good sensitivity/specificity (similar to the one reach with single gene testing) provided that the **bioinformatics (IT) pipeline** is validated correctly.

Somatic gene panel testing

Gene panel testing on tumor material reveals comprehensive tumor-genomic data, which provides important guidance in diagnostic, therapeutic and prognostic assessments. Since tumor samples are often composed of a heterogeneous mixture of cells, including both cancer cells and normal cells (from the surrounding tissue and tumor stroma), not only somatic or acquired variants specific to cancerous cells will be detected; certain germline variants (not tumor-specific) may also be identified incidentally.⁹⁷⁻⁹⁹ This often raised the question if tumor-only analysis can be used to accurately guide medical decision making in the field of inherited predisposition for cancer. This issue can also be extended to other domains like constitutional genetic disorders and PGx.

Multiple organizations, including the American College of Medical Genetics and Genomics (ACMG) and the European Society for Medical Oncology (ESMO) strongly recommend verifying the origin of a potential germline variant initially detected by somatic testing on a tumor sample, by performing an appropriate analysis on the patient's germline DNA.^{100, 101}

Below several aspects will be discussed, supporting the idea that the accurate and reliable detection of germline variants can only be obtained by performing analysis on suitable material, being non-tumor samples such as blood or saliva containing the individual's DNA.

1. Tumors undergo genetic alterations and acquire somatic variants during their development to which allelic loss, exon- or chromosome-level deletions/duplications and intronic variants can overshadow or confound the detection of germline variants,¹⁰² as they represent unique changes **specific to the tumor cells** and **do not reflect accurately an individual's inherited genetic background**. In this way, the tumor's genetic instability can be misleading in falsely identifying the absence or presence of a specific germline variant.¹⁰¹
2. Often, enrichment techniques or targeted tumor cell isolation are used to obtain a better representation of tumor cells within the collected tissue, to make sure all important somatic variants are detected. These procedures further decrease the sensitivity for detecting germline variants, as the material will not reflect an individual's germline genetic make-up.
3. Somatic gene panel analysis on solid tumor is often performed on Formalin Fixed Paraffin Embedded (FFPE) samples instead of fresh-frozen samples. The formaldehyde (the primary component of formalin) is a superior fixative for preserving tissue samples but the fixation induces some DNA damage,¹⁰³ like the creation of crosslinks between protein and DNA,¹⁰⁴ as well as fragmentation, which can lead to low amounts of amplifiable DNA.¹⁰⁵ Even long-term storage of formalin-fixed blocks can induce fragmentation.¹⁰⁶ Still numerous studies have reported the feasibility of using DNA from FFPE samples with both conventional PCR-based and NGS technologies.¹⁰⁷⁻¹⁰⁹ Nonetheless, fragmentation can be a limiting factor in approaches that use longer amplicons/reads which are sometimes needed for PGx.



4. Additionally, tumors can be very heterogeneous, consisting of subpopulations of cancer cells with varying genetic profiles. Different regions within a tumor may harbor different genetic alterations. Analyzing a single tumor sample might not capture the full spectrum of germline variants, as it represents only a fraction of the tumor's genetic landscape.
5. The bioinformatics analysis directed to the detection of somatic variants differs from the analysis focused on germline variant detection. Aspects like read alignment, variant calling and variant filtering is targeted to one specific goal and not both. So, incidentally detected variants by a specific bio-IT pipeline may not reflect the complete un-targeted genome (tumor or normal).¹¹⁰

In conclusion, tumor samples cannot provide the reference point for accurate identification of germline variants. Technical procedures on tumor tissue (tumor collection, tumor cell enrichment, bioinformatics pipeline) are focused on somatic variant detection and, more importantly, genetic alterations in the tumor may influence the presentation of the individual's real germline genetic makeup. Non-tumor samples like blood samples, buccal swabs or saliva must be considered for this purpose as they more accurately represent the germline genetic information.

3.3.3 Whole genome/exome testing (= sequencing)

Only sequencing techniques are able to test the whole genome or exome. Given the rapid technological advances in NGS, the decrease in costs and the feasibility to obtain short turn-around-times, multiple gene panel testing is gradually evolving towards whole exome and whole genome **sequencing**. This allows to move from pharmacogenetics towards pharmacogenomics. It is important to note that some non-coding parts and complex structural variants are relevant in several pharmacogenes (including CYP2A6, CYP2D6, and HLA-B), therefore, **whole exome sequencing is not sufficient** (though enrichment methods are possible).

Although very promising, this pharmacogenomic approach is currently still **in research phase**, as the clinical utility and validity needs to be demonstrated prior to entering clinical practice. Moreover, specific expertise is needed not only for the analytical phase, but certainly also for the post-analytical phase including the bioinformatics analysis for variant identification and the scientific and clinical assessment for variant interpretation and variant-gene-drug decision-making.

3.4 Comparison table of the available technologies/platforms

Thus far PGx testing often requires a combination of different approaches to comprehensively analyse all relevant genetic targets. Long-read sequencing technologies (like PacBio Single Molecule Real-Time (SMRT) sequencing and Oxford Nanopore sequencing) are emerging and offer significant advantages for pharmacogenetic testing. These technologies are characterized by their ability to produce reads that span much longer stretches of DNA compared to short-read sequencing technologies (like Illumina). This allows for more comprehensive analysis of complex genomic regions, including structural variations, repeat expansions, and allele phasing, all of which are important in the context of pharmacogenetics. These technologies are currently still expensive to implement in a clinical setting.

Microarray technology has played a significant role in PGx, but its usefulness has evolved with the emergence of NGS. While microarrays tend to be less costly for lab and yield quicker results compared to targeted NGS, NGS is capable of capturing a broader spectrum of variants, encompassing novel, rare and more complex variants.

Short read NGS panels are used in clinical practise, while long read NGS panels are still under validation for clinical use.

The technologies are compared in Table 7.


Table 7 – Comparison of available technologies/platforms

Technique	Diagnostic accuracy Sensitivity/specificity per variant possible?)	Completeness of identifying all relevant variants	Turnaround time in the lab	Advantages	Challenges
LAMP (Loop-mediated isothermal amplification)	highly sensitive and specific if primers are well designed ; CE-IVD/IVDR commercially available for limited number of targets (e.g. LaCAR: DPYD, TPMT, CYP2C9, CYP2C19)	targeted to specific alterations; only for limited number of targets available	2 hours (limited hands-on-time; 25 minutes for amplification + detection)	analysis can be directly started from blood (DNA extraction is not required, but possible)	profiles of neighbouring SNVs may resemble profiles of the targeted SNV; requires good knowledge of the variation of genomic sequences in the vicinity of the targets
HRM (high resolution melting curve analysis)	highly sensitive and specific if primers are well designed and the pCR well optimised. A lot of companies commercialize HRM kits but the primers can be designed by the laboratory.	targeted to specific alterations; only for limited number of targets available	workflow takes about 0,5 working days; hands-on: around 2 hours	In the case of UGT1A1 genotyping, allows characterization of different allelic combinations; TA repeat number 5, 6, 7 or 8. Useful as a complement to sequencing techniques, for which characterization may be more problematic.	prior knowledge of melting curves for different allelic combinations; (UGT1A1-TA repeat number 5, 6, 7 or 8).
Taqman genotyping assay	highly sensitive and specific if probes and primers are well designed ; >2700 TaqMan commercially available (e.g. SNP and CNV Genotyping Assays available via ThermoFisher)	targeted to specific alterations	workflow takes in total 3-4 hours; hands-on-time: 1-2 hours	Automatic workflow commercially available (e.g. ThermoFisher: TaqMan Genotyper Software and AlleleTyper Software)	requires good knowledge of the variation of genomic sequences in the vicinity of the targets reporting issues: e.g. ThermoFisher: generates a report per SNV and not per patient which is not convenient for clinical settings
Sanger sequencing (targeted)	highly sensitive and specific (PCR primers should be designed avoiding neighbouring SNVs to avoid allelic drop-out)	flexible design in function of the targets to be analysed	workflow takes about 2 working days; hands-on: 2 hours	very flexible, knowledge in molecular labs for PCR and Sanger sequencing available; targets can be quickly implemented with a minimum of validation; both PCR and Sanger sequencing can be automated	not suitable for high throughput: not efficient if ≥10 of targets need to be analysed; capillary electrophoresis instrument suitable for Sanger sequencing needs to be available



Technique	Diagnostic accuracy Sensitivity/specificity per variant possible?)	Completeness of identifying all relevant variants	Turnaround time in the lab	Advantages	Challenges
					variants of unclear functional impact located in the same amplicon as the target of interest
Next generation sequencing - short read targeted panels	highly sensitive and specific; All variants with a known functional impact (e.g. PHARMVAR for CYPs) can be included for each selected pharmacogene, provided that the panel design has been properly carried out.	flexible design in function of the targets to be analysed repeat/ pseudogene regions may require special design and data analysis) not all CNVs may be detectable NGS-based HLA analysis commercially available (e.g. Illumina, Agilent, IDT); for data analysis specific algorithms have been developed	workflow takes about 2-3 working days (+ 24h for sequencing; hands-on: 16 hours large number of samples can be analysed in parallel)	Parts of workflow can be automated; sequencing of regions of interest in selected pharmacogenes creates possibility to call star alleles; several software solutions available to perform automatic variant analysis and haplotype/diplotype calling; possibility of adding an integrated analysis of CNVs and structural rearrangements important for certain pharmacogenes (e.g. CYP2D6). This approach is ideal for the optimal classification of metabolizing phenotypes according to the most recent scientific knowledge (e.g.; taking into account the known effect of a rare variant that can move a phenotype from IM status in targeted genotyping to PM status using a NGS panel approach). Suitable for a preemptive panel-approach	Maintaining/updating pharmacogene coverage to meet all current international PGx recommendations Variants of unclear functional impact located in the sequenced regions
Next generation sequencing – long read: targeted gene panel	highly sensitive and specific; All variants with a known functional impact (e.g. PHARMVAR for CYPs) can be included for each selected pharmacogene.	flexible design in function of the targets to be analysed	workflow takes about 2,5 working days (+ 2 days for sequencing on a PacBio revio/sequel); hands-on: 18	Long reads provide a better mapping in repeat/ pseudogene regions, structural variants can be identified with confidence. Parts of workflow can be automated; sequencing of regions of interest in selected pharmacogenes creates possibility to call star alleles; several software solutions available to perform automatic variant	Few databases currently include long read sequencing data, correctly classifying unknown structural variants can be challenging. Maintaining pharmacogene coverage to meet all current international recommendations in the field of



Technique	Diagnostic accuracy Sensitivity/specificity per variant possible?)	Completeness of identifying all relevant variants	Turnaround time in the lab	Advantages	Challenges
			hours (96 samples)	analysis and haplotype/diplotype calling; possibility of adding an integrated analysis of CNVs and structural rearrangements important for certain pharmacogenes (e.g. CYP2D6); This approach is ideal for the optimal classification of metabolizing phenotypes according to the most recent scientific knowledge including repeat,s pseudogene regions and structural variants. Suitable for a preemptive panel approach	PGx; Adequacy of the gene panel with the recommendations of the main national and international PGx societies (e.g. RNPgX). Variants of unclear significance located in the sequenced regions
Next Generation sequencing: whole exome sequencing (WES)	sensitive and specific; variants in the pharmacogenes of interest with a known functional impact (e.g. PHARMVAR for CYPs) can be selected for by the bio-IT pipeline Depending on the coverage of pharmacogenes, the possibility of meeting almost all current international recommendations in the field of PGx (mainly CPIC and DPWG).	If the average coverage is sufficient (>100x) SNV and CNV detection is possible (no repeat/pseudogene regions)	workflow takes about 2,5 working days, 2 days for sequencing on a high output sequencing platform; hands-on: 16 hours (96 samples)	Parts of workflow can be automated; sequencing of regions of interest in selected pharmacogenes creates possibility to call star alleles; several software solutions available to perform automatically variant analysis and haplotype/diplotype calling; possibility of adding an integrated analysis of CNVs and structural rearrangements important for certain pharmacogenes (e.g. CYP2D6); Possibility of implementing a secondary analysis after other diagnostic purposes and thus a non targeted preemptive approach	Limited to variants in exonic regions Maintaining pharmacogene coverage to meet all current international recommendations in the field of PGx; all genes included. Long term data storage will be costly. Variants located in the sequenced regions with no clear functional impact in databases or newly described variants
Next generation sequencing: Whole genome sequencing (WGS)	sensitive and specific; variants with a known functional impact (e.g. PHARMVAR for CYPs) selected for by the bio-IT pipeline	If the average coverage is sufficient (>50x) SNV and CNV detection is possible	workflow takes about 1 working day, 2 days for sequencing on a high output sequencing	parts of workflow can be automated; sequencing of regions of interest in selected pharmacogenes creates possibility to call star alleles; several softwares available to perform automatically variant analysis and haplotype/diplotype calling; possibility of	Maintaining pharmacogene coverage to meet all current international recommendations in the field of PGx; all genes included.



Technique	Diagnostic accuracy Sensitivity/specificity per variant possible?)	Completeness of identifying all relevant variants	Turnaround time in the lab	Advantages	Challenges
			platform, 1 day BioIT analyses (hands-on 7 hours for 24 samples)	adding an integrated analysis of CNVs and structural rearrangements important for certain pharmacogenes (e.g. CYP2D6); Depending on the coverage of pharmacogenes, the possibility of meeting almost all current international recommendations in the field of PGx (mainly CPIC and DPWG); Possibility of implementing a secondary analysis on WGS after other diagnostic purposes and thus a non-targeted preemptive approach.	Long term data storage will be costly variants located in the sequenced regions with no clear functional impact in databases or newly described variants
Array	highly sensitive and specific (if PCR based: primers should be designed avoiding neighbouring SNVs to avoid allelic drop-out); small to large and more extensive panels on the market (up to > 6000 variants; actionable and potentially interesting)	at the start of the design it's feasible to include all needed targets to be analysed (but CNV info may be missing without special tools)	workflow takes about 3 working days; hands-on: 1-2 hours	parts of workflow can be automated; comprehensive targeted analysis creates possibility to call star alleles; several softwares available to perform automatically variant analysis, haplotype/diplotype calling and translation to therapy recommendation (CDS); relatively lower cost and shorter TAT	genotyping challenge because interference of specific highly polymorphic genes is possible ; can be challenging to detect CNV; comprehensive approach may be challenging for data processing and interpretation Difficult to change the design of the array, typing challenge because interference of specific highly polymorphic genes is possible; can be challenging to detect CNV; comprehensive approach may be challenging for data processing and interpretation depending on the design: actionable +/-potentially interesting variants +/- unknown variants



3.5 Points of attention

Currently, there is a lack of standardization concerning the variants and haplotypes which need to be tested and reported in a clinical setting. Consequently, different PGx tests may detect different sets of variants for each gene, potentially creating a limited and improper haplotype deduction based on the test-specific variants. The resulting deviation of the true haplotype in the patients' genetic makeup, results in an incorrect interpretation of the clinical impact, affecting precise treatment decisions. This practice can also lead to differences in assigned haplotypes when testing the same DNA in different laboratories, causing confusion and impeding the adoption of clinical PGx testing.

To improve patient care, consistent and reliable results are needed, which can only be ensured by implementing some points of standardization like:

1. Development of a **standardized panel of variants (including haplotypes)** that should be encompassed within PGx test panels.
2. Recommendations for the **description and reporting of all tested variants**, providing a comprehensive picture of the tested patients' genetic makeup.
3. Implementation of **guidelines** on use of different tests and technologies, including limitations, especially regarding the types of variants the test may not be able to detect.

There are sometimes remarkable differences in the frequency of PGx variants between **ethnic groups**, and these differences need to be taken into account when proposing/validating targeted genotyping tests so as to include the most frequent variants encountered in each ethnic population, in order to guarantee equity of clinical management in an ethnically diverse society.

While targeted genotyping methods are designed to search for actionable variants for which recommendations for therapeutic adaptation to a given drug exist, sequencing-based methods (panel or whole exome/genome sequencing) may also detect **rare variants** for which recommendations do not yet exist.

Except in cases where these variants are definitely associated with a change in the activity of the coded protein (e.g. frameshift mutation), extreme caution must be exercised when interpreting these variants.²² In some cases, a **parallel phenotyping test** can be used to determine the functional impact of a new variant.

When PGx analysis is performed on a blood sample, it is important to remember that the conclusions drawn in the analysis reports, proposing therapeutic adaptations (choice of drug and/or dose), are only valid if the genotype of the circulating blood cells corresponds to the genotype of the tissues responsible for metabolism (mainly the liver), and therefore in the **absence of bone marrow and/or liver transplantation**. In case of analysis based on a buccal swabs or saliva, the same limitations apply. It is recommended that this limitation be added to analysis reports intended for clinicians.

With regard to the inference of genotypes in star allele nomenclature, based on haplotypic combinations, it is important to remember that the default assignment, in the absence of variants (or combinations of variants) defining a given allele (e.g. *2, *3, *17 for CYP2C19), will automatically be *1 (wild-type). As a result, the **final genotype proposed may vary depending on which variants (or combinations of variants) are sought in a targeted genotyping method**. Only a complete gene sequencing method (including coding and non-coding sequences) can tell whether or not the sequence corresponds to the reference wild-type sequence (defined as *1).

3.6 Alternative methods to genotyping

The genotype is a prediction of how a medicine will behave in the body based on DNA, though other factors can also influence a medicine's behaviour, therefore for some medicines other testing approaches can be used to elucidate the situation in vivo, and are sometimes used in complement. Such an alternative to genotyping is often referred to as a phenotyping approach (for example assessing the enzymatic metabolic activity, or in the case of the antiplatelet 'clopidogrel' there exist platelet function tests).



3.6.1 Assessing the enzymatic metabolic activity

One way to predict/assess the function of a biotransformation enzyme is to check that the reaction catalysed by the enzyme is taking place correctly using an endogenous substrate or an exogenous substrate (also called xenobiotic) administered either in vivo or ex vivo.

In clinical laboratories, routine applications include phenotyping approaches for enzymes such as thiopurine S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD) and several cytochromes P450 (CYP).

To assess the function of **DPD enzyme** (encoded by DPYD gene), a routine phenotyping approach based on the measurement in plasma of uracil (U), the natural (endogenous) substrate of the DPD enzyme, and its metabolite dihydrouracil (UH2) has been proposed before treatment with fluoropyrimidines. Plasma concentrations of U and UH2 are commonly measured by high performance liquid chromatography (HPLC) with different possible detection methods (UV spectrophotometry, and most frequently mass spectrometry). In case of DPD deficiency, pre-treatment U or UH2/U ratio values are increased or decreased, respectively. Both UH2/U ratio and U are continuous variables. Interpretation thus requires the determination and the validation of threshold values to distinguish patients with DPD deficiency from non-deficient patients. The literature available regarding UH2/U threshold is scarce and suggests large heterogeneity between laboratories. This is primarily due to the variability in the analytical methods used and to analytical interference regarding UH2 determination. The existence of external quality control organised since 2019 (e.g. Asqualab, France) has greatly reduced this analytical variability. In contrast, several independent prospective studies converge remarkably on the threshold value of U determining a risk of toxicity: greater than 15 ng/mL for an historical study¹¹¹ and 16 ng/mL for two other studies.^{112, 113} Based on the most recent literature, a 14 ng/mL threshold has been proposed by a Belgian consortium.⁶⁶ Also, it is commonly assumed that U > 100 ng/mL is associated with DPD total deficiency (although this could not be validated prospectively, given the rarity of this phenotype).

While the EMA leaves the choice between two methods for pre-treatment DPD deficiency testing (genotyping or phenotyping),⁵⁷ both the French¹¹⁴ and Belgian⁶⁶ recommendations on detecting 5-fluorouracil and capecitabine toxicity put forward the phenotyping test because the test has a **higher sensitivity** to detect total and partial DPD deficiency, and a lower cost for phenotyping (around €50) compared with genotyping. However, the strict pre-analytical requirements for phenotyping (i.e. blood needs to be centrifuged and frozen within 1h30min)¹¹⁵ hamper its use. Several other factors must be considered to interpret this phenotyping test accurately: the concurrent fluoropyrimidine administration¹¹⁶ and renal function.¹¹⁷ The choice between DPD phenotyping and targeted DPYD genotyping as a first choice is still a matter of debate in the literature, partly because the concordance between the results of both tests remains limited (12.5% in a French study on 712 patients).^{118, 119}

There is also a phenotyping approach for assessing the deficiency of the **TPMT enzyme**. However, such an assay based on the *ex vivo* conversion of 6-thioguanine (6-TG) to 6-methylthioguanine (6-MTG) in red blood cells is time-consuming.¹²⁰ A large phenotype-genotype correlation study on healthy blood donors (n=1214 volunteers) concluded that there was an excellent concordance rate (98.4%) between the results of this test and targeted TPMT genotyping. This paved the way for the current recommendation to use genotyping as a first-tier approach to predict toxicity.¹²¹

To assess the function of the main **CYP enzymes** (encoded by CYP genes) involved in drug metabolism, phenotyping cocktails approaches have been proposed based on the simultaneous oral administration of a combination of selected probe drugs, with the subsequent measurement of these drugs and/or their metabolites in plasma or in capillary dried blood spot (DBS).¹²² In a validated protocol frequently used in routine in Switzerland and known as the "Geneva cocktail",¹²³ patients are receiving an oral cocktail capsule containing low doses of the probes caffeine (CYP1A2), bupropion (CYP2B6), flurbiprofen (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), midazolam (CYP3A) and fexofenadine (ABCB1).



Interestingly, in addition to its validation under “normal” CYP function conditions, the Geneva phenotyping cocktail combined with the DBS sampling technique has been shown to reliably predict modulation of CYP activity after pre-treatment with CYP inhibitors/inducers,¹²³ without mutual interactions between probe drugs used,¹²⁴ giving it an advantage in assessing drug-drug interactions (DDI), in addition to genotype-based activities. Although the use of such a phenotyping approach should be subject to prior approval by an ethics committee in Belgium, the safe use of this “Geneva cocktail” has been confirmed on 265 healthy adult volunteers from three different geographic origins.¹²⁵

3.6.2 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is the measurement of specific drugs and/or their metabolites in biological samples and is considered **a posteriori approach**, in contrast to genotyping and phenotyping which aim to predict before treatment initiation (*a priori*).¹²⁶ It is thus not really an alternative for genotyping, which is mostly to define the starting dose. TDM is warranted for medicines with a known narrow therapeutic range and where there is a wide inter- and intra-patient variation. Medications most often subject to TDM are immunosuppressants, antibiotics and anti-epileptic drugs. The immunosuppressants ciclosporin and tacrolimus in organ transplantation require TDM.¹²⁷ In order to assess thiopurine toxicity, the measurement of 6-thioguanine nucleotide (TGN) and 6-methylmercaptopurine (6-MMP) concentrations in red blood cells after administration of thiopurine drugs is often performed in clinical practice.¹²⁸ Potentially very useful in some cases as also the influence of several other genes, like NUDT15, can be explored.

3.7 Methods in Belgian laboratories

The analysis of the Belgian Genetic Tests Database, which is limited to the eight CHGs, showed that most PGx tests are either targeted PCR-based or real-time PCR (see Table 43 in appendix), showing a predominant single gene test approach. Sequencing is done when entire genes, multiple codons and/or more (rare) variants need to be analysed. Often they are incorporated in a NGS panel (CYP2D6 because pseudogenes and copy number variants need to be checked, entire coding region for TPMT + NUDT15). However also Sanger sequencing is performed (for DPYD). Most PGx are inhouse laboratory developed tests.

The HLA labs often use commercial CE-marked kit or panels to identify HLA variants (either PCR based PCR SSOP or NGS).

The survey showed that some molecular diagnostic labs use in-house modified NGS oncological panels with some PGx targets. As a sample they use tumour biopsy (FFPE or ctDNA).

POCT tests for PGx are, to our knowledge, not clinically implemented.

In Belgium, the phenotyping approach is limited. The survey showed that only three labs (often toxicology departments or metabolic labs, and thus not CHG) perform phenotyping for DPD deficiency with 2797 tests in 2022, and often this enzymatic test is complementary to the genotype test. The TPMT phenotyping was even more rare (two lab's indicated that applications are rare).

A reason why phenotyping (enzyme-testing) is limited in Belgium is the lack of reimbursement because there is no nomenclature available for DPD enzyme testing for clinical biology labs. At the moment the labs charge the patient between €40-50 per test. The pre-analytical requirements can be overcome with clear instructions for the clinicians.

Via the clinical biology and toxicology labs there is a specific reimbursement for TDM and identification of drugs and their metabolites (article 24 of the nomenclature), however not for all relevant drugs (for example SSRI monitoring there is no code).



Key Points

- PGx testing can either be targeted (single gene tests or more elaborate via a targeted panel), or the entire genome/exome can be analysed through whole genome/exome sequencing, though the latter is currently not validated yet for clinical use.
 - Thus far PGx testing often requires **a combination of different approaches to comprehensively** analyse all relevant genetic targets.
 - **PCR-based techniques** are widely used for **targeted testing of single genes** (loci). The selected technique depends on the technical feasibility for the gene target, and on practical considerations in the laboratory (instrument availability, cost, TAT...).
 - **Sanger sequencing** still has a place in clinical routine for PGx for **targeted testing of a limited number of gene** targets as it is very flexible in design, availability and expertise present in every lab.
 - **Next generation sequencing** techniques can be used for **targeted panel approaches**, as well as for **whole genome and exome sequencing**. Currently most applications are based on short reads, but long reads are emerging. However, cost price for the latter is still too high for implementation in routine diagnostics.
 - Long read sequencing allows characterization of repeat regions and pseudogenes and is more suitable for haplotyping complex pharmacogenes compared with short read sequencing; however, when the focus is a targeted panel approach for well-known variants (excluding rare) short read sequencing together with dedicated bio informatics is able to reliably capture all currently known variants.
 - **Micro-array** technology can be used for a **targeted panel approach**. Highly polymorphic genes and CNVs are more challenging to detect and need dedicated bio informatic tools.
- Whole genome sequencing is preferred to whole exome sequencing for PGx, as some non-coding parts of the genome are relevant in several pharmacogenes.
 - Challenges for computation of gene panels are the need for **standardization of the genes and variants** to include, as well as regular **updates**.
 - **Variants of unclear significance** require more research regarding whether and how this additional info can be clinically utilized.
 - **Guidelines on reporting are needed.**
 - Testing on tumour sample is not recommended for germline variant detection.
 - **Phenotypic approaches** can also be used, but are not available for all pharmacogenes. Moreover, it is often unclear from the scientific literature which approach is to be preferred. Both phenotypic and genotypic tests can offer valuable information and in many cases these tests are complementary.
 - **In Belgium**, the predominant strategy for PGx targets is single gene tests via PCR-based technology. However, when more genes (locations/targets) need to be checked, or more difficult regions need to be checked, sequencing is done (where bi-directional Sanger sequencing is being replaced by NGS panels).
 - **In Belgium**, NGS panels (short and long read) and micro-array panels are being developed and validated.
 - **In Belgium**, the implementation of phenotyping tests (CYPs, DPYD, TPMT) is rather limited, and hampered by lack of reimbursement as these tests are usually performed by clinical biology laboratories.



3.8 Quality monitoring of Belgian laboratories

This chapter was developed by experts from Sciensano: dr. Joséphine Lantoiné and dr. Arnaud Capron with input from Nathalie Lannoy

Quality requirements for the 8 CHGs are currently scattered over different legislative rules, with the most explicit ones in the reimbursement legislation (Article 33 of the nomenclature).

To safeguard quality, two systems of surveillance are available: certification and accreditation. Requirement to participation to external quality control is a cornerstone of both systems.

3.8.1 Legislative requirements - Certification/recognition

The legislation on the certification of centers for human genetics (CHG), which dates back to 1987, does **not specify any explicit quality assurance** criteria.⁴⁴ Since 2012 the CHGs must also comply with some general quality requirements, which includes the establishment of a Belgian College for Human Genetics and Rare diseases, and focusing on reporting activities (Royal Decree of 15 February 1999)^{q, 45, 46} This College groups medical experts from each of the eight CHGs and is responsible for the external quality check of the medical activity in the CHGs.

In contrast, the legislation on the recognition of the laboratories for clinical biology and anatomo-pathology does include explicit quality requirements.^{129, 130} Sciensano is the competent authority to grant certification and control and evaluate the quality (via nationally organized external quality assessments, audits).

In addition to the quality requirements mentioned in the certification/recognition criteria, there are **explicit quality requirements as a condition for reimbursement** by RIZIV-INAMI. These are mentioned in the respective nomenclature (articles 24, 24bis, 32, 33bis and 33ter of the nomenclature - see box 4) that apply to the pathological anatomy and clinical biology laboratories as well as to the 8 CHGs.^{47, 131-135} Although the

formulation of the quality requirements is not the same in every article, there is a recurring pattern, always mentioning accreditation (ISO15189 standard), the need to participate in internal and external quality controls, and registration of activities.

3.8.2 Accreditation

Accreditation is a quality requirement formulated in the reimbursement legislation. Accreditation involves formal approval of an institution's competence, including the quality of its structure (staff qualifications, infrastructure, documentation), the quality of its procedures (methodology, communication strategies, collaboration) and the quality of its results (diagnosis of the disease, patient satisfaction). The basis for accreditation is the ISO15189 standard, with the new 2022 version set to take effect by the end of 2025. Successful accreditation is attested by a certificate from the Belgian Accreditation Council (BELAC - FPS Economy) and has a maximum validity of five years. Institutes with a "flexible scope accreditation"^r have a list publicly available of specific activities carried out under the flexible scope accreditation. The accreditation scope issued by BELAC refers to this list.

In order to claim reimbursement for genetic tests, the CHG must be **accredited for at least 80% of the services performed** (either ISO15189 standard or another relevant accreditation). For services not covered by accreditation, the laboratory must provide proof of an internal quality control system. The FPS Public Health and the INAMI-RIZIV are responsible for monitoring compliance with these quality standards. This requirement enables a minimum quality standard to be imposed on CHG. However, the notion of 80% is subject to controversy, as it is not clear whether this refers to the volume of activity or the range of different tests provided by the CHG. It is therefore allowed for a genetic centre to provide PGx testing without being covered by accreditation for this particular testing.

^q Royal Decree of 15 February 1999 on the qualitative assessment of medical activity in hospitals.

^r For a laboratory, a flexible accreditation scope is a scope which is not limited to specific tests, but is granted for a group of tests.



An analysis of the accreditation certificates of the 8 CHGs and the BGTD showed that not all PGx tests are in the accreditation scope. One explanation might be that in some CHGs the volumes of the PGx tests are too low at the moment. However, all PGx tests are performed with molecular technologies for which the centers are accredited.

3.8.3 External quality assurance

External quality assessment (EQA) is an integral aspect of accreditation, and is conducted for tests that fall under accreditation. Moreover, external quality assurance is a requirement mentioned in the legislation.⁴⁵⁻⁴⁷ Sciensano is the competent authority to organise external quality assessments (EQAs) for clinical biology and anatomopathological laboratories, but not for the CHGs. Unlike the direct and permanent surveillance of the laboratories for clinical biology and anatomo-pathology, the external evaluation of the CHGs by Sciensano is regulated via an ad-hoc contract (convention) between the RIZIV-INAMI and Sciensano. This convention governs a monitoring process where Sciensano gets access to reports of EQAs organised by international organisations. In return, CHGs are reimbursed for their participation costs.

Within the framework of the Belgian Rare Diseases Plan, a working group was responsible for selecting EQAs, eligible for reimbursement. While this action primarily focused on genetic tests for diagnosing rare diseases, also PGx tests were considered. In 2022, for PGx, 8 EQAs covering 22 PGx indications were selected for reimbursement. As the number of CHGs in Belgium is too limited to organize national EQA, participation to international EQA is used: RfB, GenQA, INSTAND, UKNEQAS or EMQN. This international collaboration enables Belgian CHGs to compare their performance with a larger number of peers and to support quality harmonisation at an international level. National guidelines recommend a frequency of participation to EQA once every three years.¹³⁶

On the last three EQA cycles (2020, 2021 and 2022), at least 12 PGx indications (ABCB1, CYP2B6, CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP3A5, VKORC1, UGT1A1, TPMT, DPYD, and Mitochondrial non-syndromic sensorineural deafness with susceptibility to aminoglycoside exposure) have been reported to be covered by evaluation among a maximum of 6 CHGs. Most EQA for PGx give information on the genotyping technique, interpretation and clerical accuracy (i.e. accuracy in receiving, processing, reporting, and delivering laboratory test results and other lab reports). Throughout these EQA cycles, CHGs that reported participation to Sciensano received an overall satisfactory score for all assessed parameters. Sciensano has access to a selection of EQAs, namely those for which a refund is foreseen.

The Achilles' heel of all EQAs is the non-commutable characteristic of evaluated samples with those entering the lab in clinical practice. This can lead to unjustified poor performance, which makes comparison between analytical techniques a challenge.

3.8.4 Regulation of *in vitro* Diagnostic: impact on quality

The new In Vitro Devices Regulation 2017/746 (IVDR), in effect since May 2022, introduces a major update to the regulatory framework in the EU, challenging both regulators, medical technological industry, and health care institutions, laboratories.⁵³ This regulation creates greater transparency, stricter requirements and better traceability of devices, as well as the smooth functioning of the EU single market for IVD medical devices. The Federal Agency for Medicines and Health Products (FAMHP) is the competent Belgian authority. Following the IVDR classification rules, pharmacogenetic tests are classified in risk class C^s and require CE marking. However the IVDR provides an exemption to this CE requirement (article 5 (5) of IVDR) for laboratory developed tests (LDT) manufactured and used in the same health care institution on a small scale^t, for a targeted group of patients

^s IVD Regulation defines four risk classes A,B,C,D with D being the highest risk class. Class C covers a diverse mix of high-risk IVD devices which present a lesser risk to the wider population. It tends to include situations where the failure of a diagnosis could be life-threatening, including testing for infectious

diseases and cancer. It also covers fields such as companion diagnostics and genetic screening.

^t As opposite to industrial scale



whose specific needs cannot be met by an equivalent device available on the market (“inhouse” devices) (guidance on this exemption is produced by the Medical Device Coordination Group)^u.

Most PGx tests in Belgium are LDT tests. However, these LDTs are also being regulated for the first time in the context of IVDs, imposing general safety and performance requirements of the IVDR, accreditation of the lab, documentation of justification of exemption and conformity with GDPRs compliance on their development and use. Most of these requirements are scheduled to take effect by 26 May 2024. One particular requirement^v which requires a thorough market assessment is currently postponed till 2028. This EU regulation is expected to impact the test availability and the ability of the laboratories to implement LDTs as it will require re-validation of assays, new equipment and extensive documentation. All this will result in a considerable effort in terms of costs and time for the affected laboratories.^{137, 138}

LDTs have substantial medical value, playing a crucial role in diagnosing and monitoring patients across various rare and emerging diseases in medical laboratory testing. Quantitatively, they represent a significant portion of the global medical laboratory testing market. Therefore, the definition of quality, safety and performance requirements within a regulatory framework for LDTs is relevant and is expected to have a significant impact on both individual patient care and public health and safety.

Key findings

- Quality requirements for the 8 CHGs are **scattered** over different legislative rules, with the most explicit ones in the reimbursement legislation (Article 33 of the nomenclature). Moreover these requirements carry ambiguity:
 - Accreditation of the lab for at least 80% of the performed tests is subject to controversy, as it is not clear whether this refers to the volume of activity (as it has been interpreted by the CHGs) or the range of different tests.
 - Installation of a quality cycle and proof of annual participation in internal and external quality control. The EQA is formalised through ad hoc contracts (conventions) with Sciensano, outlining reimbursement for EQAs participation. This process differs from the EQA monitoring process for the clinical biology and anatomopath labs.
 - Registration in the form of annual reports, as well as a register logging all indications for genetic testing. This logging is however currently not available for all CHGs.
- At the moment, not all PGx tests in the CHGs fall under accreditation.
- Six of the eight CHGs reported to Sciensano that they participate in EQAs for their PGx tests
 - EQA for PGx tests is organised by international EQA organisations or companies such as RfB, GenQA, INSTAND, and EMQN.

^u Medical Device Coordination Group: Guidance on the health institution exemption under article 5(5): https://health.ec.europa.eu/system/files/2023-01/mdcg_2023-1_en.pdf

^v Article 5 (5) d of the IVDR: the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market.



- The CHGs that communicated their participation to Sciensano consistently received a satisfactory score for all evaluated parameters.
- Most PGx tests in the CHGs are laboratory developed tests (or inhouse modified kits).
- The new EU In Vitro Devices Regulation 2017/746 (IVDR) imposes stricter requirements, also for in-house LDTs: safety and performance requirements, documentation, regular market assessment. This poses a significant challenge in terms of costs and time for the laboratories that rely on LDTs.

4 EVIDENCE ON PHARMACOGENETIC TESTING

4.1 Sources of evidence and their methodology

There are multiple resources available to determine which drugs can possibly benefit from PGx testing, as well as resources to determine the appropriate course of action once the genotype is known. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have included PGx on their drug labels. International consortia of experts in PGx have produced guidelines and recommendations. Importantly, there is a difference between resources making recommendations on what to do when a certain variant is present (therapeutic recommendations), and resources making recommendations for PGx testing.

In this chapter, we provide an overview of the most frequently used PGx resources, their scope and methodology, with a particular focus on testing recommendations.

4.1.1 Methodology

To obtain an efficient collection of pertinent PGx clinical guidelines and resources, we conducted a pragmatic literature review. Initially, we focused on peer-reviewed articles that referenced guidelines, using the search phrase "pharmacogenomic testing" OR "pharmacogenetic testing" AND "guidelines" AND (human OR "human genetics") on PubMed with filters from 2015 to the end of 2022. Subsequently, we used a snowballing technique and feedback from experts in the field to incorporate additional relevant publications and grey literature resources. The primary aim of the review was to acquire references for possible PGx resources and compare the methodology of those most frequently used, rather than report and assess the quality of the retrieved literature. Note that our focus was on resources providing overview of PGx, and thus excluded clinical practice guidelines from medical organizations, that may as well refer to PGx testing in the clinical pathway concerning a specific disease.



4.1.2 Drug labels

For some drugs, PGx information is included in the drug label. The FDA and EMA have issued guidelines recommending drug manufacturers to include information on genetic factors that may impact drug response, including PGx information, on drug labelling when deemed “clinically relevant”.^{139, 140} However, the decision to include PGx information on drug labelling is determined on a case-by-case basis and is currently not required in all cases.

In 2011, EMA published its first PGx guideline on the use of ‘*pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products*’.^{139, 141} PGx information, **if supplied by the manufacturer**, is reported in the European Public Assessment Reports (EPARs).¹⁴² EPARs offer a thorough evaluation of both the benefits and risks associated with a medicine. The information from EPARs is included in the drug label^w only when the assessors determine it to be **clinically relevant with a high level of confidence**. However there is a lack of transparency on the evidence to decision process that leads to inclusion of PGx information in the drug label, and on the level of evidence that is considered necessary. For example the case for the medicine ‘abacavir’ and ‘siponimod’, while, for the former, data on PGx effectiveness is drawn by at least one randomised study with PGx guided therapy as the intervention, the latter only has one clinical study in 143 healthy patients with surrogate outcomes were considered.¹⁴³

The information on PGx in the drug label is not standardised (no uniform way of formulation) and can be found in different sections of the drug label: “*therapeutic indication*”, “*posology and method of administration*”, “*contraindications*”, “*special warnings and precautions for use*” or “*interaction with medicinal products and other forms of interactions*”. The EMA guideline states that if the medicine’s indication depends on a particular genotype, this should be stated in the section “*therapeutic indication*”.¹⁴⁴

The FDA maintains a list of therapeutic products that include pharmacogenomic information (i.e. biomarkers) on their labels called the “*FDA Pharmacogenomic Biomarkers in Drug Labelling*”.¹⁴⁵ The list also includes information on actions to be taken for some (but not all) of the products. The biomarkers in the table include but are not limited to germline or somatic gene variants (polymorphisms, mutations), functional deficiencies with a genetic aetiology, gene expression differences, and chromosomal abnormalities as well as specific protein biomarkers. FDA has also created a Table of Pharmacogenetic Associations, which lists pharmacogenetic associations that have been **FDA evaluated**, and are supported **by sufficient scientific evidence to suggest** that they may be beneficial to certain subgroups of the population.¹⁴⁶

4.1.2.1 FDA - Table of Pharmacogenetic Associations

The table is limited to PGx **associations** related to drug metabolizing enzyme gene variants, drug transporter gene variants, and gene variants that have been linked to a predisposition for certain adverse events. The pharmacogenetic associations are categorised into three sections based on the available evidence. Most of the associations listed have **not been evaluated in terms of the impact of genetic testing on clinical outcomes**, such as improved therapeutic effectiveness or increased risk of specific adverse events. In addition, clinical studies, if available, may only have linked genetic variation to a drug’s pharmacokinetics (such as the way in which the drug is metabolized), and differences in drug efficacy or safety across different genotype subgroups may not be known.¹⁴⁷ As of January 2023 there are 62 gene/drugs interactions reported in section 1, 22 in section 2 and 40 in section 3.

- Section 1: Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations (see Figure 7)
- Section 2: Pharmacogenetic Associations for which the Data Indicate a Potential Impact on Safety or Response

^w In this report we use the term drug label for the ease of reading, but in Europe the correct term is Summary of Product Characteristics (SmPC).



- Section 3: Pharmacogenetic Associations for which the Data Demonstrate a Potential Impact on Pharmacokinetic Properties only

Figure 7 – Example of gene-drug pair in section 1 of the FDA’s table of pharmacogenetic associations

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Abrocitinib	CYP2C19	poor metabolizers	Results in higher systemic concentrations and may result in higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.

Source: <https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations>

The FDA has **not provided a detailed description of the methodology** used to create the table. Stakeholders can provide input on associations that should or should not be included on the list. The FDA indicates on their website that they take a **community-based collaborative approach** to evaluating ongoing science.¹⁴⁷ We approached FDA to inquire about the methodology used to categorize gene-drug pairs in the three sections, but unfortunately they couldn’t share more than what is available on the FDA’s website.

Importantly, the FDA puts a **disclaimer** that the fact a particular gene-drug interaction is included in the **table does not necessarily mean the FDA advocates using a pharmacogenetic test** before prescribing the corresponding medication, unless the test is a companion diagnostic. Moreover, the FDA also cautions that this resource should not be used as a standalone document to make clinical decisions.

4.1.3 Guidelines

This section focuses on the most cited clinical guidelines on PGx, produced by dedicated PGx consortia.

4.1.3.1 CPIC guidelines

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international, multidisciplinary group of experts in pharmacogenomics. The CPIC project was founded in 2009 via a partnership between PharmGKB (see 1.3.3) and the pharmacogenomics Research Network (PGRN).¹⁴⁸ While mainly USA-based, CPIC includes over 600 members across 260 institutions belonging to 35 countries; 14 institutions are involved in CPIC as external observers including the NIH (the US National Institute of Health), the FDA and other professional societies. CPIC issues peer-reviewed, evidence-based, freely accessible **therapeutic guidelines** for gene/drug pairs.¹⁴⁹ The aim of CPIC guidelines is to provide guidance to clinicians on the appropriate use of available test results for the optimization of drug therapy. It is explicitly stated that the guidelines **do not give testing advice**, e.g. on whether a PGx test should be routinely requested or not.¹⁵⁰ One reason for this is the expectation that preemptive testing will become more accessible in the future.¹⁵¹ Another cited reason is that it could lead to liability issues, for example when it is stated that a test is recommended or required, and the clinician did not perform the test.¹⁵²

The guideline development process has been published in 2014,¹⁵¹ below is a brief summary:

- Gene-drug relationships are considered for assessment after nomination either by members of CPIC or by external experts by using surveys (2009 and 2012). Prioritization is made on perceived importance, on the test availability and on the actionability of the gene-drug pair. Monthly conference calls are organized to discuss such nominations.
- For the development of each guideline, CPIC composes a multidisciplinary writing committee with experience in the specific area, including a PharmGKB curator with expertise in literature retrieval and appraisal. The committee systematically evaluates clinical studies, case



studies, pre-clinical studies, and in vitro data on the drug(s) of interest with a genetic variant. They first make an assessment of the clinical relevance, after which they decide to develop a guideline or not. The evidence supporting the gene-drug pair is then scored by the committee and rated as *weak*, *moderate*, or *strong* evidence. Note that the rating is such that “strong” evidence may come from many “weak” papers as long as there is no contradictory evidence.

- **Therapeutic guidelines** are developed considering the collected evidence as well as any existing consensus-based guideline, and stratified by phenotype. Evidence of a potential action (alternative medication or dosing) is weighted in order to assign the strength of the recommendation:
 - **Strong recommendation** for the statement: The evidence is of high quality and the desirable effects clearly outweigh the undesirable effects.
 - **Moderate recommendation** for the statement: There is a close or uncertain balance as to whether the evidence is of high quality and the desirable clearly outweigh the undesirable effects.
 - **Optional recommendation** for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
 - **No recommendation:** There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

The guideline then undergoes internal review by members of CPIC, and external peer-review by means of publication in the journal “*Clinical Pharmacology and Therapeutics*”. The guidelines are freely accessible at the PharmGKB website (see 4.1.4). Updates are scheduled every two years. As of January 2023, 26 CPIC guidelines have been published.¹³

In addition to developing full guidelines, CPIC performs evaluations and **assigns levels to gene-drug pairs**, even to gene/drug pairs that did not undergo the full CPIC guideline process. The gene/drug pairs that have undergone full guideline process are labelled as “final”, those who haven’t are labelled “provisional”. Any update is posted on the PharmGKB website (see 4.1.4).

CPIC levels are defined as follows:

- CPIC level A: Genetic information should be used to change prescribing of affected drug.
- CPIC level B: Genetic information could be used to change prescribing of the affected drug , recommendation of at least one optional action.
- CPIC level C: No prescribing action is recommended, alternatives are unclear but testing is common.
- CPIC level D: No prescribing action is recommended, alternatives are unclear or evidence is weak, testing is rare or non-existent.

In the latest version of the CPIC website^x 99 gene-drug pairs are listed as CPIC level “A”, of which 96 are considered “final” and 3 are considered “provisional”. Eight gene-drug pairs are listed as A/B, all of them “provisional”. Level B includes 32 gene-drug pairs of which 18 “Provisional” and 14 “Final”. Level B/C includes 66 gene-drug pairs, all “Provisional”. Level C includes 206 gene-drug pairs, of which 139 “Final” and 67 “Provisional”. Level C/D includes 5 gene-drug pairs all listed as “Provisional”. Level D includes 102 gene-drug pairs all listed as “Provisional”.

^x <https://cpicpgx.org/>, accessed on Feb 26th 2024



4.1.3.2 The Dutch “DPWG” guidelines

The Dutch Pharmacogenetics Working Group (DPWG) founded by the Royal Dutch Pharmacists Association (KNMP) is a multidisciplinary group in which (clinical) pharmacists, physicians, clinical pharmacologists, clinical chemists and epidemiologists are represented.¹⁵³ DPWG guidelines aim to develop **therapeutic recommendations** (dose adjustment, alternative medication) as well as **testing recommendations**. The therapeutic recommendations are available to Dutch healthcare providers through the regularly updated “G-Standaard,” the national drug database in the Netherlands, accessible at the point of care. Updates of the guidelines are published every four months on the KNMP website, and every guideline is fully updated every 3 to 5 years. However, the primary source is the KNMP database, which is only available for subscribed members. Since recently, guidelines are also published in the peer-reviewed journal “*European Journal of Human Genetics*”. The guidelines are also endorsed by the European Association of Clinical Pharmacology and Therapeutics and the European Association of Hospital Pharmacists.

The guideline development process is described in the literature.¹⁵⁴ Here is a summary of the methodology:

- The selection of relevant gene-drug pairs is initiated by a systematic search carried out by DPWG curators on biomedical literature databases and additional material such as EMA EPARs. DPWG does not consider review articles, animal studies and in-vitro studies.
- Two DPWG members rate the **level of evidence for the drug-gene interaction** as well as the **level of clinical impact** independently. The level of evidence goes from 0 (lowest evidence) to 4 (highest evidence such as good quality studies with relevant pharmacokinetics or clinical endpoints). The clinical impact is rated via a seven-point scale that goes from AA (lowest impact) to F (highest effect such as arrhythmia, death, unanticipated myelosuppression). This clinical impact scale is based on the Common Terminology Criteria for Adverse Events (CTCAE).¹⁵⁵ The assigned scores are subsequently evaluated by the complete working group. The overall score of each drug-gene combination is the highest level of evidence and the highest level of clinical impact assigned to any of the articles included in the assessment.

- In order to assist the decision on whether or not testing for the gene-drug pair is beneficial, DPWG has developed the “**Clinical implication score**” (see Table 8).¹⁵⁶ It is based on the sum of the following criteria: severity of clinical consequences associated with the drug-gene interaction, level of evidence for the association, number of patients that have to be genotyped to prevent one patient from having an adverse event (see box 4), or to have an increased effect, and information in the drug label.
- This score classifies the desirability of **testing** gene-drug pairs to guide drug and dose selection:
 - **Essential PGx**: testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping **must** be performed before drug therapy has been initiated
 - **Beneficial**: PGx testing for this gene-drug pair is beneficial. It is advised to genotype the patient before (or directly after) drug therapy has been initiated.
 - **Potentially beneficial**: PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline.

As of January 2024 DPWG has classified as “essential” (this includes essential based on the drug label) 17 gene-drug pairs, “Beneficial” 14 gene-drug pairs and “Potentially beneficial” 34 gene-drug pairs.

**Table 8 – The criteria of the DPWG “Clinical Implication Score”**

Clinical Implication Score Criteria	Possible score
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)	
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+
• CTCAE Grade 5 (clinical effect score F)	++
Level of evidence supporting the associated clinical effect grade ≥ 3	
• One study with level of evidence score ≥ 3	+
• Two studies with level of evidence score ≥ 3	++
• Three or more studies with level of evidence score ≥ 3	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3	
• $100 < \text{NNG} \leq 1000$	+
• $10 < \text{NNG} \leq 100$	++
• $\text{NNG} \leq 10$	+++
PGx information in the Summary of Product Characteristics (SmPC)	
• At least one genotype/phenotype mentioned	+
• OR Recommendation to genotype	++
• OR At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	+++

Table adapted from Adbullah-Koolmees.¹⁵⁷ For each row one score is assigned, for example the score for row one can be 0. The scores for each individual rows are added leading to a total score ranging from 0+ to 10+. From a score of 6+ or more, PGx testing is considered essential. A score between 3+ and 5+ is considered beneficial; and a score between 0-2+ is considered potentially beneficial. CTCAE: Common Terminology Criteria for Adverse Events. PGx: pharmacogenetics. SmPC: Summary of Product Characteristics.

Box 4 – Number needed to genotype

The number needed to genotype (NNG) is a variant on the number needed to treat (NNT). It has been included in the methodology of the Dutch DPWG. As NNT is the inverse of the absolute risk reduction, the **baseline risk** is an important parameter to consider. The frequency of actionable PGx variants highly differs (range from approximately 0.1 – 7.0%), depending on the population's ethnic background. The majority of PGx studies are case-control studies showing an association between a variant and a medicine's effect or adverse event, and do not take the variant frequency into account. For these studies, it is imperative to use the formula: $\text{NNG} = \text{NNT} / \text{variant frequency}$.¹⁵⁸

The NNG also changes depending on the outcome considered. An example is abacavir related hypersensitivity. When the outcome is clinically diagnosed hypersensitivity, the NNG was 29, and when immunological confirmed hypersensitivity is considered as outcome, the NNG rose to 37 in the same study.¹⁵⁹ When mortality is considered as outcome, far larger NNG are calculated (4863 for fluoropyrimidine induced death).¹⁶⁰

Importantly, the quality of the data on which the NNG is based should be considered as small changes in assumptions on absolute risk differences will be reflected in large NNG differences

Examples of NNG available in appendix Table 45.



4.1.3.3 The French “RNPGx” guidelines

The French Network of Pharmacogenetics (RNPGx^y),¹⁶¹ is composed of about 30 members across France and French-speaking countries.¹⁵⁷ RNPGx guidelines formulate both **testing recommendations and therapeutic recommendations**. RNPGx Guidelines are published in the peer-reviewed journal “Thérapie”.

The methodology used by RNPGx in order to assign therapeutic and testing recommendations has been described by Picard et al.¹⁶² Here is a brief summary:

- The process begins with the estimation of level of evidence of the **functionality of a gene variant** and its categorization on three levels:
 - Demonstrated functionality: direct functional impact demonstrated *in vitro* with *ex vivo* data in humans corroborating its impact
 - Probable functionality: direct or indirect functional impact on the activity of a potential pharmacogene without *ex vivo* data in humans
 - Potential functionality: *in silico* predicted functional impact.
- Only if functionality is “demonstrated” or “probable” the pharmacogenes are considered for a testing recommendation.
- The **clinical utility is then judged by expert consensus**. Clinical evidence is evaluated considering RCTs as the gold standard for evaluating interventions, although evidence from retrospective studies or highly illustrative individual case reports is also included. Other aspects which are considered are the impact on effectiveness or toxicity of a drug, impact on pharmacokinetic but not clinical parameters, and the existence of alternative options.
- RNPGx has three levels of **recommendation for pharmacogenetic testing**:

- **Essential test:** *Demonstrated or probable functionality. Demonstrated impact on a major clinical phenotype (response-efficacy, resistance; toxicity) for therapeutic management; difficult or impossible to predict with a non-genetic approach; having led to expert agreement in favor of systematic testing.*
- **Advisable test:** *Demonstrated functionality, and, either demonstrated impact on an intermediary non-clinical phenotype but that is important to predict drug exposure (e.g. pharmacokinetics) for therapeutic management, having led to expert agreement in favor of testing; or demonstrated impact on a major clinical phenotype in therapeutic management but predictable by a non-genetic approach (phenotyping), having led to expert agreement in favor of testing as a complement to phenotyping or when phenotyping is not possible as a first intention approach.*
- **Possibly helpful:** *Demonstrated or probable functionality. Probable impact that remains to be demonstrated on a clinical phenotype or an intermediary (non-clinical) phenotype having led to expert consensus in favor of testing, case-by-case, depending on the clinical context (unusual response to a drug, specific disease).*

RNPGx has evaluated Pgx in 15 drugs, of these 5 are considered essential, see Table 9.

Not all drug-gene pairs are evaluated by the RNPGx (for example abacavir and HLA-A were not evaluated as this is already considered established). RNPGx considers CPIC recommendations as the reference source^z.

^y <https://rnpgx.shinyapps.io/RNPGx/>

^z Personal communication with RNPGx.



4.1.3.4 The Canadian “CPNDS” guidelines

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is composed of a multidisciplinary team of scientists and practicing physicians and was founded by provincial and federal Canadian agencies¹⁶³ in 2004. Patients and policymakers participate as well.¹⁵⁷ Its primary goal is to prevent adverse drug reactions (ADR) by identifying predictive genomic markers for specific ADRs through an active surveillance network, and providing guidance.

CPNDS produces guidelines on an **ad hoc basis** and five are published in peer review journals (for the medicines *cisplatin*, *warfarin*, *codeine*, *anthracyclines*, *carbamazepine*).¹⁶⁴⁻¹⁶⁸ CPNDS guidelines follow a standard guideline development as suggested by the Appraisal of Guidelines Research and Evaluation Enterprise (AGREE).¹⁶⁹ The guidance includes **testing recommendations** on as well as **therapeutic recommendations**. Here is a short summary:

- Appraisal of the evidence: a systematic search is performed to identify evidence on the association between genetic variants and phenotypical drug response. Studies excluded are conference abstracts, editorials, notes, short surveys and review articles. The totality of the evidence is assessed using a methodology similar to GRADE: this includes the evaluation of the consistency of independent study results, the magnitude and precision of effect sizes, indirectness of evidence, the number and quality of studies conducted, expert clinical opinion and the deliberations of the CPNDS clinical recommendations group.
- The decisions on both testing and therapeutic **recommendations** is done by a development group based on a grading scheme, based on the strength of supporting evidence, the balance between benefits and risks of genotype-guided treatment, and the likelihood of variability in the individual values and preferences of patients:
 - Strong (level A): Based on strong scientific evidence; benefits clearly outweigh risks; a recommended therapeutic option that is

expected to be chosen by a majority of informed health care providers and patients.

- Moderate (level B): Based on low confidence scientific evidence and expert opinion; benefits likely to outweigh risks; a recommendation that is expected to require individualized informed decision making by patients and health care providers, taking into account the individual needs, values and preferences of each patient.
- Optional (level C): Based mainly on expert opinion, for use with evidence development in a research context.

For testing recommendations, test performance measures (e.g. sensitivity, specificity, post-test probabilities) and calculation to estimate the number of patients needed to be genotyped were also considered while cost-effectiveness analysis was not performed.¹⁶⁷

CPNDS has evaluated PGx in 7 drugs, of these 3 are considered strong level, see Table 9.

4.1.4 Pharmacogenomics Knowledgebase - PharmGKB

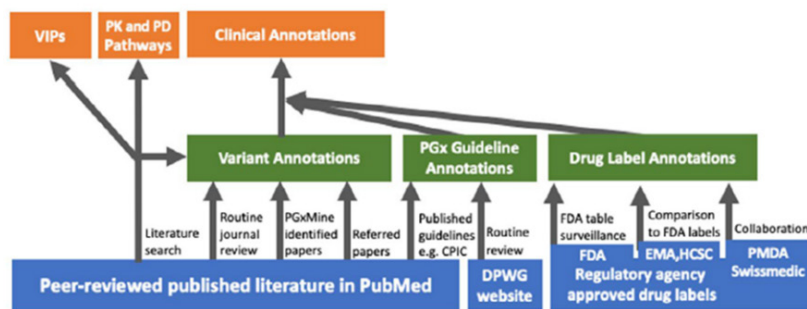
PharmGKB (Pharmacogenomics Knowledgebase)¹² is a publicly available online resource, founded in the year 2000, that curates and disseminates information related to the impact of genetic variation on drug response.¹⁷⁰ It is managed by Stanford University and receives grants from US public institutions. PharmGKB provides a comprehensive collection of pharmacogenomic knowledge, including information on variants, drug labels, clinical guidelines, drug pathways, drug-gene-disease associations, and curated literature. PharmGKB also offers tools and resources to support researchers and clinicians in the implementation of testing in clinical practice. It was the first public resource to curate PGx literature and annotate human genomes with variant-based PGx associations.¹⁷¹ All of PharmGKB data is downloadable^{aa}.

^{aa} <https://www.pharmgkb.org/downloads>



Publications for curation are either identified manually, or using PGxMine, a supervised machine learning pipeline^{bb} to extract associations between a variant and a chemical.¹⁷² For the clinical setting, the PharmGKB website provides different types of annotations which ultimately inform the clinical annotation (see Figure 8): the *drug label annotations*, the *clinical guideline annotations* and the *variant annotations*. We will discuss the testing recommendations more in detail.

Figure 8 – PharmGKB diagram of available resources



Source: PharmGKB website

4.1.4.1 PharmGKB Drug label annotations

The PharmGKB drug labels annotations are **testing recommendations**, solely based on PGx information contained in drug labels.¹⁷³ PharmGKB acquires information on FDA drug labelling via the *Table of Pharmacogenomic Biomarkers in Drug Labelling* (see 4.1.2.1). Updates relating to the table are provided by automated notifications. EMA data are retrieved by consulting the EPARs that contain PGx information of EMA-approved drugs. EMA does not provide automated updates. Swissmedic (The Swiss medicine agency), PMDA (the Japanese Pharmaceuticals and

Medical Devices Agency) and HCSC (Health Canada Santé Canada, Canada's medicine agency) do not provide automated updates and have to be manually searched.

PharmGKB assigns an interpretation of the level of actionability according to the information contained in the label, called the "PGx level".¹⁷⁴ There are 4 PGx levels and it is possible that a PGx level for the same drug/gene might differ depending on the labelling authority (EMA, FDA, etc):

- **Testing required:** The label states or implies that some sort of gene, protein or chromosomal testing, should be conducted on the gene or gene product mentioned in the annotation before using this drug for all or a particular subset of patients. If a label describes the presence or absence of a gene, genetic variant or gene product as an indication for the drug, PharmGKB considers the label to imply a testing requirement. If the label states a test "should be performed", this is also interpreted as a requirement.
- **Testing recommended:** The label states or implies that some sort of gene, protein or chromosomal testing, is recommended to be carried out on the gene or gene product mentioned in the annotation before using this drug for all or a particular subset of patients. PharmGKB considers labels that say testing "should be considered" or "consider genotyping or phenotyping" to be recommending testing. For example allopurinol and HLA-B based on the FDA label.
- **Actionable PGx:** The label may contain information about changes in efficacy, dosage, metabolism or toxicity due to gene/protein/chromosomal variants or phenotypes (e.g. "poor metabolizers"). Or the label may mention contraindication of the drug in a particular subset of patients with particular variants/genotypes/phenotypes. However, the label does not require or recommend gene, protein or chromosomal testing.

^{bb} The PGxMine code can be freely downloaded at <https://github.com/jakelever/pgxmine>



- **Informative PGx:** The label contains information stating that particular gene/protein/chromosomal variants or metabolizer phenotypes do not affect a drug's efficacy, dosage, metabolism or toxicity. Or, the label states that particular variants or phenotypes affect a drug's efficacy, dosage, metabolism or toxicity, but this effect is not clinically significant. Another possibility is that the label appears or appeared on the FDA Biomarker List but does not currently meet the requirements to be assigned as "Testing required", "Testing recommended" or "Actionable PGx". PharmGKB annotates every label that appears on the FDA Biomarker list, regardless of whether they would otherwise annotate the label.

4.1.5 Comparison of testing recommendation in different resources

Among the resources discussed above, guidelines such as DPWG, RNPGx, CNDS give explicit indications on whether a pharmacogenetic test should be performed for a certain gene-drug pair. Moreover, the PharmGKB interprets the drug labels and also assigns a recommendation for testing. CPIC does not provide explicit testing advice but is together with DPWG a comprehensive source.

Table 9 shows the medicines for which at least 1 source labels it as testing required/essential (highest level of recommendation for testing). Based on these recommendations, there are 17 "essential PGx" gene-drug pairs for DPWG (14 medications), 4 "essential test" for RNPGx (phenotyping for fluoropyrimidines not included), 3 "Strong recommendation" for CNPDS, 4 "Testing required" for EMA and 6 "Testing required" for FDA.

While there is some overlap, there are also notable differences, with some sources allocating a lower testing recommendation, or do not provide any recommendation at all. The differences may be linked to the different methodologies used to establish the recommendation for testing. In the case of capecitabine and fluorouracil, RNPGx considers phenotyping as the "essential" test, and considers genotyping advisable if phenotyping is not available. The DPWG on the other hand, considers DPYD genotyping the "essential" test. CPNDS has a special focus on the paediatric population, which is the reason why it is the only organization to assign the highest level of testing recommendation to cisplatin and codeine. Out of the five resources

compared, the highest level of agreement to consider a test "essential" is observed for the medicines 'abacavir', 'eliglustat', and 'siponimod'. Importantly, DPWG labelled eliglustat, siponimod (and also mavacantem) as "essential" based on the requirement of PGx testing mentioned in the drug label, which is also a criteria in the DPWG methodology. This highlights the **impact of the drug label**. For abacavir it is clearly mentioned in the section "*therapeutic indication*" that a genetic test is needed to identify the HLA-B*5701 allele. Also for siponimod the drug label refers to the genotype of the CYP2C9 enzyme to optimise dosing but places the info in the section "*posology and method of administration*". For eliglustat the drug label leaves the option open for either genotyping or phenotyping as it mentions in the section "*therapeutic indication*" that it is only indicated for CYP2D6 poor, intermediate or extensive metabolisers, thus excluding ultra-rapid metabolisers. The formulation and location on the drug label differ but it is clearly stated that in certain genotypes, or certain metabolisers, the medicine cannot be used. However, there appears not to be a transparent and reproducible process in place that leads to the inclusion of PGx information from a solid evidence base. Despite the limited PGx information, the FDA-approved drug label for siponimod requires CYP2C9 genotyping before treatment start.¹⁴³

The phenomenon of **discrepancies among PGx guidance** has been described in several studies.^{157, 175-177} Abdullah-Koolmees et al. explains that the variations in therapeutic guidance and genetic testing among the four consortia (CPIC, DPWG, CPNDS, and RNPGx) stem precisely from the use of distinct methodologies. However they point out that harmonization projects are ongoing and that all guidelines, because of their unique features, are of added value.¹⁵⁷ Compared to information provided on drug labels, a 2020 report revealed that out of the 54 drugs featuring actionable gene-drug interactions according to CPIC and DPWG guidelines, only 50% included PGx information on their respective labels. FDA, EMA CPIC and DPWG agreed on the actionability of gene-drug pairs in only 18% of cases, these concern 13 gene-drug pairs (abacavir, allopurinol, atomoxetine, azathioprine (2 genes), capecitabine, carbamazepine, citalopram, codeine, mercaptopurine (2 genes), and thioguanine (2 genes)).¹⁷⁶ Pritchard et al. concluded that regulatory agencies, such as the FDA, might have access to PGx information that is unavailable in published literature and have a different perspective and objective when evaluating PGx associations and



use different approaches and information resources when considering clinical validity related to specific medicines. Additionally, in the case of older medications, the drug labels may not always be promptly updated when new PGx information becomes available.¹⁷⁷

This discordance **limits clinical implementation**.¹⁷⁶ From the clinician's viewpoint or a payer's perspective it is not clear which PGx source to follow. Experts consistently point to CPIC as the reference source as it is comprehensive, though these are not explicit testing recommendations.

Table 9 – Comparison of gene-drug pairs seen as “essential” tests according to DPWG, RNPgX, CPNDS, EMA or FDA and corresponding CPIC level

Medicine	DPWG	RNPgX [€]	CPNDS	EMA [§]	FDA [§]	CPIC Level
Abacavir	HLA-B	Not evaluated	Not evaluated	HLA-B	HLA-B	A
Azathioprine	NUDT15 -TPMT	TPMT	Not evaluated	No info	Testing recommended	NUDT15: A TPMT: A
Capecitabine	DPYD	Phenotyping* essential. DPYD genotyping advisable in the absence of phenotyping	Not evaluated	Testing recommended	Testing recommended	A
Carbamazepine	Beneficial	Not evaluated	HLA-B (in Asian populations)	No info	HLA-B	A
Cisplatin	No info	Not evaluated	TPMT (in pediatric patients)	No info	Informative	Not evaluated
Clopidogrel	CYP2C19 in patients with a percutaneous coronary intervention, stroke or TIA	CYP2C19 essential for coronary angioplasty with stenting. potentially helpful in other indications	Not evaluated	Actionable	Actionable	A
Eligustat	CYP2D6**	Not evaluated	Not evaluated	CYP2D6	CYP2D6	Not evaluated
Codeine	Beneficial	Not evaluated	CYP2D6 (pediatric patients)	No info	Actionable (black box warning children)	A
Fluorouracil	DPYD	Phenotyping* essential. DPYD genotyping advisable in the absence of phenotyping	Not evaluated	No info	Actionable	A
Mavacamten	CYP2C19**		Not evaluated	CYP2C19	Actionable	Not evaluated
Irinotecan	UGT1A1	UGT1A1 essential for intensified dose (> 240 mg/m2). advisable for a standard dose.	Not evaluated	Actionable	Testing recommended	A (Provisional)
Phenytoin	CYP2C9 in those patients on maintenance therapy		Not evaluated	No info	Actionable PGx for CYP2C19, CYP2C9,HLA-B	A



Medicine	DPWG	RNPGx [£]	CPNDS	EMA ^{\$}	FDA ^{\$}	CPIC Level
Pimozide	Potentially beneficial		Not evaluated	No info	CYP2D6 doses above 0.05mg/kg/day in children, or above 4 mg/day in adults	A/B(Provisional)
Mercaptopurine	NUDT15 -TPMT	TPMT	Not evaluated	Actionable	Testing recommended	NUDT15: A TPMT: A
Simvastatin	SLCO1B1 dosing > 80 mg	Possibly helpful in the presence of other risk factors for myotoxicity	Not evaluated	No info	Criteria not met	A
Siponimod	CYP2C9 **		Not evaluated	CYP2C9	CYP2C9	A (Provisional)
Tegafur	DPYD		Not evaluated	Testing recommended	No info	C
Tetrabenazide	No info		Not evaluated	No info	CYP2D6	Not evaluated
Thioguanine	NUDT15 -TPMT		Not evaluated	No info	Testing recommended	NUDT15: A TPMT: A

DPWG: Dutch Pharmacogenetics Working Group (version of January 2024), CPNDS: Canadian Pharmacogenomics Network for Drug Safety, RNPGx: French Network of Pharmacogenetics, FDA: US Food and Drug Administration, EMA: European Medicines Agency. ^{\$} This is based on the PharmGKB interpretation of the drug label * RNPGx sees phenotyping by determining the serum UH2/U ratio or lymphocyte DPD activity as essential. ** DPWG classifies this as “essential” based on the information in the drug label. [£] RNPGx did not evaluate all relevant medicines and refer to CPIC as an important source – for example they consider abacavir – HLA-B as essential.



Key points

- Dedicated PGx consortia (CPIC, DPWG, RNPgX, CPNDS) as well as drug labels give guidance on PGx. CPIC and DPWG are those that have systematically investigated the higher number of gene-drug pairs.
- PharmGKB is a publicly available online resource in PGx that curates PGx information from a wide variety of sources.
- Some guidelines are limited to therapeutic recommendations (adapt the dose, change the medicine) once the genotype is known (CPIC), whereas others also include recommendations on the need to test (DPWG, RNPgX, CPNDS).
- Discordance between the resources exists, reflecting the use of distinct methodologies.
- In every reported methodology the strength of an association between a variant and an outcome is appraised. However, translating the literature on associations into testing recommendations requires appraisal of additional criteria in order to judge clinical utility: the frequency of the gene variant in the population, the frequency of the outcome, possible alternatives and cost-effectiveness. On all these additional criteria, methodologies differ.
- With regard to testing recommendations, the highest concordance between resources was seen for those medicines that have the PGx info clearly stated in the drug label: abacavir, eliglustat, siponimod.

4.2 Case studies on available evidence on the intervention of pharmacogenetic testing

We explored the existing evidence on the value of PGx testing through two case studies. This approach was adopted due to practical limitations that prevented us from examining all evidence for each indication/drug-gene pair. In the economic chapter 5, we also address the studies on which the economic analyses are built.

The first case explores the evidence behind PGx testing for the drug-gene pair **clopidogrel/CYP2C19** (a reactive testing approach). This case study was inspired on the possible inclusion of genotyping for clopidogrel in the NHS England test-database and the current NICE guideline development for clopidogrel genotyping after ischaemic stroke or transient ischaemic attack.

The second case study explores the evidence supporting **pharmacogenetic panel testing** (semi-preemptive approach) and examines the in 2023 published results of the PREPARE study.

4.2.1 A targeted PGx test for the effectiveness and safety of clopidogrel

Clopidogrel is a P2Y₁₂ inhibitor and prevents the formation of blood clots. Clopidogrel is used in **secondary prevention after a cerebrovascular (stroke) or a cardiovascular event**.

For the secondary prevention of ischemic stroke, clopidogrel is a first line therapy.^{178, 179} In the cardiovascular field, more potent alternatives such as prasugrel and ticagrelor are recommended as first line antiplatelet agents for acute myocardial infarction, despite the higher bleeding risk and higher price.¹⁸⁰ Nonetheless, clopidogrel still has a place in the therapeutic management of cardiovascular disease, as it is recommended in patients with a chronic coronary syndrome and, more recently, also as maintenance after an initial period of more powerful antiplatelets (de-escalation strategies).¹⁸¹



Clopidogrel is a prodrug which requires hepatic biotransformation to form an active metabolite that selectively and irreversibly inhibits platelet aggregation. The **CYP2C19 enzyme is needed to activate clopidogrel**. A poor or intermediate CYP2C19 metaboliser can result in a less effective antiplatelet function of clopidogrel, and therefore induce a higher risk for secondary ischaemic attacks. Individuals who have 2 loss-of-function copies of the CYP2C19 gene are classified as CYP2C19 poor metabolizers. Intermediate metabolisers have one loss-of-function copy of CYP2C19, with either one normal function copy or one increased function copy. Individuals of East Asians ancestry are more likely to be a poor metaboliser (see Table 10).¹⁸²

Both genotyping CYP2C19 before prescription of clopidogrel or the phenotypic alternative 'platelet function testing' are possible strategies to guide antiplatelet therapy. The optimal choice between these two strategies represents a topic of debate as they have never been compared directly in RCTs and both have their advantages and disadvantages.¹⁸³ In order to respond to clinical needs, the test results should be **rapidly accessible** to inform the prescription of antiplatelet therapy. For both testing strategies, point-of-care tests are available.^{184, 185} In a 2022 publication in the '*Nederlands tijdschrift voor geneeskunde*', it is recommended to conduct CYP2C19 genotyping in patients at high risk of or currently experiencing a recurrent ischemic event, while awaiting additional research findings.¹⁸⁶ However, the 2023 European Society of Cardiology guideline for acute coronary syndrome states that it remains unclear whether platelet function testing or genetic testing to guide de-escalation of oral P2Y12 receptor inhibitors after the first month of therapy following PCI improves clinical management and outcomes.¹⁸⁷

Table 10 – Therapeutic recommendations and frequency of predicted phenotype for different populations

Predicted CYP2C19 phenotype*	Frequency of phenotype in Dutch population**	Frequency of phenotype in Asian population [§]	Required therapeutic action (based on CPIC)
Normal metabolisers	67.3%	38% in East Asian, and 3.5% in Oceanians	No action
Intermediate metaboliser	24.5%	46% in East Asian, and 37% in Oceanians	Avoid standard dose of 75mg. Consider alternative
Poor metaboliser	3.7%	13% in East Asian, and 57% in Oceanians	Avoid clopidogrel if possible
Ultra-rapid metaboliser	4.5%	0.004% in East Asian, and 0.03% of Oceanians	No action

* Genotypes are translated into predicted phenotype categories based on allele frequencies (combination of variants). ** Frequency based on Dutch sample (n=1023) Van der Wouden 2022 article.¹⁶⁰ § Frequency based on CPIC https://files.cpicpgx.org/data/report/current/frequency/CYP2C19_frequency_table.xlsx.



4.2.1.1 Evidence

Most of the clinical evidence for CYP2C19 guided antiplatelet therapy has been produced in the context of cardiovascular disease, i.e. in acute coronary syndrome and Percutaneous Coronary Intervention (PCI). In the recent years, **two large RCTs on genotype-guided therapy in patients with a percutaneous coronary intervention** were published: the **TAILOR-PCI**¹⁸⁸ including 5302 patients enrolled at 40 centers in the US, Canada, South Korea, and Mexico, and the **POPular Genetics**⁹⁰ including 2488 patients treated in 10 European sites (1 Belgian). In the former study, the results indicated that using a genotype-guided strategy showed a numerical but not statistically significant reduction in the primary endpoint - a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, or severe recurrent ischemia at 12 months - when compared to the standard use of clopidogrel (hazard ratio [HR]: 0.66, 95%CI: 0.43–1.02, p=0.06). However this primary analysis only included patients with a LOF carrier in both arms. When the analysis was done on all randomised patients, the effect was diluted (HR: 0.84, 95%CI: 0.65–1.07, p=0.16). The adverse event endpoint 'bleeding risk' did not differ between the two compared strategies. In the latter study, the results demonstrated that the genotype-based approach was not inferior to the standard care (ticagrelor) in terms of efficacy. Additionally, there was a significant decrease in bleeding incidents with the genotype-guided treatment, primarily attributed to a reduction in minor bleeding events.

Methodology

The KCE rapid review methodology foresees in updating a good quality SR. However, there were many recent SRs, but all with a slightly different research question or inclusion criteria, which resulted in a different selection of primary evidence per SR. Hence, we adopted a pragmatic, narrative approach. In order to give an overview of the existing evidence, we checked on which primary evidence the published SRs and meta-analyses (MA) were based upon. We only report those SRs and MA that included the most recent primary evidence (i.e. the TAILOR-PCI and POPular Genetics study in the cardiovascular field).

A search limited to Pubmed was done on the 7th of December 2023: the search string (pharmacogen* OR genotype OR guided) AND (clopidogrel OR antiplatelet OR "P2Y12"), with systematic review and meta-analysis filter and limited to reviews from 2021 onwards, resulted in 55 publications. After assessment of the title and abstract, 25 were retained for full text screening. In addition, the report on clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack, commissioned by NICE was included.¹⁸⁹

Of those 26 reviews, there were fourteen in the cardiovascular field (on acute coronary syndrome and percutaneous coronary intervention), five in the cerebrovascular field (on stroke and transient ischemic attack), one on peripheral artery disease and six more general (see Table 46). Seven were not systematic reviews and were excluded.

Results: systematic reviews and meta-analyses

Cardiovascular disease

In the field of **cardiovascular disease** (acute myocardial infarction and stenting), RCTs have been conducted and a plethora of systematic reviews and meta-analysis have been published (see appendix). In many SRs the intervention under study is "guided selection of antiplatelet". This term often combines studies investigating the genotyping approach or the platelet function tests. In our analysis we were interested in the results from the genotyping approach, though often, there was no separate analysis available for genotyping. In our pragmatic review we only reported those SRs that showed data specifically for genotyping and included the two most recent good quality RCTs, the TAILOR-PCI¹⁸⁸ and POPular Genetics.⁹⁰

The more recent (network) SRs focussed on de-escalation strategies (switching from a potent to a less potent antiplatelet or lower dose 1 month after the acute phase) (Kuno et al 2023, Kang et al 2023, Patti et al 2022, Tavenier et al 2022, Kuno et al 2022). De-escalation can either be unguided based on a standardised protocol, or this can be done via a guided selection of antiplatelet. The two SRs from **Kuno and co-authors** were the only ones which included the two most recent RCTs^{90, 188} and did a sensitivity analysis for the genotype strategy.^{181, 190} In both papers, the authors performed a network MA and concluded that the unguided de-escalation strategy is



preferred over the guided selection strategy (i.e. unguided de-escalation was associated with a decreased risk of bleeding without an increase of major cardiovascular events (MACE). The risk for of MACE between genotype and unguided de-escalation was not significant (pooled HR: 1.21, 95%CI: 0.65–2.27, n=3883), while bleeding was higher with genotyping (pooled HR: 2.04, 95%CI: 1.27–3.26, n=3883).¹⁹⁰ The results were similar when the guided selection strategy was divided into platelet function- and genotype-guided strategies.¹⁹⁰

While the above-mentioned SRs only included the RCTs with a larger sample size, there are some SRs including a wider range of RCTs (smaller pilot studies, studies with a higher risk of bias):

Malik and co-authors performed a MA comparing genotype-guided strategy to standard of care.¹⁹¹ They included seven RCTs but the comparator differed between studies (in one it is ticagrelor⁹⁰ while in others it is clopidogrel,^{188, 192} or a mix¹⁹³) as well as the outcomes (three were pilot/proof of concept studies with surrogate outcomes and limited follow-up).^{194–196} Combining these seven RCTs in a MA, the genotype guided strategy was associated with decreased MACE compared to conventional strategy (pooled RR: 0.72, 95%CI: 0.55–0.95, p=0.02, n=6204). Sensitivity analyses using “leave-one-out” analyses showed that the results might have been influenced by the PHARMCLO study.¹⁹³

Tang and co-authors also performed a MA comparing genotype-guided strategy to standard of care.¹⁹⁷ They included eleven RCTs, the ones mentioned in the Malik study supplemented with two Chinese^{198, 199} and a Saudi Arabian study.²⁰⁰ The overall MA showed a lower rate of MACE in the genotyped group (RR: 0.60, 95%CI: 0.44–0.82, p=0.001, n=11 740). A sensitivity analysis based on *ethnicity* showed that the effect was only significant in the Chinese subgroup. The effect of genotyping on MACE was only significant when in the standard of care group clopidogrel was administered, not when ticagrelor or prasugrel was used. This highlights the importance of ethnicity and the specific antiplatelet agent in the comparator group.

Yamani and co-authors compared individualised guided selection of antiplatelet therapy to standard of care in PCI patients.²⁰¹ In the general analysis genotyping and platelet function tests were combined. The sensitivity analysis with the five studies on genotyping showed a non-significant reduced risk of MACE (RR: 0.77, 95%CI: 0.56–1.08, n=9756).^{90, 188, 192, 193, 202} Their risk of bias analysis only labelled the TAILOR-PCI and POPular Genetics trial as having a low risk, though no additional sensitivity analysis was carried out.

In **Galli and co-authors'** paper on patients with a PCI,¹⁸³ the main objective was to compare guided versus standard care, with guided care encompassing both genotyping and platelet function tests. A sensitivity analysis focussing on genotyping included five RCTs^{90, 188, 192, 193, 202} and three observational studies and showed a reduced risk for MACE in the genotyped group (RR: 0.77, 95%CI: 0.59–0.99). They labelled only two studies as having a low risk of bias, but no additional sensitivity analyses were carried out. Another Galli et al paper focused on patients with acute coronary syndrome with the majority undergoing a PCI.²⁰³ A sensitivity analysis on genotyping included three RCTs,^{90, 188, 193} but was not able to show statistically significant superiority towards standard of care with clopidogrel, prasugrel or ticagrelor, as it lacked statistical power.

Cerebrovascular disease

In the field of **cerebrovascular disease** (after stroke or a TIA), the **NICE report** is the most comprehensive high quality SR.¹⁸⁹ Based on evidence assessment for several research questions, they suggested that **CYP2C19 testing** followed by tailored treatment (a higher dose of clopidogrel if there is only 1 loss of function (LOF) allele or change to alternative, e.g. aspirin or ticagrelor), **is likely to be effective**.¹⁸⁹ For the research question “*Do people who have genetic testing for clopidogrel resistance, and who are treated based on these results, have a reduced risk of secondary vascular occlusive events compared to those who are not tested and are treated with clopidogrel following standard guidelines?*”, there were only two controlled trials from China, each with a high risk of bias (Lan et al 2019 and Xia et al 2021). Both studies were small (80 and 190 patients) and reported a reduced risk, but confidence intervals were wide (HR: 0.50, 95%CI: 0.09–



2.74 and HR: 0.53, 95%CI: 0.24–1.18).²⁰⁴ The bulk of literature is on assessing whether patients with a CYP2C19 LOF allele and treated with clopidogrel have an increased risk of secondary vascular events without analysing genotyping as an intervention. Based on 20 cohort studies and 5 post-hoc analyses of RCTs, the MA stated there is strong evidence that people with LOF alleles treated with clopidogrel (or clopidogrel plus short-term aspirin) have a greater incidence of secondary vascular events (HR: 1.72, 95%CI: 1.43–2.08), stroke (HR: 1.46, 95%CI: 1.09–1.95) and ischaemic stroke (HR: 1.99, 95%CI: 1.49–2.64) than those without LOF alleles.

Most literature originates from East-Asia (Han-Chinese) and the evidence in non-East Asian populations is limited.¹⁸⁴ The **Cargnin et al.** is the most recent published SR (December 2023) with a focus on **non-east Asian studies**. This meta-analysis includes 1673 stroke/TIA patients from 8 non-East Asian observational studies. The pooled results showed that carriers of CYP2C19 LOF alleles are at significant higher risk of stroke after receiving clopidogrel-based antiplatelet therapy, compared to non-carriers (RR: 1.68, 95%CI: 1.04–2.71), and this association was scored by the authors as “moderate quality” using the GRADEpro tool. The authors conclude that these results provide **some evidence of potential clinical utility** of CYP2C19 genotyping to personalize antiplatelet therapy in non-East Asian patients with stroke/TIA, including those of European ancestry. However, this was not a study evaluating the genotyping as an intervention and, due to the limited sample size of this systematic review, further large and possibly multicentric studies enrolling stroke/TIA patients of European and other non-East Asian ancestry are warranted. Such studies are strongly needed to confirm the findings and also to investigate confounding factors for the association of CYP2C19 genotype with efficacy and safety of clopidogrel in patients with stroke or TIA.

Key points

- Most evidence is based on association studies showing a link between a certain genotype (carrier status) and effect of medicine, and thus not on PGx testing as the intervention.
- Specifically for patients with myocardial infarction and/or stenting, RCTs that investigate PGx testing before clopidogrel as an intervention are available.
 - The single RCTs were not able to show effectiveness, though one showed a reduced risk of minor bleedings.
 - However, several SRs and MAs demonstrated a potential benefit, depending on the research questions and included primary evidence. The evidence seems however only consistent in populations where CYP2C19 slow metabolisers are more common e.g Han-Chinese.
- For secondary prevention of stroke the evidence is weak as no good quality RCTs on the intervention of PGx testing are available. However, a multitude of observational studies show an association of people with a loss of function CYP2C19 allele on clopidogrel and a higher risk of secondary ischemic effects, suggesting a potential benefit. NICE concluded that genotyping followed by tailored treatment is likely to be effective.



4.2.2 A semi-preemptive panel approach – the PREPARE study

The much anticipated EU Horizon 2020 sponsored PREPARE study published its results in February 2023.²⁶ This open-label, cluster-randomised crossover trial assessed the impact of genotype-guided prescribing using a 12-gene pharmacogenetic panel, on the incidence of clinically relevant adverse drug reactions across various therapeutic areas and different health-care systems. It is the first large scale study in seven EU countries on a panel-approach, as well as the largest worldwide. The results suggest a 30% reduction of clinically relevant adverse drug reactions (not further specified) when PGx-based guidance was offered, compared to when no PGx-based guidance was offered (details in Table 11).

However, careful interpretation is warranted as several limitations were identified. Several researchers concluded that the reported benefits of pharmacogenetic testing are unclear as the effectiveness of the intervention has been overstated due to bias caused by an absence of blinding.²⁰⁵⁻²⁰⁸

The primary analysis, which was on a subgroup of **patients with an actionable variant** (22% of the total included population), showed a difference in reported ADR of 30% (27.7% in the control group with no PGx recommendations versus 21.0% in the group with recommendations). However, a similar difference in ADR was reported in the group of patients that had an **no actionable genotype** for their prescribed drug (28.8% in the control group and 21.7% in the group with test results and genotyped), which hampers the interpretation.²⁰⁹

The Cochrane risk of bias tool for cluster-randomised trials was used to assess risk of bias (see appendix).²¹⁰ This assessment showed a high risk of bias. Authors highlighted the external validity of the trial as it was set up to test feasibility, acceptability, and effectiveness of panel-based pharmacogenetic testing in a real-world setting.²⁶ The PREPARE study showed promising results, although additional studies addressing uttered concerns are necessary before broad uptake.^{208, 211}

Key points on evidence on (preemptive) panel testing

The PREPARE study is the first European large trial on PGx panel-testing, a (semi) preemptive approach promoted by PGx experts. However, in this study a 30% reduction in clinically relevant adverse drug reactions was not only seen after PGx-based guidance, but also in the group without actionable gene-variants noted. This observation hinders the interpretation of the study results.



Table 11 – Details on the PREPARE trial

PICO	
Population	Patients were recruited in Austria (Medical University of Vienna), Greece (Psychiatric Clinic, University of Patras General Hospital and 2nd Psychiatric Clinic, ATTIKON University General Hospital, Athens), Italy (three sites of the Medical Oncology Department of the Centro di Riferimento Oncologico Aviano; Department of Medical Oncology, San Filippo Neri Hospital; and Department of Medical Oncology, Cà Foncello Hospital, Treviso), the Netherlands (28 community pharmacies and the neurology department of the Leiden University Medical Centre), Slovenia (six community health centres; five clinics and hospitals), Spain (San Cecilio University Hospital, Granada; Hospital Universitario Virgen de las Nieves, Granada; Zaidín South Primary Care centre, Granada; and Zaidín Speciality Centre, Granada), and the UK (The Royal Liverpool University Hospital; Vauxhall Primary Health Centre; and Fulwood Green Medical Centre, all in Liverpool; Patients were assessed for eligibility by the treating physician or pharmacist. Patients aged 18 years or older who were receiving a first prescription (defined as no prescription for the drug in the preceding 12 months) for a drug that had an actionable recommendation in the DPWG as part of routine care. Exclusion criteria included previous genetic testing (direct-to-consumer or clinical) for a gene relevant to the index drug, a planned duration of treatment less than 7 consecutive days, and severe renal or liver insufficiency.
Intervention	No randomization on patient level, but the country was randomized. Within each country a cross-over was foreseen so every country had a period with the intervention and a control period. Providing DPWG recommendations relevant for a prescribed medicine based on a patient's genotype (for example lower dose, change medicine...). The aim was to deliver the recommendations within 7 days after taking the DNA sample. Panel at the start of the study comprised 50 germline-variant alleles, located within 12 genes (CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1, VKORC1) The adoption of the DPWG recommendations was high, and overall 69.9% of these recommendations were accepted by the physicians and pharmacists. However there was no specific analysis reported on whether the provided guidelines were followed and the therapy was changed. Moreover, in order to reflect the real-world aspects of the intervention, pharmacogenetic guidelines were updated throughout the study, and the panel composition changed.
Comparator	The control patients received standard clinical care and a plastic card indicating their participation in the PREPARE study (in place of a Medication Safety Code card). Genotyping of patients in the control group was done after completion of follow-up.
Outcome	The outcome was binary, and reports the incidence of an adverse drug reaction attributed to the prescribed drug in the 12- weeks follow-up. Patients were contacted at baseline (t=0, plus or minus 1 week), 4 weeks (plus or minus 2 weeks), 12 weeks (plus or minus 3 weeks), and at the end of the time block (plus or minus 4 weeks) to go through a scripted questionnaire and to collect data on the occurrence and severity of adverse drug reactions. While the ADRs were self-reported by the patient, a trained physician or pharmacist from the local study team assessed severity and causality of the ADR with a standardized method, Common Terminology Criteria for Adverse Events (CTCAE) and Liverpool Causality Assessment Tool (LCAT), respectively. If a patient reported multiple ADRs within the 12-week follow-up period, the most severe causal adverse drug reaction was used for the primary analysis.



4.3 Ongoing RCTs

We performed a search in the Clinicaltrials.gov website with the search terms “(RCT OR Randomized OR Randomised) AND (pharmacogenomics OR Pharmacogenetics OR pharmacogenomic OR pharmacogenetic OR Pgx or Pgt)”. This search yielded 296 hits, of which 51 were classified as ongoing (Not yet recruiting, active not recruiting or recruiting). Among these 24 had PGx testing as the trial intervention.

The areas that are concerned by ongoing trials are:

- **Psychiatric disease:** 10 RCTs
- **Pain management:** 4 RCTs
- **Preemptive panel testing** across specialties: 3 RCTs
- **Oncology:** 3 RCTs
- **Perioperative management:** 2 RCTs
- **Anticoagulant treatment:** 1 RCT
- **Asthma treatment:** 1 RCT

Among these trials, 5 plan to include 1500 patients or more (see Table 12).

Table 12 – PICO of ongoing RCTs in pharmacogenetics enrolling more than 1500 patients

Trial info	Population	Intervention	Comparator	Outcome	Recruitment	Planned end date
ADOPT Pgx (depression) NCT05966155 USA	Patients older than 8y with at least 3 months of depressive symptoms requiring new or revised antidepressants	Genetic testing of CYP2D6 and CYP2C19. Therapy guided by PGx data based on existing CPIC guidelines from the	Care as usual. Delayed genetic testing (after 6 months)	3 Month Depression Symptom Control Change from Baseline	1512 (branch of the ADOPT study, total number of planned included patients: 4509) Several locations in USA	30/04/2024
ADOPT Pgx £(acute pain) NCT05966129	Patients older than 8y. Elective/planned surgery types with planned or anticipated to be treated with tramadol, hydrocodone, or codeine pain management	Genetic testing of CYP2D6 and CYP2C19. Therapy guided by PGx data based on existing CPIC guidelines	Care as usual. Delayed genetic testing (after 6 months)	10 Day Silverman Integrated Analgesic Assessment SIA Score Change from Baseline	993 (branch of the ADOPT study, total number of planned included patients: 4509) Several locations in USA	30/04/2024
ADOPT Pgx (chronic pain) NCT05966142	Adults with history of pain for at least the last 3 months Currently treated or being considered for treatment with tramadol, hydrocodone,	Genetic testing of CYP2D6 and CYP2C19. Therapy guided by PGx data based on existing CPIC guidelines	Care as usual. Delayed genetic testing (after 6 months)	3 Month Pain Control Change from Baseline	2400(branch of the ADOPT study, total number of planned included patients: 4509)	30/04/2024



Trial info	Population	Intervention	Comparator	Outcome	Recruitment	Planned end date
	or codeine to improve pain management				Several locations in USA	
IMPRESS Trial NCT03729180	Adult patients who have planned elective surgical procedures at the University of Chicago	Preemptive genotyping. A Genomic Prescribing System (GPS) produces a profile describing drugs that may be high-risk, those that should be used with caution, or drugs that are favourable to use.	Care as usual . Genotyping results will be at the 6-month unblinding timepoint	The frequency of GPS use by providers during the perioperative period. Rate of high-risk drug use in perioperative setting	1900 participants University of Chicago, USA	22/8/2025
PsyPgx NCT05656469	Patients between 16 and 65 suffering from a depressive and/or anxiety disorder of at least moderate intensity and have had an inadequate response to at least one psychotropic treatment	Personalised medication advice based on pharmacogenetic testing	Dosing as usual	Patient recovery, as assessed using the Patient Recovery Assessment scale - Domains and Stages (RAS-DS) at 24 weeks	2500 participants The Netherlands USA, Germany, Spain, UK, Serbia, Romania)	March 2025
Personalised Therapeutics @LUMC NCT05508763	Adults undergoing medication verification in the LUMC hospital	Preemptive panel (14 pharmacogenes)	Standard of care	occurrence of drug-genotype associated ADR in the first 12 months . The outcome is dichotomized at $\geq$ grade 3 CTC-AE	2000 participants The Netherlands – Leiden university medical centre	Oct 2024
GENPAD study NCT04619927	Patients with peripheral arterial disease consulting a vascular surgeon for diagnosis and/or treatment, receiving clopidogrel according to the guidelines	Testing for CYP2C19*2 and *3 LoF PM: rivaroxaban+acetylsalicylic acid IM: 2 times clopidogrel 75mg NM: 75mg clopidogrel	75mg clopidogrel without PGx guidance	Occurrence of adverse clinical events related to arterial thrombosis at 24 months	2276 participants 11 hospital sites in The Netherlands	Dec 2024

CPIC: Clinical Pharmacogenetics Implementation Consortium, PM: poor metaboliser, IM: intermediate metaboliser, NM: normal metaboliser.



5 EVIDENCE ON THE COST-EFFECTIVENESS OF PHARMACOGENETICS TESTING

5.1 Methods

5.1.1 Search strategies

A systematic search was performed in 08/2023 to retrieve studies about the cost-effectiveness of pharmacogenetic (PGx) testing published from 2010 until the search date. The following databases were searched: the international INAHTA (International Network of Agencies for Health Technology Assessment) HTA database, the CRD (Centre for Reviews and Dissemination) NHS EED (National Health Service Economic Evaluation Database) database, Medline(Ovid) and Embase. A grey literature search for HTAs was also performed on the websites of the HTA-agencies listed on the INAHTA website.

For the economically oriented databases (INAHTA HTA and NHS EED) the MeSH term "Pharmacogenetics"[mh] was used. For the medical databases (Medline and Embase), PGx-related MeSH/EMTREE terms and text words were combined with a broad range of economic filters. For the search on the HTA agencies websites, the text words "Pharmacogenomic*" and "Pharmacogenetic*" were used. Appendix 4.1 details the literature search strategies and terms used.

5.1.2 Eligibility criteria

The selection criteria in terms of population, intervention, comparator, and design are listed in Table 13.

Only full economic evaluations were considered, i.e. studies comparing at least two alternative treatments in terms of both costs and health outcomes. Cost-minimization analyses (CMA), cost-utility analyses (CUA, with results expressed as incremental cost per quality-adjusted life year (QALY) gained), cost-effectiveness analyses (CEA, with results expressed as incremental cost per life-year (LY) gained), cost-benefit analyses (CBA, with a monetary valuation of health outcomes), and cost-consequence analyses (CCA^{cc}) were eligible. Partial economic evaluations such as cost-comparisons or cost-description (both not considering health outcomes) were not eligible. Both primary and secondary studies (reviews of economic evaluations) were relevant. HTA reports were selected when they included a review of full economic evaluations and/or an original economic model.

Letters, news and editorials were removed. Only articles published in English were considered.

5.1.3 Literature screening

All retrieved references were assessed against the pre-defined selection criteria listed in Table 13. The selection was performed in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment if the title, abstract or keywords suggested relevant information, or if no abstract was available. Study selection was performed by one researcher, and a second researcher was involved in case of doubt.

The reference lists of selected articles were scrutinized for additional relevant reference.

^{cc} CCAs examine incremental costs and consequences, without the necessity of focusing on a single consequence and without combining disparate consequences into a single, commensurable measure.

**Table 13 – Selection criteria for the economic evaluations**

	Inclusion criteria	Exclusion criteria
Population	Adults	Children or adolescents
Intervention	Germline PGx testing (single/multiple-gene tests, reactive or preemptive)	Somatic mutations for cancer targeted therapies
Comparator	Non-PGx-guided treatment (standard of care) Germline PGx testing *	Other
Design	Full economic evaluations and reviews of economic evaluations	Other designs (e.g. cost-comparisons, cost-description)
Other	North-western countries	Developing countries, Asia

*PGx: pharmacogenetic. * Economic evaluations where e.g. reactive versus preemptive PGx approaches or multi- versus single-gene testing are compared.*

5.1.4 Literature search results

The database search of the economic literature yielded 255 unique citations published between 2010 and 08/2023. Four (4) additional citations were identified from other sources, for a total of 257 citations after removing duplicates. Among those citations were 2 recent and comprehensive systematic reviews of the literature, evaluating the cost-effectiveness of PGx testing for a broad range of gene-drug pairs and therapeutic area. In Turongkaravee et al. (2021),²¹² the literature was searched from database inception up to 10/2019 and 59 full economic evaluations were reviewed. In Morris et al. (2022),²¹³ the literature was searched until 06/2021 and 108 full economic evaluations were reviewed.

The methodology of the current review was thus revised and restricted to an update of both reviews, considering articles published after 06/2021.

Of the 257 citations identified in our initial literature search (with publication date between 2010 and 08/2023), 48 were published after 06/2021. Thirty-two (32) citations were excluded based on information in the title and abstract (most of which were not an economic study) and 16 were potentially relevant for full-text assessment. Fifteen (15) studies met the inclusion criteria: 8 reviews of the literature and 9 primary economic evaluations. Of note, 2 HTAs included both a review of the literature and a primary economic evaluation.^{214, 215} The flow chart of the selection process can be found in a. An update of the search was performed in 01/2024 and retrieved another full economic evaluation published in late 2023. In 02/2024 another full economic evaluation was identified and included.²¹⁶

5.2 Overview of the economic studies included

The main characteristics of the 8 literature reviews are presented in Table 15. A total of 138 unique primary economic evaluations were covered by those reviews (see appendix 4.2 for the list of articles covered in each review). The 11 additional full economic evaluations published after 06/2021 are briefly described in Table 16. In Table 14 a summary of the available economic evidence per therapeutic area is presented.

Table 14 – Available economic evidence per therapeutic area

Disease area	Literature reviews	Economic evaluations covered by the reviews	New economic evaluations (> 06/2021)	Total number of economic evaluations
CVD/CeVD	5	56	5	61
Psychiatry	5	21	4	25
Oncology	2	10	2	12
Auto-immune	2	12	-	12
HIV	2	12	-	12
Gout	2	10	-	10
Epilepsy	2	8	-	8
Other	2	9	-	9
Total	-	138	11	149

CVD: cardiovascular. CeVD: Cerebrovascular disease.



Table 15 – Selected reviews of economic evaluations of PGx testing (published since 2021)

Author	Year	Country	Disease area	Drug	Gene	Economic evaluations reviewed and time covered
Several therapeutic area						
Morris et al. ²¹³	2022	USA	Multiple diseases	All gene-drug pairs with CPIC level A or B evidence and published guidelines		108 economic evaluations DB inception to 06/2021
Turongkaravee et al. ²¹²	2021	Thailand	Multiple diseases	All relevant gene-drug pairs aimed at preventing adverse drug reactions		59 economic evaluations DB inception to 10/2019
Psychiatric disorders						
Young et al. ²¹⁷	2023	Canada	Psychiatric disorders	Psychotropic drugs	CYP, HLA	1 review of 18 EE and 1 EE 01/2020 to 01/2023
Karamperis et al. ²¹⁸	2021	USA	Psychiatric disorders	Psychotropic drugs	All relevant genes	18 economic evaluations DB inception to 08/2020
Ontario Health Quality HTA ²¹⁴	2021	Canada	Major depressive disorder	All relevant drugs	All relevant genes	4 economic evaluations DB inception to 01/2020
Cardiovascular and cerebrovascular diseases						
Bristol TAG HTA (NICE) ¹⁸⁹	2023	UK	Minor stroke Transient ischaemic attack	Clopidogrel	CYP2C19	5 economic evaluations DB inception to 08/2022
Kamil et al. ²¹⁹	2022	USA	Atrial fibrillation	Warfarin, acenocoumarol, phenprocoumon	CYP2C9/ VKORC1	18 economic evaluations DB inception to 06/2020
Lim et al. ²²⁰	2021	UK	Venous thromboembolism	Warfarin, acenocoumarol	CYP2C9/VKORC1	3 economic evaluations DB inception to 06/2020

CPIC: Clinical Pharmacogenetics Implementation Consortium, DB: database, EE: economic evaluation



Table 16 – Selected primary economic evaluations of PGx testing (published since 2021)

Author	Year	Type of economic evaluation	Country	Disease area	Drug	Gene	Single or panel test
Several therapeutic area							
van der Wouden et al. ¹⁶⁰	2022	Mathematical model CCA	Netherlands	All areas related to drug-gene pairs categorised as 'essential' by DPWG	Clopidogrel, capecitabine, systemic fluorouracil, azathioprine, tioguanine mercaptopurine, irinotecan	CYP2C19, DPYD, TPMT, UGT1A1	Single
Psychiatric disorders							
Skokou et al. ²¹⁶	2024	Piggyback CUA	Greece	Major depressive disorder	Amitriptyline, Aripiprazole, Carbamazepine, Citalopram, Clomipramine, Doxepine, Escitalopram, Haloperidol, Paroxetine, Pimozide, Sertraline, Venlafaxine, Zuclopenthixol	CYP2C19, CYP2D6	Panel *
Carta et al. ²²¹	2022	Markov model CUA	Italy	Major depressive disorder	Antidepressants	CYP2C19, CYP2D6	Single
Ninomya et al. ²²²	2022	Markov model CUA	UK	Schizophrenia	Clozapine	HLA-DQB1, HLA-B, SLCO1B3, SLCO1B7	Panel
Ontario Health Quality HTA ²¹⁴	2021	Markov model CUA	Canada	Major depressive disorder	Antidepressants	GeneSight (Myriad)	Commercially available panel
Cardiovascular and cerebrovascular diseases							
Dong et al. ²²³	2023	Decision tree CUA	USA	Acute coronary syndrome post-percutaneous coronary intervention	Clopidogrel	CYP2C19	Single
Koufaki et al. ²²⁴	2023	Piggyback CUA & CEA	Spain	Acute coronary syndrome	Clopidogrel	CYP2C19	Single *
Bristol TAG HTA (NICE) ¹⁸⁹	2023	Markov model CUA	UK	Stroke, transient ischaemic attack	Clopidogrel	CYP2C19	Single
Claasens et al. ²²⁵	2022	RCT-based CUA	Netherlands	Acute coronary syndrome	Clopidogrel	CYP2C19	Single
Oncology							
Fragoulakis et al. ²²⁶	2023	Piggyback CUA	Italy	Colorectal cancer	Fluoropyrimidines and/or irinotecan	DPYD/UGT1A1	Panel *
Brooks et al. ²²⁷	2022	Markov model CUA	USA	Colorectal cancer	Fluoropyrimidines	DPYD	Single

* Economic evaluations performed alongside the PREPARE study that investigated a (semi) preemptive PGx panel test of 12 genes. In the economic evaluations, only 1 or 2 of the panel's genes are used reactively and assessed. CCA: cost-consequence analysis, CEA: cost-effectiveness analysis, CUA: cost-utility analysis.



5.3 Review of the literature

5.3.1 Economic evaluations of pharmacogenetic testing in multiple therapeutic area

5.3.1.1 Morris et al. 2022

In 2022, Morris et al.²¹³ performed an extensive systematic review of economic evaluations of PGx-guided treatment for all drugs with CPIC level A or B evidence and with published guidelines as of 06/2021. A total of 108 economic evaluations were identified, covering 39 drugs. Most studies were conducted in North America (n=51, 47%), followed by Europe (n=26, 24%), Asia (n=28, 26%), and Australia (n=3, 3%). Multigene testing was evaluated in 28 studies (26%), mostly for warfarin or antidepressant treatments.

Of the 108 studies included, 44% demonstrated pharmacogenetic testing was cost-effective, 27% cost-saving, 20% not cost-effective, and 9% uncertain. **Hence 71% of the economic evaluations found PGx-guided treatment to be cost-effective (n=48) or cost-saving (n=29).**

Clopidogrel had the most publications (n=23) with 96% (n=22) concluding that CYP2C19 genotyping was cost-effective or cost-saving in cardiovascular diseases (CVD). Also in CVD, warfarin had 16 economic evaluations on the cost-effectiveness of CYP2C9 / VKORC1 testing with mitigated results as only 44% (n=7) of the studies suggested cost-effectiveness. HLA testing for abacavir (HIV n=8), allopurinol (gout n=10) and carbamazepine (epilepsy n=8) was evaluated in 26 studies. Cost-effectiveness could only be demonstrated for the **abacavir**-HLA-B*51:01 drug-gene pair for HIV in the 6 European/North American studies (the other 2 being Asian studies and not cost-effective). Thiopurines and TPMT for autoimmune diseases had 11 studies, of which 8 (73%) suggested cost-

effectiveness or cost-saving. The 9 studies evaluating multi-gene testing for **antidepressant** all concluded that testing was cost-effective or cost-saving, while the 2 studies based on single-gene testing concluded to cost-ineffectiveness. In oncology, the 5 studies evaluated testing DPYD for **fluoropyrimidines** all concluded to cost-effectiveness or cost-saving, while results for CYP2D6 and tamoxifen (n=3) were uncertain.

Morris et al.²¹³ did not conclude on the following gene-drug pairs for which evidence was considered too scant: CYP2B6-efavirenz for HIV (n=2), CYP2C19 for the antifungal voriconazole (n=2), IFNL3 (IL-28B) and Peg IFN alpha (n=2), mt-RNR1 and tobramycin (aminoglycosides, n=1), CYP2D6-codeine (n=1), CYP2C19-omeprazole/lansoprazole (n=1), and UGT1A1-atazanavir (n=1).

The quality of the economic evaluations was appraised with the Quality of Health Economic Studies (QHES^{dd}) tool.²²⁸ For each study Morris et al.²¹³ answered the 16 questions of this questionnaire and reported a summary score on a scale from 0 (poor quality) to 100 (excellent quality). The quality of the studies was rated high with a score above 75/100 in 87% of the studies (94/108 studies). More specifically, the relevance of the data used for clinical effectiveness in the economic evaluations was appraised with this question of the QHES tool: "Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?" Unfortunately, the answer to this specific question and the related rating were not separately reported. On this topic, Morris et al.²¹³ mention that of the 108 studies included, 75 (69%) used hypothetical populations (which may not translate to real-world practice) with model parameter estimates derived from previously published randomized controlled trials or observational studies; and that 7 studies (6%) were economic evaluations done alongside a RCT.

^{dd} The Quality of Health Economic Studies (QHES) instrument evaluates the studies against sixteen criteria: study characteristics (funding information, patient subgroups, time horizon), study design (variable estimation, perspective), findings, conclusions, and discussion (sensitivity analysis,

reliability of costs and outcomes, economic model, bias assessment, limitations, and future recommendations). The QHES checklist generates a score between 0 and 100, while a score of 75 and more is of the highest quality.



5.3.1.2 Turongkaravee et al. 2021

In 2021, Turongkaravee et al.²¹² reviewed the economic literature of PGx testing for the prevention of adverse drug reactions (ADR), for the gene-drug pairs listed in the clinical practice guidelines from CPIC, DPWG, or CPNDS. As of 10/2019, 59 economic evaluations published between 2002 and 2018 were identified. Two third of the studies were conducted in Europe and North America (73%, n=43), while only one third were in Asia mainly on HLA genotyping for allopurinol and carbamazepine.

Results were similar to those reported in Morris et al.²¹³ **Clopidogrel** had 9 publications, all concluding that CYP2C19 was cost-effective in CVD. Warfarin had 14 studies reporting mitigated results for CYP2C9/VKORC1 testing with only 64% of studies (n=9) suggesting cost-effectiveness. For HLA testing, cost-effectiveness could be demonstrated for HIV patients treated with **abacavir** (6 European/North American studies), but results were uncertain for allopurinol in patients with gout (n=8) and for carbamazepine (n=6) in epileptic patients. The cost-effectiveness of TPMT testing before thiopurines for autoimmune diseases was mitigated with 62.5% of the studies (5/8) reporting cost-effectiveness or cost-saving.

For the following gene-drug pairs, economic evidence was too scant to draw conclusion: UGT1A1-irinotecan (n=2) and DPYD-fluoropyrimidines (n=1) in oncology, CYP2B6-efavirenz for HIV (n=1), CYP2D6-notriptyline in depression (n=1), and Factor V Leiden and estrogen (n=1).

Turongkaravee et al.²¹² indicated that results were mostly sensitive to the effectiveness of PGx testing to prevent ADRs, followed by the probability of drug induced-ADRs, the cost of testing, and the cost of alternative drugs in patients who tested positive.

The quality of evidence for input parameters used in the economic evaluations was assessed using the hierarchy of data sources.²²⁹ Inputs were evaluated and given a rank ranging from 1 to 6. For the clinical effect sizes, the following rank was given if the input data were obtained from:

- rank 1+: meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes,
- rank 1: single RCT with direct comparison between comparator therapies, measuring final outcomes,
- rank 2: single RCT with direct comparison between comparator therapies, measuring surrogate outcomes,
- rank 3: single placebo-controlled RCTs with similar trial population, measuring surrogate outcomes,
- rank 4: case-control or cohort studies,
- rank 5: non-analytical studies (e.g. case report or case series),
- rank 6: expert opinion.

Turongkaravee et al.²¹² report that data sources to estimate the **clinical effectiveness of PGx testing** to prevent ADRs were very **limited** and of **low quality** as only 27% of the studies (16/59) obtained effectiveness data from RCTs with direct comparison (high-quality evidence, rank 1): the PREDICT-1²³⁰ and the ARIES^{ee 231} trials for HLA-abacavir in HIV, the TARGET²³² trial for TPMT-azathioprine, the COUMAGEN²³³ trial for CYP2C9/VKORC1-warfarin and the substudy of the PLATO^{ee 234, 235} trial for CYP2C19-clopidogrel. Yet, of these RCTs, few supported pharmacogenetic testing to prevent severe ADRs induced by abacavir (PREDICT-1). The other RCTs failed to demonstrate any significant effect in ADR. Another group of 8 (14%) studies obtained clinical effectiveness data from a meta-analysis of case-control studies with direct comparison (not listed in the

^{ee} Although Turongkaravee et al.²⁰⁸ classify the ARIES and PLATO trials as rank 1 RCTs with direct comparison, they do not have PGx testing as the trial intervention (see below for a description of those trials).



hierarchy of data sources). Estimates for clinical effectiveness from the remaining studies were poor, with 29 (49%) studies retrieving evidence from case-control or cohort studies (rank 4), 2 (3%) from expert opinion and 4 (7%) being unclear about their data sources.

For health state utilities, data were mostly (93%) obtained from previous studies in which utilities were measured directly in patients with the disease of interest.

5.3.1.3 *van der Wouden et al. 2022*

The 2022 Dutch study by van der Wouden et al.¹⁶⁰ is an economic evaluation of selected gene-drug pairs categorized as essential in the DPWG guidelines and with the potential of a gene-drug related death. Interactions between four single genes and seven drugs were selected (Table 17). This is a cost-consequence analysis^{ff} with clinical effectiveness measured in terms of death prevented.

Table 17 – Selected gene-drug pairs

Gene	Drug	Indication
CYP2C19	clopidogrel	PCI, stroke, TIA
DPYD	capecitabine, fluorouracil	Oncology
TPMT	azathioprine, mercaptopurine, tioguanine	Irritable bowel syndrome
UGT1A1	irinotecan	Oncology

Source: van der wouden et al.¹⁶⁰ PCI: percutaneous coronary intervention, TIA: transient ischemic attack.

^{ff} In cost-consequence analyses (CCA), health outcomes are measured in (several) natural units instead of life-years gained (as in a cost-effectiveness analysis) or quality-adjusted life year gained (as in a cost-utility analysis).

A mathematical model was developed comparing PGx-guided treatment versus standard care to avoid gene-drug-related deaths from a 1-year Dutch health care payer (HCP) perspective.

On a population of 17 million Dutch inhabitants, it was estimated that 148 128 would initiate 1 of the 7 selected drugs in a given year – clopidogrel being the most frequently initiated drug (80% of the drug initiators), and would be tested with single-gene tests. Of all drug initiators, van der wouden et al.¹⁶⁰ estimated that 35 762 (24.1%) would have an actionable drug-gene-interaction, requiring an alternative dose or drug.

Compared with treatment as usual, the PGx strategy resulted in a net additional cost of €21.4 million: €19.4 million for the single-gene tests (mean €131 per patient), €0.5 million for the interpretation of the actionable results and €1.5 million for the alternative drug or dose (€2.4 million additional costs as a result of alternative drug treatment and €0.9 million saved as a result of dose lowering). The PGx strategy further resulted in 419 deaths avoided (roughly 0.3% of the drug initiators), Table 18. Van der Wouden et al.¹⁶⁰ concluded that nation-wide adoption of a PGx-guided strategy for essential drug-gene-interactions can potentially save the lives of patients at reasonable extra costs.

A strong limitation in van der Wouden et al.¹⁶⁰ is the estimates for the 1-year risks of gene-drug related death that were based on studies measuring intermediate outcomes and not on drug-induced mortality. Further, the clinical impact of PGx testing to prevent gene-drug related death was extracted from observational studies. Ideally, these would be extracted from (very large) RCTs directly comparing PGx intervention to standard of care.

When computed, the resulting ICERs of CCA are thus not comparable with those of other full economic evaluations, and they further cannot be appraised against conventional ICER thresholds. Incremental costs and incremental effects are thus usually considered in disaggregated form.

**Table 18 – Total incremental costs and number of deaths prevented per gene-drug tested**

Drug (gene tested)	Total number of drug initiators	Total incremental costs PGx vs standard care*	Total number of deaths prevented	Results per person	
				Incremental costs	Deaths prevented
Azathiopirine (TPMT)	6979	€854 659	2.3	€122	0.0003
Capecitabine (DPYD)	886	€775 246	1.8	€875	0.0020
Clopidogrel (CYP2C19)	117 900	€18 923 430	410.8	€161	0.0035
Fluororacil (DPYD)	6765	€880 112	1.4	€130	0.0002
Irinotecan (UGT1A1)	2593	-€481 019	0.6	-€186	0.0002
Mercaptopurine (TPMT)	2177	€114 172	0.7	€52	0.0003
Tioguanine (TPMT)	2854	€359 471	0.9	€126	0.0003
Total	148 128	€21 426 070	419	€145	0.0028

Source: van der Wouden et al. 2022¹⁶⁰ * Total direct costs of the PGx testing strategy (costs of the tests, interpretation of the actionable results, drugs treatment) minus total direct costs of standard care (drugs treatment costs).

5.3.2 Economic evaluations of pharmacogenetic testing in cardio/cerebrovascular diseases

We identified 5 reviews (with publication dates between 2020 and 2023) of economic evaluations assessing PGx-testing to guide treatment for cardiovascular or cerebrovascular events. A total of 56 unique references were covered by those reviews: 5 in the Bristol TAG HTA for NICE,¹⁸⁹ 41 in Morris et al.,²¹³ 18 in Kamil et al.,²¹⁹ 23 in Turongkaravee et al.²¹² and 3 in Lim et al.²²⁰

We further identified 4 primary economic evaluations published after the most recent search date of the reviews (06/2021), all of them evaluating CYP2C19-testing to guide antiplatelet therapy: Koufaki et al.,²²⁴ Dong et al.²²³, Bristol TAG HTA¹⁸⁹ and Claassens et al.²²⁵

The reviews by Kamil et al.²¹⁹ and Lim et al.²²⁰ focused on economic evaluations of CYP2C9 and VKORC1 PGx testing when prescribing warfarin to patients with atrial fibrillation or venous thromboembolism. Warfarin drug

therapy has been established for decades but its use is now drastically declining because of the discovery of new anticoagulants. The results for the cost-effectiveness of PGx testing for warfarin can be found in appendix.

5.3.2.1 Reviews of economic evaluations

The **Bristol TAG HTA for NICE**¹⁸⁹ reviewed 5 CEA of CYP2C19-testing for guiding clopidogrel treatment after an ischaemic stroke or a transient ischaemic attack (TIA). The 5 studies were published between 2020 and 2023 and were assessed to be of high quality. Most models used a decision tree structure for the short-term impacts of CYP2C19 testing followed by a long-term Markov model. The Bristol TAG review is narrative, describing each study separately without presenting a critical assessment of the studies' results. The 5 studies found that CYP2C19 testing is likely to be cost-effective. NICE's major concern about those results is that the clinical evidence on which those models rely is weak as no good quality RCT on CYP2C19-testing for clopidogrel in cerebrovascular diseases are available.

**Table 19 – Reviews of economic evaluations of PGx testing in cardiovascular/cerebrovascular diseases**

Reference	Disease area	Review period	Drug	Gene	# EE	Review main conclusion
Clopidogrel (27 unique economic evaluations: 22 in cardiovascular disease, 5 in cerebrovascular disease)						
Morris et al. ²¹³ 2022, USA	Cardiovascular disease	up to 06/2021	Clopidogrel	CYP2C19	23	Cost-effective (22 studies CE or CS, 1 not CE)
Turongkaravee et al. ²¹² 2021, Thailand	Cardiovascular disease	up to 10/2019	Clopidogrel	CYP2C19	9	Cost-effective (all 9 studies)
Bristol TAG HTA (NICE) ¹⁸⁹ 2023, UK	Cerebrovascular disease (minor stroke, TIA)	up to 08/2022	Clopidogrel	CYP2C19	5	"CYP2C19 testing is likely to be cost-effective."
Multiple cardiovascular medications (3 unique economic evaluations)						
Morris et al. ²¹³ 2022, USA	Cardiovascular disease	up to 06/2021	Warfarin, Clopidogrel, Simvastatin	CYP2C9/VKORC1, CYP2C19, SLCO1B1	2	Cost-effective
Turongkaravee et al. ²¹² 2021, Thailand	Cardiovascular disease	up to 10/2019	Statins	Hypothetical PGx test *	1	Cost-effective

* Hypothetical test assumed to be perfect. CE: cost-effective, CS: cost-saving, EE: economic evaluation, HTA: health technology assessment, TIA: transient ischaemic attack.

5.3.2.2 Primary economic evaluations

Since the search date limit (06/2021) of the Morris et al.²¹³ review, 5 new economic evaluations of CYP2C19 testing to guide clopidogrel treatment for cardiovascular or cerebrovascular diseases have been published.^{160, 189, 223-225} Patients who underwent PGx testing and had an actionable phenotype due to a variation in the CYP2C19 gene had either a dose adjustment or an alternative drug (ticagrelor, prasugrel or dipyridamole) to reduce the risk of death and other less severe adverse drug reactions. The comparator to PGx-guided treatment was conventional antiplatelet treatment without PGx.

With the exception of Van der Wouden et al.,¹⁶⁰ all studies were full economic evaluations, measuring health outcomes in QALYs (CUA), and also in LY (CEA) in Koufaki et al.²²⁴ The study by Van der Wouden et al.¹⁶⁰ was a CCA with health outcomes expressed in terms of death averted (see also supra). All studies adopted a HCP perspective, considering direct medical costs only.

Two economic evaluations were conducted alongside clinical studies, hence collecting clinical and economic data directly from them, i.e. the (Spanish sites) of the PREPARE study for Koufaki et al.²²⁴ and the POPular Genetics RCT for Claassens et al.²²⁵ In Koufaki et al.²²⁴ the time horizon of the

economic evaluation was limited to the trial duration (18 months). In Claassens et al.²²⁵ data from the 1-year duration POPular Genetic trial were extrapolated in a lifelong Markov model. The modelling techniques were a 1-year-time decision-tree in Dong et al.²²³ and a lifelong Markov model in Bristol TAG HTA.¹⁸⁹ A mathematical model was used in Van der Wouden et al.¹⁶⁰

The relative effects of a CYP2C19 genotype-guided strategy compared with a strategy without PGx were measured by cardiovascular events (bleeding, myocardial infarction, stroke) and mean survival. In Koufaki et al.²²⁴ and in Claassens et al.,²²⁵ these effects were directly obtained from the PREPARE study and POPular Genetics RCT. In Dong et al.,²²³ data were extracted from the TAILOR-PCI and the POPular Genetics RCTs. In the Bristol TAG HTA, which focuses on cerebrovascular events,¹⁸⁹ model inputs were derived from their clinical effectiveness review that highlighted the CHANCE and CHANCE-2 studies as the most appropriate sources for relative efficacies. However, in none of those studies was PGx the trial intervention and evidence was based on association studies showing a link between loss-of-function status and drug effect. In van der Wouden et al.¹⁶⁰ the risks of death were extracted from observational studies^{236, 237} reporting intermediate outcomes.



Sources used in the economic evaluations to estimate the relative effects of CYP2C19 testing for clopidogrel

Studies directly comparing different testing and targeted treatment strategies (PGx is the trial intervention)

- The Spanish sites of the PREPARE²⁶ (see chapter 0) totalled 243 patients suffering from ACS: 113 in the PGx group and 130 in the control group. Effectiveness results for the Spanish population on the specific CYP2C19-clopidogrel pair were not reported.
- POPular Genetics⁹⁰ (Patient Outcomes after primary PCI) is an open-label, multicenter RCT in 2488 patients with myocardial infarction undergoing primary PCI: 1242 in the PGx group and 1246 in the control group. POPular Genetics demonstrated that CYP2C19 testing for selection of oral P2Y₁₂ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a **lower incidence of bleeding** (minor bleedings).
- TAILOR PCI¹⁸⁸ is an open-label, multicentre RCT that included 5302 patients undergoing PCI, with 2652 patients in the PGx-guided group and 2650 patients in the conventional clopidogrel therapy group. TAILOR PCI found **no statistically significant difference** between the PGx-guided and the control groups in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia at 12 months.

Studies stratifying outcomes on allele carrier status (LOF/No LOF)

- PLATO²³⁵ is a prospective double-blind RCT of ticagrelor vs. clopidogrel for the treatment of ACS. The PLATO genetic substudy used genetic samples from 10 285 patients and compared clopidogrel vs. ticagrelor for CYP2C19 LOF and no LOF variant.
- CHANCE²³⁸ compares clopidogrel and aspirin vs. aspirin alone for Asian patients with acute cerebrovascular events. A secondary

analysis of a subpopulation of the study (73/114 sites) stratified results among LOF and non LOF patients.

Studies carried out only on carriers of LOF alleles

- CHANCE-2²³⁹ is a multi-centre (Asia), placebo-controlled trial that compares ticagrelor versus clopidogrel in LOF patients with acute cerebrovascular events.

Utility weights describing the health-related quality of life associated with different health states were directly collected from the POPular Genetics trial in Dong et al.,²²³ with the EQ-5D-5L questionnaire administered to both arms of the trial. In the other three cost-utility analyses^{189, 224, 225} utility weights were extracted from the literature.

The CUAs all reported that, for their base-case analysis, a CYP2C19 genotype-guided strategy resulted in a decrease in health care costs (cost-savings) and generated more QALYs compared with a strategy without PGx testing. Decreases in health care costs ranged between \$530 (roughly €480) to £1640 (roughly €1880) per patient and were statistically significant. The mean gains in QALYs were small (ranging 0.0027 to 0.17 per person) but **statistically significant** based on the incremental cost-effectiveness planes shown in Dong et al.,²²³ Claassens et al.,²²⁵ and in the Bristol TAG HTA.¹⁸⁹ In Koufaki et al.²²⁴ (PREPARE) the incremental cost-effectiveness planes and the reported confidence intervals both indicated that there was **no statistically significant difference between the groups in terms of QALYs**. Despite this Koufaki et al.²²⁴ concluded that CYP2C19-guided clopidogrel treatment is a cost-effective option. Without clear evidence of a gain in QALYs, it is not clear however whether an intervention can be labelled as cost-effective in a cost-utility analysis. In Dong et al.,²²³ Claassens et al.²²⁵ and in the Bristol TAG HTA¹⁸⁹ the conclusion that the CYP2C19-guided strategy was dominant (i.e. less costly and more clinically effective) over standard treatment was tested in several sensitivity (including probabilistic) and scenario analyses, that all proved the robustness of this finding. The CCA by Van der Wouden et al.¹⁶⁰ found that, compared to standard practice, a CYP2C19 strategy to guide antiplatelet treatment would save 0.0035 death and cost an extra €161 annually per clopidogrel initiator.



Table 20 – Overview of primary economic evaluations of PGx testing in cardio/cerebro-vascular diseases (since 06/2021)

Reference	Perspective Time horizon Model-type	Disease area	Gene-drug association Intervention Comparator	Sources for effectiveness of intervention	Results (per patient)	Conclusion of the authors
Koufaki et al.²²⁴ 2023, Spain	HCP 18 months Piggyback CUA & CEA	Acute coronary syndrome	CYP2C19 – clopidogrel I: PGx-guided selection of antiplatelet C: conventional treatment without PGx test	Clinical impact: PREPARE (Spanish sites) QALYs: literature	QALYs I: 1.07 (95%CI: 1.04–1.10) C: 1.06 (95%CI: 1.03–1.09) LY I: 1.24 (95%CI: 1.20–1.26) C: 1.23 (95%CI: 1.19–1.26) Incremental costs -€873 (95%CI: -€2189–€389)	“PGx-guided clopidogrel represents a cost-effective option”
Dong et al.²²³ 2023, USA	HCP 1 year CUA Decision-tree	Acute coronary syndrome post-PCI	CYP2C19 – clopidogrel I: PGx-guided selection of antiplatelet C: conventional treatment without PGx	Clinical impact: TAILOR-PCI and POPular Genetics trials QALYs: literature	QALYs gained: 0.0027 Incremental costs: -\$527 PSA: PGx is dominant in >97% of the simulations	PGx is dominant (more clinically effective and less costly)
Bristol TAG HTA (NICE)¹⁸⁹ 2023, UK	HCP Lifetime CUA Markov model	Ischaemic stroke and transient ischaemic attack	CYP2C19 – clopidogrel I: PGx-guided selection of antiplatelet C: conventional treatment without PGx	Clinical impact: CHANCE and CHANCE-2 trials QALYs: literature	QALYs gained: 0.17 Incremental costs: -£1641 PSA: PGx is dominant in ~100% of the simulations	PGx is likely to be effective and cost-effective
Claasens et al.²²⁵ 2022, The Netherlands	HCP Lifetime CUA RCT-based	Acute myocardial infarction post-PCI	CYP2C19 – clopidogrel I: PGx-guided selection of antiplatelet Co: conventional treatment without PGx	Clinical impact: POPular Genetics trial QALYs: POPular Genetics trial and literature	QALYs gained: 0.009 Incremental costs: -€725 PSA: PGx remains dominant in ~100% of the simulations	PGx is dominant (more clinically effective and less costly)
van der Wouden et al.¹⁶⁰ 2022, The Netherlands	HCP 1 year CCA Mathematical model	PCI, stroke and transient ischemic attack	CYP2C19 – clopidogrel I: PGx-guided selection of antiplatelet C: conventional treatment without PGx	Clinical impact: observational studies reporting intermediate outcomes	Death prevented: 0.0035 Incremental costs: €161 No sensitivity analysis Number of patients initiating clopidogrel (2018): 117 900	PGx can potentially save the lives of patients at reasonable extra costs

95%CI: 95% confidence interval, C: comparator, CCA: cost-consequence analysis, CEA: cost-effectiveness analysis, CUA: cost-utility analysis, CVD: cardiovascular disease, HCP: health care payer perspective (including direct medical costs), I: intervention, LY: life-year, PCI: percutaneous coronary intervention, PSA: probabilistic sensitivity analysis, QALY: quality-adjusted life-year.



5.3.3 *Economic evaluations of pharmacogenetic testing in psychiatric disorders*

We identified 5 reviews of economic evaluations assessing PGx-testing in psychiatric conditions. A total of 21 unique references were covered: 11 in Morris et al.,²¹³ 1 in Turongkaravee et al.,²¹² 19 in Young et al.,²¹⁷ 18 in Karamperis et al.²¹⁸ and 4 in the Ontario Health Quality HTA.²¹⁴

We further identified 4 relevant primary economic evaluations published after 06/2021: the Ontario Health Quality HTA,²¹⁴ Ninomiya et al.,²²² Carta et al.²²¹ and Skokou et al.²¹⁶

5.3.3.1 *Reviews of economic evaluations*

In 2021, **Karamperis et al.**²¹⁸ reviewed 18 studies published between 2005 and 2019 that assessed the cost-effectiveness of PGx testing to inform treatment (antidepressants and antipsychotics) versus treatment as usual in adults with psychiatric illness. The psychiatric conditions were major depressive disorder (MDD, n=7), schizophrenia (n=4), depression and anxiety (n=3) and a variety of psychiatric disorders (n=4). Information regarding the prescribed treatment was not always clearly stated (n=3). Most studies were from the US (n=11) or Europe (n=5). Twelve studies evaluated panels of genes (ranging from 2 to 10 genes), including commercially available tests (GeneSight and NeurolDgenetix), whereas 6 studies evaluated single genes (CYP2D6, 5-HTTLPR or HTR2A). The quality of the studies was assessed using the QHES²²⁸ instrument (cfr supra) and was rated high (QHES score ranging from 73 to 98).

Results of the 6 single-gene economic evaluations were inconsistent. In MDD patients treated with antidepressants, 2 studies found that testing for 5-HTTLPR to guide treatment was cost-effective and 1 study found that HTR2A testing was uncertain. For CYP2D6-guided treatment, studies found PGx was cost-effective (risperidone in schizophrenic patients), uncertain (antidepressants in MDD) or not-cost-effective (nortriptyline in MDD). Results for the 2-gene panels (CYP2D6/CYP2C19 and HLA-DBQ1/HLA-B) to guide antipsychotic treatment against schizophrenia were equally inconsistent with studies reporting cost-saving, uncertain and cost-ineffective results. By contrast, the 12 studies evaluating larger panels of genes (6 genes or more)

reported favorable results, stating that PGx to guide treatment against psychiatric disorders is dominant or cost-saving.

Karamperis et al.²¹⁸ highlighted that the relevance of PGx testing for certain drugs as assessed in the economic evaluations (e.g., bupropion-5-HTTLPR/HTR2A) can be questioned since there is little evidence of an association for these gene-drug pairs.

The 2023 publication by **Young et al.**²¹⁷ is not a systematic review but a narrative description of two studies: the 2021 review by Karamperis et al.²¹⁸ described above and the 2020 study by Tanner et al.²⁴⁰ which is covered by Morris et al.²¹³ Tanner et al.²⁴⁰ evaluated the commercial GeneSight® multi-gene test to guide the treatment of moderate to severe depression compared with treatment as usual from a Canadian HCP perspective. Effectiveness of the test was based on the results of their meta-analysis. Using a 5-year time horizon, the base-case model projected that patients whose treatment was informed by the panel would gain an additional 0.14-0.19 QALYs compared with usual care, and this would result in cost savings of CAN\$1690-3060 per patient. Tanner et al.²⁴⁰ concluded that GeneSight panel testing is dominant (i.e. less costly and more clinically effective) compared with treatment as usual for moderate to severe depression.

The 2021 **Ontario Health Quality HTA**²¹⁴ was a systematic literature search on the cost-effectiveness of multi-gene PGx testing that include a decision-support tool to guide medication in MDD patients. Four model-based CUA were included, published between 2015 and 2020, with a 3-, 5-year, or a lifetime time horizon. Three studies were from the USA and 1 from Canada. Effectiveness of the tests (NeurolDgenetix® and GeneSight®) was based on the results of manufacturer-supported RCTs^{241, 242} or on meta-analyses of prospective studies and trials. All economic analyses consistently found that antidepressant treatment guided by multi-gene PGx tests was associated with cost savings and greater QALYs, dominating treatment as usual. Ontario Health Quality²¹⁴ emphasized that those results are highly uncertain as the long-term effectiveness of the intervention has not been investigated (the follow-up times for the RCTs on GeneSight® and NeurolDgenetics® are 8 and 12 weeks, respectively) and as data had to be extrapolated based on assumptions not completely substantiated by current evidence.


Table 21 – Reviews of economic evaluations of pharmacogenetic testing in psychiatry

Author	Disease area	Review period	Drug	Gene	# EE	Review main conclusion
Single genes (6 unique economic evaluations: 3 for CYP2D6, 2 for 5-HTTLPR, 1 for HTR2A)						
Karamperis et al. ²¹⁸ 2021, USA	Major depression	up to 08/2020	Citalopram, bupropion	5-HTTLPR	2	Cost-effective
Karamperis et al. ²¹⁸ 2021, USA	Major depression	up to 08/2020	Citalopram, venlafaxine, nortriptyline, mirtazapine. Bupropion	HTR2A	1	Inconclusive
Turongkaravee et al. ²¹² 2021, Thailand	Major depression	up to 10/2019	Nortriptyline	CYP2D6	1	Not cost-effective
Morris et al. ²¹³ 2022, USA	Major depression	up to 06/2021	Fluoxetine, citalopram, venlafaxine, amitriptyline, nortriptyline, mirtazapine.	CYP2D6	2	Not cost-effective (1 study not CE, 1 uncertain)
Karamperis et al. ²¹⁸ 2021, USA	Major depression	up to 08/2020	Fluoxetine, citalopram, venlafaxine, amitriptyline, nortriptyline, mirtazapine	CYP2D6	2	Not cost-effective (1 study not CE, 1 uncertain)
Karamperis et al. ²¹⁸ 2021, USA	Schizophrenia	up to 08/2020	Risperidone	CYP2D6	1	Cost-effective
Multigene panels (15 unique economic evaluations: 3 for panels of 2 genes and 12 for panels of ≥6 genes)						
Karamperis et al. ²¹⁸ 2021, USA	Schizophrenia	up to 08/2020	Antipsychotics	CYP2D6/CYP2C19	1	Cost-saving
			Clozapine	HLA-DBQ1/HLA-B	2	Not cost-effective (1 study not CE, 1 uncertain)
Young et al. ²¹⁷ 2023, Canada	Moderate to severe depression	from 01/2020 to 01/2023	Antidepressant	GeneSight	1	PGx is dominant **
Ontario Health Quality HTA ²¹⁴ 2021, Canada	Major depression	up to 01/2020	Antidepressant	NeuroIDgenetix GeneSight	4	PGx is dominant **
Morris et al. ²¹³ 2022, USA	Psychiatric disorders	up to 06/2021	Antidepressant	Panels ranging from 6 to 13 genes	9	Cost-saving or dominant **
Karamperis et al. ²¹⁸ 2021, USA	Psychiatric disorders, depression & anxiety, major depression	up to 08/2020	Antidepressant, antipsychotic	In-house and commercial panels*	9	Cost-saving or dominant**

* Multigene panel ranging from 6 to 10 genes: 1) in house panel CYP1A2, CYP2C19, CYP2C9, CYP2D6, HTR2A and SLC6A4, 2) in house panel CACNA1C, COMT, CYP2C19, CYP2D6, DRD2, MTHFR and SLC6A4, 3) GeneSight commercial panel CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, HTR2A and SLC6A4, 4) NeuroIDgenetix commercial panel COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, HTR2A, MTHFR and SLC6A4. ** A strategy is dominant when it is less costly and more clinically effective than its alternative. EE: economic evaluations.



5.3.3.2 Primary economic evaluation

Since 06/2021, 4 new economic evaluations of PGx testing for psychiatric diseases have been published: an evaluation performed within the Ontario Health Quality HTA,²¹⁴ a UK study by Ninomiya et al.,²²² an Italian study by Carta et al.²²¹ and a Greek study by Skokou et al.²¹⁶ Various PGx tests (single-gene, 2/4-genes and commercial panels) were assessed for various classes of drugs in various psychiatric conditions (major depression, schizophrenia).

Ontario Health Quality HTA, 2021

Ontario Health Quality²¹⁴ developed a 1-year state-transition model to determine the cost-effectiveness of the commercial GeneSight test versus treatment as usual for people with MDD who had inadequate response to one or more antidepressant medications. A health care payer perspective, limited to direct medical costs, was adopted.

Model input were obtained from the GUIDED trial,²⁴² a large RCT that examined the effectiveness of GeneSight among 1398 patients during 24 weeks (unblinding occurred after week 8). Due to its short duration, this trial did not report data on long-term outcomes (e.g. recurrence of depression symptoms or recovery) or on outcome of interest (e.g. quality of life or suicide). The GUIDED trial was further appraised by Ontario Health as being at high risk of bias and offering low confidence in the evidence provided. Utilities were derived from the literature.

The base-case analysis found that multi-gene PGx testing was associated with **significant additional QALYs (0.03, 95%CI: 0.005–0.072)** and **additional costs (CAN\$1906, 95%CI: 688–3360)**, resulting in an ICER of \$60 564 per QALY gained. The probability of PGx being cost-effective (vs. treatment as usual) was 36.8% at a WTP threshold of \$50 000 per QALY.

This suggests that the cost-effectiveness of multi-gene pharmacogenomic-guided treatment with GeneSight is uncertain. The results need to be interpreted with caution given that the clinical evidence that informed the economic modeling was of low to very low quality and therefore uncertain.

The price of the test, efficacy of the intervention, time horizon, and analytic perspective were major determinants of the cost-effectiveness results.

Ninomiya et al. 2022

Ninomiya et al.²²² assessed the cost-effectiveness of adding SLCO1B3/SCLO1B7 to the HLA-DQB1 and HLA-B genes, as a new **hypothetical PGx test**, to guide third-line antipsychotic medication with clozapine in schizophrenic patients. The PGx-guided strategy was compared with treatment as usual from a UK HCP perspective. The benefit of PGx testing was estimated as a 30% (20-80%) reduction in the risk of clozapine-induced adverse reaction, based on **assumptions** by the authors. Utility weights were obtained from the literature. Using a 10-year time horizon, the Markov model predicted that PGx-guided treatment would result in an ICER of £16 215 per QALY gained (details on costs and QALYs were not reported), which is below the lower limit of UK threshold (£20 000 - £30 000 per QALY gained). The probability that the ICER falls below the £30 000 upper limit of the ICER threshold was 87.8%. Ninomiya et al.²²² concluded that a hypothetical multi-gene PGx test based on the SLCO1B3-SCLO1B7, HLA-DQB1 and HLA-B variants to guide clozapine administration could be cost-effective.

Carta et al. 2022

Carta et al.²²¹ assessed single-gene CYP2C19 and CYP2D6 testing to guide antidepressant treatment in patients with MDD compared with treatment as usual from an Italian societal⁹⁹ perspective. Due to a lack of high-quality

⁹⁹ The societal perspective means that direct costs, such as treatment costs, and indirect costs, such as productivity losses due to illness, are considered. In a health care payer perspective, only direct medical costs are considered.

The health care payer perspective is the perspective recommended in the Belgian guidelines for economic evaluations and budget impact analyses.²³⁹



evidence, the probabilities of having side-effects or having a positive response to treatment in patients who had a genetic test, compared to those without a genetic test could not be estimated accurately and were obtained from **observational studies making no distinction by LOF status**²⁴³⁻²⁴⁵ or were based on **assumptions**. Utility weights were obtained from the literature.

Over a short 18-week time horizon, the base-case Markov models for CYP2C19 and CYP2D6 projected that PGx testing resulted in a gain of 0.0020 and 0.0022 QALYs at an additional cost of €120 and €104 per patient, respectively. This resulted in ICERs of €60 000 per QALY gained for CYP2C19 testing and of €47 000 per QALY gained for CYP2D6 testing. The 95%CI around those estimates were not reported. At an ICER threshold of €75 000 per QALY, the probabilities that CYP2C19 and CYP2D6 PGx testing are cost-effective were estimated at 58% and 63%, respectively. In the sensitivity analyses, the probabilities of having side-effects or of having a positive response to treatment and the costs of the PGx tests were identified as major determinants of the cost-effectiveness results.

Carta et al.²²¹ conclude that screening either the CYP2C19-gene or the CYP2D6-gene to guide antidepressant treatment could be cost-effective.

Skokou et al. 2024

Skokou et al.²¹⁶ assessed the cost-effectiveness of CYP2C19/CYP2D6-guided treatment of patients suffering from MDD compared with treatment as usual from a Greek health care payer perspective and with an 18-month time horizon. This is an economic evaluation in which data (costs, QALYs and the relative effects of a PGx-guided strategy) were obtained from the two Greek sites of the PREPARE study (494 MDD patients of which 261 in the PGx arm and 233 in the control arm). Skokou et al.²¹⁶ found that health care costs were significantly reduced in the CYP2C19/CYP2D6-guided arm (mean cost of €1302 per patient) compared with treatment as usual (mean cost of €2526 per patient). The 95%CI around those estimates were not reported but results from their probabilistic sensitivity analysis show that all

bootstrap replications are in the south quadrants of the cost-effectiveness plane, indicating that the reduction in costs from PGx testing is statistically significant. Important note is that a major driver for the costs is hospitalisations, and in the Greek sites of PREPARE, the hospitalisation rate was indeed significantly higher in the control group. However the difference cannot be linked to the lack of PGx guided therapy as the prevalence of hospitalisation was highest in the nonactionable control group, indicating a large heterogeneity between the groups.

By contrast, there was **no statistically significant difference between the groups in terms of QALYs**, with a mean of 0.93 QALYs (95%CI: 0.85–0.99) in the PGx-guided group versus 0.92 QALYs (95%CI: 0.86–0.99) for the control group. Despite this Skokou et al.²¹⁶ conclude that CYP2C19/CYP2D6-guided antidepressant treatment in MDD patients is potentially cost-effective. It can be questioned however whether an intervention could be cost-effective without a proof of clinical benefit in terms of QALYs. The same cost-effectiveness analysis was performed for schizophrenic (n=330) and bipolar (n=252) patients, but the results indicated no difference in the PGx-guided treatment versus control arm in terms of costs or QALYs. The argument was raised that self-reported quality of life is not ideal in patients with schizophrenia and manic episodes.



Sources used in the economic evaluations to estimate the relative effects of PGx testing in psychiatry

Studies directly comparing different testing and targeted treatment strategies (PGx is the trial intervention).

- Bradley et al.²⁴¹ performed a 12-week RCT of the commercial NeurolDgenetix test in 685 patients suffering from depression or anxiety: 352 patients in the PGx group and 333 in the control group. They found that response rates and remission were significantly higher in the PGx-guided group as compared to standard care for patients with depression.
- GUIDED²⁴² is an 8-week RCT of the commercial GeneSight test that included 1398 patients with MDD (681 in PGx-guided treatment, 717 in treatment as usual). GUIDED found that PGx testing did not significantly improve mean symptoms at 8 weeks but did significantly improve response (26.0% vs. 19.9%) and remission (15.3% vs. 10.1%) rates over standard of care.
- The Greek subanalysis of the PREPARE study,²⁶ totalled 1076 psychiatric patients (494 with MDD, 330 with schizophrenia, 252 with bipolar disorder): 547 in the PGx group and 529 in the control group. Among the patients that had an actionable CYP2C19 or CYP2C9 variant, the clinically relevant ADR were lower in the PGx guided group compared to standard of care (10.37% versus 19.05%, adj OR=0.48, p=0.049 – these are the outcome for all patients (not MDD specific). The secondary outcome, i.e. non-ADR related hospitalisations, differed significantly between the two cohorts, which shows different characteristics of the two cohorts.

The Bradley et al.²⁴¹ and GUIDED²⁴² RCTs were manufacturer-supported and were appraised as being of low quality and at high risk of bias by the recent Ontario Health Quality HTA.²¹⁴


Table 22 – Overview of primary economic evaluations of PGx testing in psychiatry (since 06/2021)

Reference	Perspective Time horizon Model-type	Disease area	Gene-drug association Intervention Comparator	Sources for effectiveness of intervention	Results (per patient)	Conclusion of the authors
Ontario Health Quality HTA²¹⁴ 2021, Canada	HCP 1 year CUA Markov model	Major depressive disorder	GeneSight multi-gene panel – antidepressants I: PGx-guided antidepressant C: conventional treatment without PGx test	Clinical impact: GUIDED trial ²⁴² QALYs: literature	QALYs gained: 0.03 (95%CI: 0.005–0.072) Incremental costs: CAN\$1906 (95%CI: CAN\$688–3360) ICER: \$60 564 per QALY Probability of being cost-effective: 36.8% at \$50 000 /QALY threshold	“The cost-effectiveness of multi-gene PGx-guided treatment with GeneSight is uncertain”
Carta et al.²²¹ 2022, Italy	Societal 18 weeks CUA Markov model	Major depressive disorder	CYP2C19 – antidepressants I: PGx-guided antidepressant C: conventional treatment without PGx test	Clinical impact: observational studies and assumptions QALYs: literature	QALYs gained: 0.0020 Incremental costs: €120 ICER: €60 000 per QALY Probability of being cost-effective: 58% at \$75 000 per QALY threshold	“The genetically informed characterisation of CYP2C19 and CYP2D6 metabolizing profiles could be cost-effective.”
			CYP2D6 – antidepressants I: PGx-guided antidepressant C: conventional treatment without PGx test		QALYs gained: 0.0022 Incremental costs: €104 ICER: €47 000 per QALY Probability of being cost-effective: 63% at \$75 000 per QALY threshold	
Ninomiya et al.²²² 2022, UK	HCP 10 years CUA Markov model	Schizophrenia	SLCO1B3/SCLO1B7/HLA-DQB1/HLAB – clozapine I: PGx-guided clozapine C: conventional treatment without PGx test	Clinical impact: assumptions QALYs: literature	ICER: £16 215 per QALY Probability of being cost-effective: 87.8% at £30 000 per QALY threshold	“Multi-gene PGx test based on SLCO1B3-SCLO1B7, HLA-DQB1 and HLA-B variants to guide clozapine could be cost-effective.”
Skokou et al.²¹⁶ 2024, Greece	HCP 18 months Piggyback CUA	Major depressive disorder	CYP2C19/CYP2D6 – antidepressants I: PGx-guided treatment C: conventional treatment without PGx test	Clinical impact: PREPARE (Greek sites) QALYs: VAS scores collected during the trial	QALYs I: 0.93 (95%CI: 0.85–0.99) C: 0.92 (95%CI: 0.86–0.99) Costs : I: €1302, C: €2526 (95%CI not reported)	“PGx-guided treatment could be a cost-effective option”

C: comparator, CUA: cost-utility analysis, HCP: health care payer perspective (including direct medical costs), I: intervention, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life-year.



5.3.4 Economic evaluations of pharmacogenetic testing in oncology

We identified 2 reviews of economic evaluations of PGx testing in oncology covering 10 unique references (published between 2009 and 2019): 8 in Morris et al.²¹³ and 3 in Turongkaravee et al.²¹²

We further identified 2 primary economic evaluations, published after (06/2021), evaluating PGx testing (DPYD and DPYD/UGT1A1) for fluoropyrimidine/irinotecan treatment against colon cancer.^{226, 227}

5.3.4.1 Reviews of economic evaluations

Five European studies assessed the cost-effectiveness of DPYD testing before prescription of fluoropyrimidines to prevent severe hematologic and gastrointestinal toxicity due to fluoropyrimidine. All studies found genotyping would be cost-saving or cost-effective compared with no testing. The quality of the studies was variable with 2 studies rated 80/100 on the QHES score but 3 rated between 54 and 66.²¹³

Two economic evaluations (France and the USA) evaluated the cost-effectiveness of UGT1A1 testing before prescribing irinotecan to prevent severe neutropenia in metastatic colorectal cancer. The results demonstrated that genotyping would be a cost-effective intervention.

Three high-quality (QHES scores between 87 and 94) economic evaluations assessed the cost-effectiveness of CYP2D6 genotype testing to guide tamoxifen as adjuvant hormonal therapy in breast cancer patients. While the two Asian studies found genotyping would be cost-effective, the European study reported that cost-effectiveness was uncertain.

5.3.4.2 Primary economic evaluation

Fragoulakis et al.²²⁶ performed an evaluation of PGx-guided treatment of fluoropyrimidines and/or irinotecan in colorectal cancer. The cost-effectiveness of multiple-gene (DPYD and UGT1A1) testing was investigated from an Italian HCP perspective, using the real-world data of the Italian sites (366 patients) of the PREPARE^{26, 246} study.

Utility values were also obtained from this study, in which patients were asked to evaluate their health state with a Visual Analogue Scale (VAS) at 4 different time points. The time horizon was limited to the duration of the trial (18 months). Fragoulakis et al.²²⁶ found that the PGx-guided treatment strategy resulted in less (but non-statistically significant) costs than conventional treatment (−€185, 95%CI: −€385–€737) and fewer adverse drug events (i.e. 0.34% less). Although an improvement in LY was observed (0.08, p-value=0.04), **the gain in QALYs (−0.01, 95%CI: −0.11–0.10) was marginal and not statistically significant.** The probabilistic sensitivity analysis indicated that the PGx-guided strategy was dominant in 28% of the bootstrap replications and potentially cost-effective in 3% of the replications, implying that in the remaining 69% of the replications, PGx resulted in fewer QALYs than in standard treatment. Despite this Fragoulakis et al.²²⁶ concluded that DPYD and UGT1A1 genotyping is cost-effective by improving the safety of treatments with fluoropyrimidines and/or irinotecan. Again, it can be questioned whether an intervention can be cost-effective in the absence of a significantly demonstrated clinical benefit in terms of QALYs.

Brooks et al.²²⁷ explored the cost-effectiveness of DPYD testing to prevent severe toxicity following fluoropyrimidine chemotherapy for colon cancer. A 5-year time horizon Markov model was developed from the US HCP perspective. Utility values were derived from published studies of patients with colorectal cancer. The clinical impact of DPYD genotyping on toxicity and mortality was obtained from 2 prospective studies^{247, 248} of dose-reduced chemotherapy and assumptions. DPYD genotyping was found to prevent 1 treatment-related death per 764 patients screened. Compared to usual care (no testing), DPYD genotyping resulted in an incremental gain of 0.0038 QALYs per patient and increased per-patient costs by \$78, leading to an ICER of \$20 500/QALY. DPYD genotyping was dominant (i.e., it generated lower costs and higher QALYs compared to no genotyping) in 47.5% of the simulations and cost-effective in 96.2% of simulations at a WTP threshold of \$50 000/QALY.



Sources used in the economic evaluations to estimate the relative effects of PGx testing for fluoropyrimidine therapy

Studies directly comparing different testing and targeted treatment strategies (PGx is the trial intervention).

- The Italian subanalysis of the PREPARE study,²⁶ which is a prospective, open-label, multinational cluster randomised/cross-over controlled study with an 18-month duration that assessed the impact of PGx-guided prescribing using a 12-gene panel. The Italian sites included 366 patients diagnosed with colorectal cancer of which 155 in the PGx-guided arm and 211 in treatment as usual. Fragoulakis et al.²²⁶ report that patients in the Italian DPYD/UGT1A1-guided arm had a slightly lower possibility to experience at least one ADR (PGx-guided arm = 9.09%, control arm = 9.43%), a difference of 0.34% in favor of PGx-guided treatment.

Cohort studies with historical cohort comparators

- Henricks et al.²⁴⁸ did a prospective observational study in 1103 patients and compared the frequency of Severe Adverse Events in heterozygous variant carriers (n=85) receiving PGx guided dose-reduced chemotherapy with wild type patients treated with a standard dose. They then calculated RR of SAEs between variant carriers and wild type patients in the current cohort and compared it historical cohort of DPYD heterozygous variant carriers who received standard-dose chemotherapy. In the comparison between prospective and historical cohort genotype-guided dosing reduced the relative risk of severe toxicity in DPYD carriers from 2.87 (95%CI: 2.14–3.86) when treated with full dose fluoropyrimidine (historical cohort) to 1.31 (0.63–2.73) when treated with individualised dose (prospective cohort).

- Deenen et al.²⁴⁷ did a prospective observational study in 1631 patients and compared the toxicity of PGx guided dose-reduced chemotherapy in DPYD variant carriers (n=18) with a historical cohort of 48 DPYD variant patients who received standard-dose chemotherapy. The risk of severe toxicity was significantly reduced from 73% (95%CI: 58–85%) in historical controls to 28% (95%CI: 10–53%) by genotype-guided dosing. Drug-induced death was reduced from 10% to 0%.



Table 23 – Reviews of economic evaluations of pharmacogenetic testing in oncology

Reference	Disease area	Review period	Drug	Gene	# EE	Country / Region	Review main conclusion
Fluoropyrimidines and DPYD (5 unique economic evaluations)							
Morris et al. ²¹³ 2022, USA	Cancer	up to 06/2021	Fluoropyrimidines	DPYD	5	Europe	CS (4 studies), CE (1 study)
Turongkaravee et al. ²¹² 2021, Thailand	Cancer	up to 10/2019	Fluoropyrimidines	DPYD	1	Europe	Cost-saving
Tamoxifen and CYP2D6 (3 unique economic evaluations)							
Morris et al. ²¹³ 2022, USA	Breast cancer	up to 06/2021	Tamoxifen	CYP2D6	3	Asia, UK	Inconclusive (2 studies CE, 1 uncertain)
Irinotecan and UGT1A1 (2 unique economic evaluations)							
Turongkaravee et al. ²¹² 2021, Thailand	Colorectal cancer	up to 10/2019	Irinotecan	UGT1A1	2	France, USA	Cost-effective

CE: cost-effective, CS: cost-saving, EE: economic evaluation.

Table 24 – Overview of primary economic evaluations of PGx testing in oncology (since 06/2021)

Reference	Perspective Time horizon Model-type	Disease area	Gene-drug association Intervention (I) Comparator (C)	Sources for effectiveness of intervention	Results (per patient)	Conclusion of the authors
Fragoulakis et al. ²²⁶ 2023, Italy	HCP 18 months Piggyback CUA & CEA	Colorectal cancer	DPYD/UGT1A1 (panel) and fluoropyrimidines/irinotecan I: PGx-guided treatment C: conventional treatment without PGx test	Clinical impact: PREPARE (Italian sites) QALYs: VAS scores collected during the trial	LY: I: 1.58; C: 1.50 QALYs I: 0.80 (95%CI: 0.76–0.84) C: 0.81 (95%CI: 0.78–0.88) QALYs gained: -0.01 (95%CI: -0.11–0.10) Incremental costs -€185 (95%CI: -€385–€737)	“Pre-treatment genotyping of DPYD and UGT1A1 variants is cost-effective.”
Brooks et al. ²²⁷ 2022, USA	HCP 5 years CUA Markov model	Colorectal cancer	DPYD and fluoropyrimidines I: PGx-guided treatment C: conventional treatment without PGx test	Clinical impact: observational studies and assumptions QALY: literature	QALYs gained: 0.0038 Incremental costs: \$78 ICER: \$20 500 per QALY PSA: PGx was dominant in 47.5% of the simulation. Probability of being cost-effective: 96% at \$50 000/QALY threshold	“DPYD genotyping is highly likely to be cost-effective from a US health care perspective.”

95%CI: 95% confidence interval, C: comparator, CEA: cost-effectiveness analysis, CUA: cost-utility analysis, HCP: health care payer perspective (including direct medical costs), I: intervention, LY: life-year, PSA: probabilistic sensitivity analysis, QALY: quality-adjusted life-year, VAS: visual analogue scale.



5.3.5 Economic evaluations of pharmacogenetic testing in autoimmune diseases

We identified 2 reviews of the literature assessing the cost-effectiveness of PGx testing to guide treatment in autoimmune diseases. A total of 12 unique references published between 2002 and 2019 were covered: 11 in Morris et al.²¹³ and 8 in Turongkaravee et al.²¹² The search for additional full economic evaluations published after 06/2021 did not return any further reference.

The 12 publications addressed the cost-effectiveness of single TPMT-gene testing to guide treatment with thiopurines in patients with autoimmune diseases, inflammatory bowel disease, idiopathic pulmonary fibrosis, Crohn's disease, rheumatoid arthritis, idiopathic pulmonary fibrosis, acute lymphoblastic leukemia or systemic lupus erythematosus.

The general quality of these studies was rated high by Morris et al. with QHES scores well above 80/100.²¹³ The economic evaluations originated mainly from Europe (n=5) and North America (n=5), with 1 study performed in Australia and another in Asia. Two studies were economic evaluations done alongside the TARGET²³² and the TOPIC⁶⁷ trials with PGx as the intervention. The other studies were model-based, relying on published data to estimate the parameters. The studies' results differed greatly. Two-third of the studies (8/12) found that TPMT-testing would be a cost-effective or cost-saving intervention to prevent severe ADRs as compared with no testing. By contrast 4 studies found TPMT-testing would not be cost-effective or was uncertain.

Sources used in the economic evaluations to estimate the relative effects of PGx testing in autoimmune diseases

Studies directly comparing different testing and targeted treatment strategies (PGx is the trial intervention).

- TOPIC⁶⁷ (Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics) is a prospective RCT of TPMT genotyping to optimize initial thiopurine treatment dose versus standard dosing without genotyping. 783 patients (405 in the PGx and 378 in the control group) were followed for 20 weeks. TOPIC showed no significant difference in the risk of ADR between the groups. However, a significantly smaller proportion of carriers of the TPMT variants in the intervention group (2.6%) developed hematologic ADRs compared with patients in the control group (22.9%) (RR: 0.11, 95%CI: 0.01–0.85).
- TARGET²³² is a prospective RCT in patients with inflammatory diseases that explored whether TPMT genotyping helped prevent ADRs associated with azathioprine. A total of 333 patients were randomised into PGx group or control group. The follow-up was 4 months. No difference in ADRs was noted between the two groups, it was not adequately powered. However, the single patient with TPMT homozygosity experienced severe neutropenia.

Table 25 – Reviews of economic evaluations of pharmacogenetic testing in autoimmune diseases

Reference	Disease area	Review period	Drug	Gene	# EE	Country / Region	Review main conclusion
12 unique economic evaluations							
Morris et al.²¹³ 2022, USA	Autoimmune diseases	up to 06/2021	Azathioprine, mercaptopurine	TPMT	11	Europe (5), North America (4), Asia (1), Australia (1)	Inconclusive (8 studies CE or CS, 2 not CE, 1 uncertain)
Turongkaravee et al.²¹² 2021, Thailand	Autoimmune diseases	up to 10/2019	Azathioprine, mercaptopurine	TPMT	8	North America (4), Europe (2), Asia (1), Australia (1)	Inconclusive (5 studies CE or CS, 3 not CE)

CE: cost-effective, CS: cost-saving, EE: economic evaluation.



5.3.6 Economic evaluations of pharmacogenetic testing in gout

Morris et al.²¹³ and Turongkaravee et al.²¹² reviewed a total of 10 unique economic evaluations on this topic, all published between 2014 and 2020: 10 in Morris et al.²¹³ and 8 in Turongkaravee et al.²¹² No more recent primary or secondary economic evaluation was identified in our complementary search.

The 10 publications addressed the cost-effectiveness of HLA-B*58:01 genetic testing prior to initiation of allopurinol treatment in patients with gout to prevent severe cutaneous ADR. The evaluations were mainly performed in Asia (n=8), with 1 in the UK and 1 in the USA.

Results were inconsistent. While the UK study found HLA-B*58:01 genotyping was not cost-effective, the US study showed that cost-effectiveness varied substantially across racial or ethnic groups, following by their HLA-B*58:01 frequency. Their conclusion was that genotyping would likely be cost-effective for Asians and African Americans, but not for Caucasians or Hispanics. This was however not confirmed by the 8 Asians studies, half of them (n=4) reporting that HLA-B*58:01 genotyping was cost-effective and the other half (n=4) that it was not cost-effective.

Table 26 – Reviews of economic evaluations of pharmacogenetic testing in gout

Reference	Disease area	Review period	Drug	Gene	# EE	Country / Region	Review main conclusion
10 unique economic evaluations							
Morris et al.²¹³ 2022, USA	Gout	up to 06/2021	Allopurinol	HLA-B*58:01	10	Asia (8), Europe (1), USA (1)	Inconclusive (5 studies CE or CS, 5 not CE)
Turongkaravee et al.²¹² 2021, Thailand	Gout	up to 10/2019	Allopurinol	HLA-B*58:01	8	Asia (6), Europe (1), USA (1)	Inconclusive (4 studies CE or CS, 4 not CE)

CE: cost-effective, CS: cost-saving, EE: economic evaluation



5.3.7 Economic evaluations of pharmacogenetic testing in HIV

Morris et al.²¹³ and Turongkaravee et al.²¹² reviewed a total of 12 unique studies on this topic, all published between 2004 and 2019: 11 in Morris et al.²¹³ and 8 in Turongkaravee et al.²¹² No more recent primary or secondary economic evaluation was identified in our complementary search.

Nine (9) studies assessed the cost-effectiveness of HLA-B*57:01 before prescribing abacavir to HIV positive patients to prevent hypersensitivity reactions. Five (5) studies were conducted in Europe, 2 in the USA and 2 in Asia. The 7 European/North American studies found genotyping to be cost-effective or cost-saving, while it was not cost-effective or uncertain in the Asian studies. One of the Asian studies²⁴⁹ suggested that the cost-effectiveness of genotyping varied according to allele frequency, that was shown to be much higher in Europe and the US than in the Asian population.

Two studies (Europe and North America) evaluated the cost-effectiveness of CYP2B6 genotyping before prescribing efavirenz to prevent central nervous system toxicity in HIV patients. They both conclude that genotyping was cost-saving compared with no testing. The US study that assessed the cost-effectiveness of UGT1A1 genetic testing to inform atazanavir prescribing in HIV patients reported that genotyping was not cost-effective.

Sources used in the economic evaluations to estimate the relative effects of HLA testing for abacavir on HIV

Studies directly comparing different testing and targeted treatment strategies (PGx is the trial intervention)

- PREDICT-1²³⁰ is a prospective, double-blind, multi-center RCT to evaluate the utility of HLA-B*57:01 screening in preventing hypersensitivity to abacavir (AHS). A total of 1956 predominantly white HIV-infected patients were randomized to HLA testing (n=980) or standard approach (n=976) and followed for a 6-week observation period. PREDICT-1 showed that incidence of AHS was significantly reduced in the tested group, with a calculated OR of 0.03 (95%CI: 0.00–0.18, p<0.001).

Studies carried out in HLA-B*57:01 non carriers

- ARIES was an RCT comparing two common HIV regimens, including abacavir. Within this trial, Young et al.²³¹ recruited 517 HLA-B*57:01-negative HIV-infected racially diverse North American patients to be randomised between two treatment regimens that included abacavir. Abacavir hypersensitivity rates over the 30-week study was < 1%.

Table 27 – Reviews of economic evaluations of pharmacogenetic testing in HIV

Reference	Disease area	Review period	Drug	Gene	# EE	Country / Region	Review main conclusion
Abacavir and HLA-B*57:01 (9 unique economic evaluations)							
Morris et al. ²¹³ 2022, USA	HIV	up to 06/2021	Abacavir	HLA-B*57:01	7	Europe, North America	Cost-effective or cost-saving
					2	Asia	Not cost-effective
Turongkaravee et al. ²¹² 2021, Thailand	HIV	up to 10/2019	Abacavir	HLA-B*57:01	7	Europe, North America	Cost-effective or cost-saving
					1	Asia	Not cost-effective
Efavirenz and CYP2B6 (2 unique economic evaluations)							
Morris et al. ²¹³ 2022, USA	HIV	up to 06/2021	Efavirenz	CYP2B6	2	Europe, North America	Cost-saving
Turongkaravee et al. ²¹² 2021, Thailand	HIV	up to 10/2019	Efavirenz	CYP2B6	1	North America	Cost-saving
Atazanavir and UGT1A1 (1 unique economic evaluation)							
Morris et al. ²¹³ 2022, USA	HIV	up to 06/2021	Atazanavir	UGT1A1	1	North America	Not cost-effective

EE: economic evaluation.



5.3.8 Economic evaluations of pharmacogenetic testing in epilepsy

Morris et al.²¹³ and Turongkaravee et al.²¹² reviewed a total of 8 unique economic evaluations on this topic, all published between 2012 and 2021: 8 in Morris et al.²¹³ and 6 in Turongkaravee et al.²¹² No more recent primary or secondary economic evaluation was identified in our complementary search.

Seven (7) studies assessed the cost-effectiveness of HLA-B*15:02 genotyping to prevent the risk of serious ADR in patients being prescribed carbamazepine against epilepsy. All studies were carried out in Asian populations. Results were unclear with 3 studies reporting that genotyping would be cost-effective or cost-saving, and 4 studies reporting that it would not be cost-effective.

The UK study evaluating HLA-A*31:01 testing prior to initiation of carbamazepine in epilepsy showed that testing would be cost-effective.²⁵⁰

Sources used in the economic evaluations to estimate the relative effects of HLA testing for carbamazepine in epilepsy

Cohort studies with historical cohort comparators

- Chen et al.²⁵¹ did a prospective study in which 4877 Taiwanese patients requiring carbamazepine were recruited and genotyped for HLA-B*15:02. Of these, 372 (7.7%) tested positive and were advised to take an alternative medication. There were no Stevens-Johnson syndrome or toxic epidermal necrolysis observed among any participants in the study ($p < 0.001$ when comparing to assumed incidence based on historical records).

Table 28 – Reviews of economic evaluations of pharmacogenetic testing in epilepsy

Reference	Disease area	Review period	Drug	Gene	# EE	Country / Region	Review main conclusion
Carbamazepine and HLA-B*15:02 (7 unique economic evaluations)							
Morris et al. ²¹³ 2022, USA	Epilepsy	up to 06/2021	Carbamazepine	HLA-B*15:02	7	Asia, USA (patients with Asian origin)	Inconclusive (3 studies CE or CS, 4 not CE)
Turongkaravee et al. ²¹² 2021, Thailand	Epilepsy	up to 10/2019	Carbamazepine	HLA-B*15:02	5	Asia	Inconclusive (3 studies CE or CS, 2 not CE)
Carbamazepine and HLA-A*31:01 (1 unique economic evaluation)							
Morris et al. ²¹³ 2022, USA	Epilepsy	up to 06/2021	Carbamazepine	HLA-A*31:01	1	UK	Cost-effective
Turongkaravee et al. ²¹² 2021, Thailand	Epilepsy	up to 10/2019	Carbamazepine	HLA-A*31:01	1	UK	Cost-effective

CE: cost-effective, CS: cost-saving, EE: economic evaluation



5.3.9 Preemptive versus reactive testing

There are no cost-effectiveness studies on preemptive testing based on real evidence. In our literature review, we identified only 1 hypothetical model where the cost-effectiveness of preemptive and reactive PGx testing versus usual care (no testing) to guide treatment choices for a population with average CVD risk was explored.²¹ Preemptive testing was defined as PGx testing of everyone before disease develops and drug therapy is indicated. The results are then integrated into the patients' health records, making this information available at the point of care. Reactive testing was defined as tests administered after a first disease is diagnosed and drug therapy is indicated, but before the treatment is initiated. Although it is covered by the review of Morris et al.,²¹³ a separate description of this study is provided here as all other economic evaluations published so far (and included in our review) assessed reactive testing only (i.e., gene(s) tested once a drug is prescribed).

Zhu et al.²¹ developed a lifelong Markov model from the US payer's perspective for a hypothetical cohort of 10 000 patients aged ≥45 years old. PGx testing was panel-based and included the following gene-drug pairs: CYP2C19-clopidogrel, CYP2C9/VKORC1-warfarin, and SLCO1B1-statins. When PGx testing suggested genetic variations associated with potential harm, the following alternative drugs were used: ticagrelor instead of

clopidogrel, NOACs instead of warfarin, and PCSK9 inhibitors instead of statins. Health states utilities were obtained from the literature. Estimates for the clinical impact of the intervention were obtained from the PLATO trial, an RCT comparing alternative treatment drugs (ticagrelor versus clopidogrel) and in which the PGx is not the trial intervention. Costs included were direct medical costs of medication, PGx testing, and treatment of disease and drug side effects.

Preemptive testing was found to be cost-effective compared with usual care (ICER \$86 230/QALY) at the \$100 000/QALY WTP threshold while reactive testing was not (ICER \$148 730/QALY). Compared with reactive testing, preemptive testing was found to be cost-effective with an ICER of \$64 920/QALY. At the same WTP threshold and compared with usual care, the probability that preemptive testing is cost-effective was 98.1%. This probability was 100% when preemptive testing was compared with reactive testing.

The sensitivity analyses highlighted that the cost-effectiveness of preemptive PGx testing varied by age, with higher (less cost-effective) ICERs in older age groups. Hence from a cost-effectiveness point of view PGx information should be tested earlier. It is noteworthy however that Zhu et al.²¹ did not account for the cost of IT and storing the patient's PGx information overtime which favours the preemptive strategy in their model.

Table 29 – Cost-effectiveness results of preemptive testing, reactive testing and usual care

	Average values			Incremental values		
	Usual care (no testing)	Reactive testing	Preemptive testing	Reactive testing versus usual care	Preemptive testing versus usual care	Preemptive versus reactive testing
Direct medical costs	\$175 400	\$188 750	\$205 840	\$13 340	\$30 430	\$17 090
QALYs	5.85	5.94	6.20	0.09	0.35	0.26
ICER	-	-	-	\$148 730	\$86 230	\$64 920

Source: Zhu et al. 2021²¹ ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year.



Key points on the cost-effectiveness of PGx testing

A search of the economic literature on PGx testing was performed in 08/2023 (updated 01/2024). A total of 8 literature reviews (covering 138 unique economic evaluations) and 11 additional primary economic evaluations were identified, covering many therapeutic areas. Most studies were performed in Europe and North America.

All (but one) economic evaluations assessed reactive testing, where gene(s) are tested once a drug is prescribed. Only 1 study assessed the cost-effectiveness of preemptive testing, based on a hypothetical model and without considering the costs of IT and storing the patient's PGx information over time.

• PGx in **cardiovascular diseases**

- Testing CYP2C19 for clopidogrel in cardiovascular diseases was cost-saving or cost-effective in all economic evaluations (n=26).
- CYP2C19 testing for clopidogrel in cerebrovascular diseases was likely to be cost-effective (n=6).

• PGx in **psychiatry** (n=24)

- The cost-effectiveness of single/two-gene testing (5-HTTLPR, CYP2C19, CYP2D6, HTR2A, CYP2D6/CYP2C19, HLA-DQB1/HLAB) for antidepressants or antipsychotics was uncertain due to the great diversity in the studies' results (n=12).
- Multiple-gene (>6 genes) testing for antidepressants or antipsychotics was dominant or cost-saving in all but one studies (n=13).

• PGx in **oncology** (n=12)

- Testing DPYD to guide fluoropyrimidine-treatment was cost-saving or cost-effective (n=6).
- Testing UGT1A1 for irinotecan was cost-effective (n=2).

- The cost-effectiveness of CYP2D6-testing for tamoxifen was uncertain (n=3).

- The results of the studies for TPMT-thiopurine (**auto-immune diseases**, n=12) and HLA-allopurinol (**gout**, n=10) were highly heterogenous (also for Asians with HLA), implying that the cost-effectiveness of PGx testing of those genes is uncertain.
- In **HIV**, testing HLA for abacavir was cost-effective in Europe/ north America (n=7) but not cost-effective in Asia (n=2). Testing CYP2B6 for efavirenz (n=2) was cost-effective but testing UGT1A1 for atazanavir (n=1) was not cost-effective.
- In **epilepsy**, the cost-effectiveness of HLA testing for carbamazepine was uncertain as results of the studies were heterogenous (n=8, 7 in Asia and 1 in the UK).

The **evidence used in the economic evaluations to inform the clinical effectiveness of PGx testing is limited and of low quality**. Many evaluations relied on observational studies or RCTs in which PGx was not the trial intervention. The RCTs with PGx as trial intervention referred to in the economic evaluations were:

- POPular GENetics and TAILOR-PCI, and PREPARE (Spanish sites, no randomisation on patient level and no published effectiveness data for this trial) for CYP2C19-clopidogrel (in patients with cardiovascular disease),
- GUIDED (Genesight) and the NeuroIDgenetix RCT, PREPARE (Greek sites, no randomisation on patient level), for antidepressants,
- PREPARE (Italian sites, no randomisation on patient level) for DPYD/UGT1A1-fluoropyrimidine/irinotecan in colorectal cancer ,
- TOPIC and TARGET for TPMT-thiopurine in autoimmune diseases,
- PREDICT-1 for HLA-abacavir in HIV.

Since few RCTs have been performed comparing PGx-guided therapy to standard therapy without PGx, there is uncertainty about the clinical



benefit if not based on such RCTs, and this cascades down to the economic evaluations.

The RCTs were of short duration and usually reported intermediate outcomes. The time horizons of the economic evaluations were also usually limited. Extrapolation of the cost-effectiveness results of PGx-guided treatment over longer time horizons would thus be highly uncertain. Longer-term data on the clinical effectiveness of PGx are required, also to feed the economic evaluations.

Very few economic evaluations obtained data for the effect on quality of life directly from measurements within their underlying trial (e.g., the PREPARE and POPular Genetic trials). In most economic evaluations, QoL data were obtained from previous studies in patients with the disease of interest, and the effect of PGx on QALYs was modelled indirectly.

In the recent CUAs, the gains in QALYs from the PGx strategy (versus no PGx) were very small and (when this info was reported) usually non significant. Despite this a lack of evidence on the clinical effectiveness of PGx, most economic evaluations derived an ICER and concluded that PGx testing might be cost-effective. It can be questioned however whether an intervention could be cost-effective without the proof that it can offer better health outcome in terms of QALYs.

The benefits of PGx testing in the whole populations might be difficult to demonstrate. Indeed, most patients experience neither benefit nor harm from PGx testing, while all the benefits of testing (both in terms of QALYs gains or hospital costs avoided) occur in a small proportion of patients with detectable and actionable pathogenic gene variants.

Differences in parameters, methods and outcomes across studies as well as population-level and system-level differences may lead to difficulties in comparing cost-effectiveness results across countries.

6 BUDGET IMPACT ANALYSES

6.1 Research question

This chapter aims to predict the possible budget impact for the national health insurance (RIZIV-INAMI) and the patients if PGx testing would become more widely implemented. A limited number of scenarios is drafted based on the selection of medications for which a PGx test is considered "essential", also taking into account the type of test (targeted to single-gene or more complex tests including panel test).

6.2 Methodology

Costs were estimated from the health care payers' perspective, and a distinction is made between RIZIV-INAMI and patient shares. The analysis is limited to the cost of the tests, without consideration of other costs or savings that may occur over time such as (additional or avoided) medications, procedures, or hospitalizations. Consultations were not considered either, as we presume the tests occur reactively, coinciding with an existing prescription and interaction with a physician.

Ambiguity remains regarding which PGx tests should be prioritized for implementation into routine care.¹⁶⁰ Therefore, we had to make our own **selection of medicines**. The available literature on explicit guidelines on testing was analysed (see chapter 3). The recommendations of the DPWG were selected as a basis as these are the most detailed and comprehensive guidelines. We selected the medications which were labeled as "essential" to test. From this list of medications, drug labels as well as prevailing clinical guidelines of medical professional societies were checked. We started with a **conservative approach** featuring 9 drugs considered "essential" for Belgium (abacavir, systemic fluorouracil, capecitabine, tegafur, azathioprine, mercaptopurine, thioguanine, siponimod, eliglustat) and explored an extension of this selection to two other drugs (irinotecan and clopidogrel). Both irinotecan and clopidogrel are considered essential by the Dutch DPWG but the medical professional guidelines or drug labels did not include a clear recommendation to test. Hence, they were not included in



the conservative approach. However, for irinotecan there are indications that PGx tests are performed, and for clopidogrel the anticipated guideline of NICE might evoke a change in practice.²¹⁵ Therefore, these two medicines were considered in an **extended approach**. The Dutch DPWG also labels maintenance therapy on phenytoin and simvastatin when dosed at more than 80 mg as “essential”. As the medical specialist guidelines and drug labels are not clear on testing, these were not considered. Mavacantem, introduced on the EU market in June 2023 (not currently reimbursed in Belgium but in a medical need program^{hh}) is also considered essential. However, as this is very recent and not reimbursed yet, no data on incident users could be retrieved (see further). This selection of medications was presented to and approved by Belgian experts.

The **number of patients** who qualified for a PGx test was extracted from the number of new medication users (incident users) from the year 2019ⁱⁱ of the national reimbursement database (InterMutualistisch Agentschap – Agence InterMutualiste, IMA-AIM), using the ATC codes of the corresponding medication (see appendix 7). Data on more recent medications such as mavacantem, indicated for patients with a hypertrophic cardiomyopathy and for which testing is essential according to drug label, was not available, and therefore not included in the budget impact analysis (BIA).

The **uptake of the PGx test** was assumed to be 100%, meaning that all new users of any of the selected drugs would comply with the test. We also assumed that incident users would only be tested once. To identify the **cost per PGx test**, two approaches were simulated. One was a targeted approach (single-gene test), where the prevailing nomenclature code with the lowest price was used (565390-565401 with a fee of €185.18 per test on 01/01/24); in the second approach the use of a more complex test to identify more complex variants was assumed (565456-565460 with a fee of €426.41

per test on 01/01/24). For these more complex variants, at the moment, sequencing and panel tests are used (see chapter 3.7). For hospitalized patients, the total fee is at the RIZIV-INAMI's charge, and the patient share is €0. When the test is done ambulatory, patients without a preferential reimbursement status pay €8.68 per test as co-payment and the remainder of the fee is at the RIZIV-INAMI's charge (i.e., €176.50 for a simple test and €417.73 for a complex test). In our BIA we assumed that 78% of the PGx tests would be done ambulatory, and the remaining 22% in hospital. This proportion was obtained from the IMA-AIM database reporting the cumulative number of PGx tests performed over the years 2014-2021 and the setting in which those tests were performed (ambulatory versus hospitalized) for the 11 drugs listed above.

We developed a **base-case BIA** in which we assumed that single-gene tests would be used for all drugs, except for eliglustat and thiopurines (azathioprine, mercaptopurine, thioguanine) which require more complex (and expensive) tests to detect CYP2D6 and TPMT/NUDT15 respectively. We assumed that 100% of eliglustat-initiators and 50% of thiopurine-initiators would be tested with such a complex test. We further explored two variations of this base-case, assuming 1) that all drug initiators would be tested with single-gene PGx tests (PGx Minimum) and 2) that all drug initiators would be tested with complex PGx tests (PGx Maximum).

In a scenario analysis (**Scenario 1: PGx/Phenotype**), the availability of alternatives to genotyping was explored, e.g. phenotyping. We assumed that 50% of patients initiating a treatment with fluorouracil, capecitabine, tegafur or clopidogrel would be phenotyped, while all other incident users (on those and other drugs) would be genotyped. Just as for PGx tests, the uptake of phenotyping was set at 100%. It was assumed that incident users would only take one of the two tests, either the phenotype or genotype test. This is a simplification, as in reality, some patients may require a combination of PGx

^{hh} Medical need program: a program for a group of patients with a life-threatening disease, a chronic disease or a seriously debilitating disease which cannot be satisfactorily treated with a product that is licensed, commercially available in Belgium and reimbursed for this indication.

ⁱⁱ Although 2021 is the most recent year available from the IMA-AIM database, we have chosen not to use this data. Because of the COVID-19 pandemic, 2020 and 2021 were considered not representative of the general trend data.



and phenotype tests. The cost of phenotyping was valued at €50 per test for capecitabine, fluorouracil and tegafur (based on info from the survey, see chapter 3.7), and €31.22 per test for clopidogrel (nomenclature code 554013- 554024), both assumed to be totally at the RIZIV-INAMI's charge. As for the base-case BIA, two approaches were adopted: one in which genotyping is performed with single-gene tests (PGx/Phenotype Minimum) and another in which genotyping is done with complex PGx test (PGx/Phenotype Maximum).

In a second scenario analysis (**Scenario 2: Phenotype**) it was assumed that all patients initiating a treatment with fluorouracil, capecitabine, tegafur or clopidogrel would be phenotyped, while incident users of other drugs would all be genotyped, with a 100% uptake for both types of tests. Here again two approaches were taken: one in which genotyping is performed with single-gene tests (Phenotype Minimum) and another in which genotyping is done with a complex test (Phenotype Maximum).

The base-case and scenarios analyses are performed for both the **conservative** (9 drugs) and the **extended approaches** (11 drugs). A summary of the simulated scenarios is presented in Table 30

6.3 Result

6.3.1 Conservative approach

The conservative approach covered nine drugs, including abacavir, systemic fluorouracil, capecitabine, tegafur, azathioprine, mercaptopurine, thioguanine, siponimod, and eliglustat. According to the IMA-AIM data from 2019, an estimated 10 271 patients would initiate one of these 9 drugs per year, of which systemic fluorouracil initiators were the largest group (n=7148, nearly 70%), see Table 31.

The **base-case analysis** assumed the use of targeted single-gene tests for all drugs, except for eliglustat and thiopurines (azathioprine, mercaptopurine, thioguanine), which require more complex (and costly) approaches (in 50% of the thiopurine-initiators and 100% of the eliglustat-initiators). Assuming a 100% PGx test adoption rate among the incident users, the total cost of PGx testing for the 9 drugs would be €2 095 933.

Most of this cost (€2 026 394) would be covered by RIZIV-INAMI. If single-gene tests were used for all drugs, the total cost would be €1 901 984 (€1 832 445 for RIZIV-INAMI), while if complex tests were used, the total costs would be €4 379 657 (€4 310 118 for RIZIV-INAMI). Patients' costs would be constant at €69 539, as the co-payment for ambulatory PGx testing is fixed at €8.68, regardless of whether the PGx approach is simple or complex.

In the **first scenario analysis**, which considers phenotyping in 50% of the patients initiating a treatment with fluorouracil, capecitabine, or tegafur and genotyping for all other patients, the total costs would be lower compared to the base-case analysis, at €1 324 630 (€1 284 008 for RIZIV-INAMI) assuming a targeted single-gene approach for genotyping and €2 772 010 (€2 731 388 for RIZIV-INAMI) assuming a complex approach to genotyping.

The **second scenario analysis** considers phenotyping all patients who initiate a treatment with fluorouracil, capecitabine, or tegafur. This leads to the cheapest alternative, with total costs below €1.2 million: €747 276 (€735 570 for RIZIV-INAMI) for the simple approach to genotyping, and €1 164 363 (€1 152 657 for RIZIV-INAMI) for the complex approach to genotyping.

6.3.2 Extended approach

In this extended approach, the BIA considered two additional drugs, irinotecan and clopidogrel, in addition to the 9 drugs included in the conservative approach. The number of patients eligible for a PGx test was estimated to be 10 271 in the conservative approach. The inclusion of irinotecan would increase the number of eligible patients by 22% to 12 557. In contrast, with 36 919 new incident users, the additional inclusion of clopidogrel in the list of essential drugs would result in a 4-fold increase in the total number of incident users, from 12 557 to 49 476 patients.

Compared to the conservative approach, the base-case budget of the extended approach increased proportionally with the additional number of patients on the new drugs.



In the **base-case analysis**, the addition of **irinotecan** to the 9 initially selected drugs increases the total budget from €2 095 933 to €2 519 254 (€2 434 238 for RIZIV-INAMI). If simple PGx tests were used for all drugs, the total costs would be €2 325 305 (€2 240 289 for RIZIV-INAMI). If only complex PGx tests were used, the total costs would be €5 354 430 (€5 269 414 for RIZIV-INAMI). The patients' costs would be €85 016. The subsequent inclusion of **clopidogrel** would significantly increase the total budget, to €9 355 915 (€9 020 942 for RIZIV-INAMI), ranging from €9 161 966 (€8 826 993 for RIZIV-INAMI) assuming all PGx tests are valued at the lowest fee (single-gene test) of the prevailing nomenclature, up to €21 097 061 (€20 762 089 for the RIZIV-INAMI) if the highest fee of the nomenclature is used (complex tests). The patients' costs would also increase to €334 972.

The budgets for the base-case analyses of the extended approach could be reduced if patients were tested based on phenotyping instead of genotyping for certain drugs.

In the **first scenario analysis**, where phenotyping is considered for 50% of the patients on fluorouracil, capecitabine, tegafur or clopidogrel and genotyping for the other 50% (and for 100% of the other drugs), the budget for testing 10 drugs (the 9 drugs of the conservative approach plus **irinotecan**) ranged from €1 747 951 (€1 691 852 for RIZIV-INAMI) for the simple test to €3 746 783 (€3 690 684 for RIZIV-INAMI) for the complex test. When further adding **clopidogrel**, the budget would range from €5 742 587 (€5 561 510 for RIZIV-INAMI) for the simple test to €12 194 404 (€12 013 327 for RIZIV-INAMI) for the complex test.

In the **second scenario analysis**, where all patients starting treatment with fluorouracil, capecitabine, tegafur or clopidogrel would be phenotyped, the budget would be further reduced compared to the base-case or the first scenario analysis. When testing for 10 drugs (the 9 drugs of the conservative approach plus **irinotecan**), the total costs would range from €1 170 598 (€1 143 415 for RIZIV-INAMI) for the simple approach to genotyping to €2 139 136 (€2 111 953 for RIZIV-INAMI) for the complex approach to genotyping. When including **clopidogrel** in the list of drugs, the total budget

would range from €2 323 209 (€2 296 026 for RIZIV-INAMI) for the simple test to €3 291 747 (€3 264 564 for RIZIV-INAMI) for the complex test.

6.4 Limitations of the budget impact analysis

The main limitation of this BIA is that the costs considered were limited to the cost of the tests, without considering the other costs or savings that may occur over time, such as the (additional or avoided) adverse event, drugs, procedures or hospitalizations. Moreover, the costs of the tests were based on the current fees of RIZIV-INAMI.

The limitative list with PGx indications is larger than the drugs selected for this BIA. For example, genotyping relevant CYP enzymes for possible ineffectiveness or side-effects for antidepressants, or tacrolimus were not considered in the BIA. In 2022 the volume of PGx tests for CYP was 728. This will probably increase as for the recent drug mavacantanem it is stated in the drug label to genotype CYP2C19 in order to determine the appropriate dose. Consequently, the possible budget impact might be larger.

We should also note that a PGx test can also be requested as part of a diagnostic bilan (without leading to a prescription for the drug). Therefore, the number of PGx tests is likely to be much larger than the number of patients who actually initiate treatment. In this sense, our budget impact analysis is an underestimate of reality.

We assumed a test uptake of 100%, which might not reflect reality (for example only a subgroup of patient might be tested in the case of clopidogrel only patients at high risk of recurrent ischemic events).¹⁸⁶ We also assumed that patients would only be tested once with either a phenotype or a genotype test. This is a simplification, as in reality some patients may need a combination of PGx and phenotype tests.

This BIA is therefore more a theoretical exercise, aimed mainly at highlighting the volumes of eligible patients and the options for testing them.



Key points

- Based on the analysis of existing explicit guidelines on testing and on expert consultation, a selection was made of **nine drugs** for which PGx testing was considered “**essential**” in Belgium, including abacavir, systemic fluorouracil, capecitabine, tegafur, azathioprine, mercaptopurine, thioguanine, siponimod, and eliglustat. It was estimated that an average of 10 300 patients would start one of these 9 drugs per year. The systematic implementation of genotyping for these 9 drugs would represent a budget of between €1.9 and 4.4 million per year, depending on the complexity of the PGx approach (i.e. whether a single gene test or a more complex test is used).
- The addition of **irinotecan** to the list of drugs would increase the number of patients to be tested by 22% to 12 557 new patients per year. The subsequent inclusion of **clopidogrel** would increase the total number of patients fourfold, from 12 557 to 49 476 patients. The introduction of genotyping for these two new drugs would significantly increase the budget.
- For certain drugs, patients can be tested using **phenotyping** instead of genotyping. This is the case for fluorouracil, capecitabine, or tegafur, which represent just over 8500 new patients per year. Phenotyping of clopidogrel users is also an option, concerning almost 37 000 new patients per year. At the current fees for genotyping and phenotyping, phenotyping is by far the least expensive option. If all patients on fluorouracil, capecitabine, tegafur, or clopidogrel were phenotyped and those on the other drugs on the list were genotyped, the budget would be between €2.3 and €3.3 million at most.



Table 30 – Scenarios for the budget impact analyses

	PGx	Base-case		Scenario 1		Scenario 2	
		PGx Minimum	PGx Maximum	PGx/Phenotype Minimum	PGx/Phenotype Maximum	Phenotype Minimum	Phenotype Maximum
Drugs	Conservative approach: abacavir, systemic fluorouracil, capecitabine, tegafur, azathioprine, mercaptopurine, thioguanine, siponimod, eliglustat. Extended approach: irinotecan, clopidogrel						
Genotype / phenotype	Genotype all			Phenotype for fluorouracil, capecitabine, tegafur and clopidogrel			
PGx test	Complex* PGx test for: - 100% eliglustat - 50% thiopurines Simple PGx test otherwise	Simple PGx test	Complex* PGx test	Simple PGx test	Complex* PGx test	Simple PGx test	Complex* PGx test
% PGx tests done ambulatory	78%	78%	78%	78%	78%	78%	78%
% incident users that undergo phenotyping	0%	0%	0%	Fluorouracil, capecitabine, tegafur, clopidogrel: 50% Otherwise: 0%		Fluorouracil, capecitabine, tegafur, clopidogrel: 100% Otherwise: 0%	
Uptake PGx	100%	100%	100%	100%	100%	100%	100%
Uptake Phenotype	-	-	-	100%	100%	100%	100%
Cost PGx test	Simple: €185.18 Complex: €426.41	€185.18	€426.41	€185.18	€426.41	€185.18	€426.41
Cost phenotype	-	-	-	€31.22 for clopidogrel, €50 otherwise		€31.22 for clopidogrel, €50 otherwise	

* Complex PGx test meaning more difficult gene variants or multiple genes need to be checked. This is the case for CYP2D6 (relevant for eliglustat) and thiopurines (azathioprine, mercaptopurine, thioguanine). At the moment sequencing and panel tests can be used for this.



Table 31 – Results of the budget impact analyses

Drug	Incident users IMA-AIM data 2019		Base-case			Scenario 1		Scenario 2	
			PGx	PGx Minimum	PGx Maximum	PGx/phenotype Minimum	PGx/phenotype Maximum	Phenotype Minimum	Phenotype Maximum
1 Abacavir	0,3%	125	€23 148	€23 148	€53 301	€23 148	€53 301	€23 148	€53 301
2 Systemic fluorouracil	14,4%	7 148	€1 323 667	€1 323 667	€3 047 979	€840 533	€1 702 689	€357 400	€357 400
3 Capecitabine	2,8%	1 385	€256 474	€256 474	€590 578	€162 862	€329 914	€69 250	€69 250
4 Tegafur	0,0%	9	€1 667	€1 667	€3 838	€1 058	€2 144	€ 450	€ 450
5 Azathioprine	2,6%	1 282	€392 029	€237 401	€546 658	€237 401	€546 658	€237 401	€546 658
6 Mercaptopurine	0,4%	206	€62 994	€38 147	€87 840	€38 147	€87 840	€38 147	€87 840
7 Thioguanine	0,2%	112	€34 249	€20 740	€47 758	€20 740	€47 758	€20 740	€47 758
8 Siponimod	0,0%	0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
9 Eliglustat	0,0%	4	€1 706	€ 741	€1 706	€ 741	€1 706	€ 741	€1 706
10 Irinotecan	4,6%	2 286	€423 321	€ 423 321	€ 974 773	€423 321	€ 974 773	€423 321	€ 974 773
11 Clopidogrel	74,6%	36 919	€6 836 660	€6 836 660	€15 742 631	€3 994 636	€8 447 621	€1 152 611	€1 152 611
Total (conservative approach, drugs 1-9)	10 271		€2 095 933	€1 901 984	€4 379 657	€1 324 630	€2 772 010	€ 747 276	€1 164 363
RIZIV-INAMI			€2 026 394	€1 832 445	€4 310 118	€1 284 008	€2 731 388	€ 735 570	€1 152 657
Patient			€69 539	€69 539	€69 539	€40 622	€40 622	€11 706	€11 706
Total + irinotecan (drugs 1-10)	12 557		€2 519 254	€2 325 305	€5 354 430	€1 747 951	€3 746 783	€1 170 598	€2 139 136
RIZIV-INAMI			€2 434 238	€2 240 289	€5 269 414	€1 691 852	€3 690 684	€1 143 415	€2 111 953
Patient			€85 016	€85 016	€85 016	€56 100	€56 100	€27 183	€27 183
Total + irinotecan + clopidogrel (drugs 1-11)	49 476		€9 355 915	€9 161 966	€21 097 061	€5 742 587	€12 194 404	€2 323 209	€3 291 747
RIZIV-INAMI			€9 020 942	€8 826 993	€20 762 089	€5 561 510	€12 013 327	€2 296 026	€3 264 564
Patient			€334 972	€334 972	€334 972	€181 078	€181 078	€27 183	€27 183

IMA-AIM data: national reimbursement database (InterMutualistisch Agentschap – Agence InterMutualiste).



7 INTERNATIONAL COMPARISON OF PGX IMPLEMENTATION

This chapter provides several sources of inspiration for optimising pharmacogenetic testing in Belgium. How do other countries implement PGx in their health system and can we learn from them?

7.1 Methodology

The countries for this international comparison (The Netherlands, France, Switzerland, and the United Kingdom) were selected based on their contributions to the international research community related to PGx, the extent to which it is currently implemented, and their comparability to the Belgian health care system. The information for each selected country was retrieved primarily using desk research (peer-reviewed scientific publications and grey literature as well as official government databases and websites) and semi-structured interviews with international experts of each selected country. Experts were selected based on their membership of (national) pharmacogenetics working groups, their involvement in (local) clinical trials or government projects related to pharmacogenetics, and/or their authorship of leading scientific publications in the field. The list of consulted international experts as well as the interview questions are included in Table 49 and Table 50 in appendix. To validate our findings, each overview was reviewed by at least one additional expert of the respective country. In each country section there is a paragraph on challenges related to PGx, which is primarily based on expert input (which is more subjective to the individual's opinion or experiences).

7.2 The Netherlands

The Netherlands is considered to be at the forefront of PGx in Europe, both in terms of research as in the implementation in clinical practice. The guidelines of the Dutch Pharmacogenetics Working Group (DPWG) are internationally recognised as a PGx resource.^{26, 160, 248, 252-254}

7.2.1 *Who is entitled to prescribe and perform pharmacogenetic tests?*

Most PGx testing is performed in the hospital setting based on the prescription of a specialist (e.g. oncology, psychiatry).²⁵⁵

Since 2017, a limited number of policlinics in “pharmacogenetics”, often linked to or part of academic hospitals, have started to emerge, where patients requiring medication optimization can access specialist care. In most cases an explicit referral by a physician (GP or specialist) is necessary (e.g. policlinic for psychopharmaca).^{256, 257} These clinics are staffed with clinical pharmacologists, which, in the Netherlands, is a specific specialisation open for physicians and (hospital)pharmacists.

In primary care, general practitioners (GPs) rarely prescribe PGx tests. In addition, fuelled by the many research initiatives, the pharmacists can also take the initiative to test, but require the confirmation of a physician to be eligible for reimbursement.²⁵⁸ According to local experts, the role of the Dutch pharmacists in PGx might increase further in the future as they are specifically being trained on the topic and are already involved in several pilot studies. Moreover, the DPWG guidelines disseminated by the Dutch Association of Pharmacists are internationally renowned.

In the Netherlands, 19 (in 2024) specialized labs currently perform PGx testing. Erasmus MC is designated as the national reference centre for PGx.²⁵⁹ Dutch labs performing PGx testing require the ISO15189 accreditation.²⁵⁸ The Dutch law on population screening states that offering direct-to-consumer (DTC) genetic testing towards cancer and untreatable disease is illegal in the Netherlands.²⁶⁰ However, PGx seems to be in a legislative grey zone where there is no prohibition, but also no clear allowance of DTC PGx. In addition, citizens can order the tests online from foreign suppliers. Several local sources warn for the potential disadvantages



of DTC genetic testing on the Dutch health care system (e.g. overdiagnosis, overtreatment, unknown or low clinical validity), especially on Dutch GPs as DTC companies often refer patients to GPs for more information or further diagnoses based on their DTC test results.^{261, 262} Recently, a group of pharmacies have started to offer a pharmacogenetic panel test (27 genes) based on a buccal swab to all clients (i.e. with or without medical indication) at a cost of €299.²⁶³

7.2.2 Which tests are (recommended to be) performed for which drug-gene interactions?

A primary source are the guidelines of the **DPWG** which include **testing recommendations** as well as associated **therapeutic (dosing) recommendations**.¹⁴ For more information on the DPWG guidelines, we refer to chapter 4.1.3.2 of this report. The DPWG list of recommended tests is categorised in “essential”, “beneficial” and “potentially beneficial”. This is a source of information for prescribers and labs and is currently not enforced by the Dutch government nor always reflected in practice guidelines of the medical scientific associations, but it can be used by health insurers to check whether sufficient evidence is available to offer reimbursement (see section 7.2.4).²⁵⁸

While the DPWG suggests PGx tests before prescribing certain medications, the Dutch Association of General Practitioners (NHG) takes a more cautious approach. NHG recommends against routine PGx testing before initiating drug treatment but considers it an option when side effects or inefficacy arise. The guideline emphasizes the importance of assessing other potential risk factors (such as smoking, comorbidities, nutrition, adherence, etc.) before resorting to pharmacogenetic testing. PGx testing is presented as one of the alternatives alongside prescribing a different drug or employing therapeutic drug monitoring. When considering PGx, GPs are advised to discuss the added value of such a test with a pharmacist or lab specialist.²⁵⁵ The Dutch Association for Psychiatry also published a guideline related to PGx in the daily psychiatric practice with a focus on the CYP enzymes. Similar to NHG, the guideline for psychiatrists advises to consider genotyping CYP2D6 and CYP2C19 only when drug ineffectiveness or adverse drug reactions cannot be explained by other factors (e.g. smoking behaviour, therapy adherence, nutrition, etc.).²⁶⁴

In the Netherlands, there are no legal restrictions on when the pharmacogenetic testing can be performed; either reactively (i.e. upon prescribing the drug when specified in drug label, after the start of the drug treatment when the drug treatment is ineffective or in case of adverse drug reactions), semi-preemptively (i.e. panel of genes but with a medical indication for at least one drug-gene combination in the panel), and preemptively (i.e. without medical indication). However, **only reactive testing is covered by the Dutch health care insurance** (basic package). The semi-preemptive testing strategy with panel testing is only covered in a supplemental insurance package (anno 2023 only one health care insurer). More information on the reimbursement of PGx is available further in section 7.2.4. Labs offer different PGx panels to patients (e.g. PGx passport, cardiovascular panel, oncological panel, psychiatry panel, etc.).²⁶⁵

Unfortunately, no data on the national volumes of PGx tests could be retrieved. Based on data of the Leiden University Medical Centre (LUMC), which is one of the labs responsible for the highest testing volumes in the Netherlands, a clear and steady upward trend is visible in the volumes of pharmacogenetic tests. Starting with less than 500 tests in 2011, volumes in this hospital's laboratory have risen to approximately 2750 tests in 2021.²⁶⁶

7.2.3 Communication

In the Netherlands, it is not required for the patient to sign an informed consent prior to PGx testing.

If the prescribing physician is affiliated to the same hospital as the testing lab, in the contacted Dutch hospitals, the results are **inserted in the hospital Electronic Health Records (EHR) as a contra-indication** (e.g. similar to an allergy), which enables the PGx test result to be flagged in the hospital EHR when drug(s) are prescribed. Several clinician, hospital and pharmacist guidelines indicate the contra-indications as the designated place to store known PGx information.^{255, 264, 267, 268} This implies that when the patient revisits the physician after test completion (or another physician in the hospital), the physician prescribing the drug will receive a pop-up showing a message that the patient possesses an actionable gene-variant associated to this drug. In addition, the pop-up also immediately shows the (dosing) recommendations based on the DPWG guidelines, which are



embedded in the Dutch drug repository (i.e. Z-index in G-standaard) and are updated every month.^{258, 266} Unfortunately, transferring the results from the lab results section in the EHR to the contra-indications in the EHR currently still requires a manual intervention.²⁶⁶

If the prescriber of the PGx test is not based in the same hospital as the testing lab, the test results are communicated to the prescriber via a report (e.g. GP, pharmacist, physician based in other hospital). The prescriber is then required to **manually enter the test results as a contra-indication** in their respective software(s) if they want to benefit from the automated pop-ups and automatic linkage with the DPWG recommendations (if their software includes this feature).²⁶⁶

Sharing the PGx results nationally with other treating physicians or pharmacists (via *Landelijk Schakel Punt*ⁱⁱ), requires the **explicit consent of the patient**. A few hospital labs offer a **PGx passport** (e.g. credit-card format, app, etc.) to patients, which contains the results of an in-house developed panel test.^{258, 266}

In general, the turnaround time between arrival of the sample in the lab and delivering the results varies between three days and two weeks but is highly dependent on the requested test and the executing lab. The turnaround times for DPYD and TPMT are generally the shortest.²⁶⁹

The communication of the results to the patient and possible adaptations to the drug therapy are generally done by the prescriber (clinical pharmacologist consultations are possible see 7.2.1). The consultation is reimbursed by health insurers only when the prescriber is a physician.²⁵⁷

7.2.4 How is pharmacogenetics funded & reimbursed?

The billing of PGx testing in the Netherlands follows the general Dutch health care billing system which distinguishes between health care within and outside the hospital setting. In general, when the test is prescribed by a GP, the laboratory executing the test will bill the patient or his/her health insurer. When the test is performed in the hospital setting, the test will not be billed separately but is part of a disease-specific lump sum covering the treatment trajectory (i.e. Diagnosis-Treatment Combinations; “*Diagnose Behandel Combinaties*”; DBCs).^{270, 271} In the Netherlands, approximately 4500 DBCs are defined with an associated pre-specified price level based on the average cost of the treatment trajectory.²⁷²

The reimbursement of health care interventions in the Netherlands is embedded in the Health Insurance Act (Zorgverzekeringswet; ZVW). The ZVW defines a limitative list of broadly described categories of health care interventions (i.e. “*basispakket*”, hereafter referred to as “basic package”) which have to be reimbursed to persons falling under the obligatory insurance by every health insurer. The insured first have to pay a pre-determined sum themselves for a set of interventions before being eligible for reimbursement (i.e. “*eigen risico*”, hereafter referred to as “deductible”). In 2023, this deductible was €385 or higher for subjects preferring to pay a lower fee for health insurance.²⁷³

PGx testing, as part of the broad category of laboratory examinations, falls within **the basic package** if there is a **specific medical need** to perform the test (i.e. in case of drug ineffectiveness, adverse drug reactions, or when specified in the drug label). How this general principle of medical necessity is interpreted by the health insurers may differ among the various insurers and additional criteria may need to be met in order to receive reimbursement. As an example, we highlight the criteria of a major Dutch health insurer. This specific insurer generally reimburses PGx testing when two conditions are met. First, the patient should receive drugs which are

ii The “Landelijk Schakelpunt” is designed as a technological health infrastructure in which health professionals can participate with the purpose of sharing medical data. More information is available on <https://www.volgjezorg.nl/uitwisseling>.



(quasi-)ineffective or experience adverse drug reactions in line with the abovementioned general principle. Second, there should be evidence available that the adverse drug reactions or drug ineffectiveness are possibly caused by genetic predisposition and alternatives for the drug should be available. To evaluate this second criterium, the health insurer relies on the assessment of the treating physician. This particular health insurer additionally stipulated that in order to receive reimbursement for a PGx test performed **before** the drug therapy has started (e.g. when specified in the drug label), the test should be prescribed by a specialist as these types of tests are not reimbursed when being prescribed by GPs.²⁷⁰

Preemptive testing without a medical necessity is not reimbursed by the health insurers within the basic package. Some Dutch health insurers (we identified one) offer a **supplemental insurance plan** (+€66.66/month) which does reimburse amongst others **semi-preemptive testing** for a maximal amount of €350/year under conditions similar to the setting of the PREPARE study, in which semi-preemptive panel testing was performed in case of a first-time prescription of a drug included in the DPWG guidelines.

^{26, 274}

The Dutch Association of Clinical Chemistry and Laboratory Medicine (NVKC) as well as ERASMUS MC publish prices of PGx tests publicly. The prices of single-gene tests range between €59 and €378, but are highly variable between individual tests and laboratories. In addition, price deals are often made between health insurers and laboratories leading to different prices for PGx tests. Panel tests are generally more expensive, with prices ranging from €470 for an oncological panel to €912 for a full PGx passport.

^{269, 275}

7.2.5 *What are the remaining challenges for pharmacogenetics in the Netherlands?*

Local experts consider the semi-preemptive panel strategy the most (cost-)effective way of embedding PGx in the Dutch health care system. However, the Dutch minister recently expressed that there is currently insufficient proof on both the effectiveness and cost-effectiveness (limited number of studies and pilots) to justify the inclusion of panel-testing in the basic coverage.²¹¹ Moreover, the potential need to foresee pharmacist compensation has been cited as a barrier for implementation from a health care payer's view.

Several initiatives are ongoing to enlarge the evidence base (a cost-effectiveness study on the data of the PREPARE study, a local pilot project on PGx testing before the prescription of antidepressants in primary care, the European H2020 PSY-PGx study^{kk} on reactive testing for antidepressants and antipsychotics, etc.).²¹¹ In addition, the Dutch health care research funding agency ZonMw^{ll} launched a call in October 2023 to submit proposals for pilot projects aimed at embedding PGx panel tests (PGx passport) and pharmacogenetics-based prescribing in cardiology and psychiatry.

While the PGx info already has a place in the EHR (in the contra-indication section) in the Netherlands, it is limited to the phenotype (i.e. ultrarapid metabolizer, intermediate metabolizer, extensive/normal metabolizer, poor metabolizer). It would be more optimal to also include the genotypes and mutations, and ideally the raw data. This is a necessary condition for a future automatic translation of DPWG guideline updates into the contra-indications.²⁶⁶ Moreover, the automatic linkage between the lab information systems to the software packages of the health care professionals should be improved (as entering the PGx information in the contra-indications is performed manually) and an automated pop-up on testing requirements if a drug from the DPWG guidelines is prescribed to a patient who has not yet been tested could increase awareness among prescribers.²⁶⁶

^{kk} <https://www.psy-pgx.org/PSY-PGx>

^{ll} <https://www.zonmw.nl/en/about-zonmw>



7.3 France

In France, there is a legal base^{mm} and specific legislation aimed at genetic testing, including PGx: a *Décret*ⁿⁿ and an *Arrêté*.^{oo, 276} Both are in relation to constitutional genetics, but the former formulates a more basic regulatory framework and the latter is more detailed in its scope as it stipulates the organization of (pharmaco)genetic testing and defines the good clinical practice guidelines.

7.3.1 Who is entitled to prescribe and perform pharmacogenetic tests?

A PGx test, like any genetic test, can only be prescribed by:

- A physician with specialization in genetics (“*Un médecin généticien*”);
- A physician without a specialization in genetics who is familiar with the clinical situation (disease, therapeutic treatment) and the consequences for the family and who is able to interpret the result of the test. This physician must work in collaboration with a clinical genetics team.²⁷⁶

In addition to the *arrêté*, the French public health code additionally foresees that a genetic counsellor working under the supervision of a physician with a specialization in genetics is also allowed to prescribe PGx tests.^{277, 278}

Both the *décret* of 4 April 2008 and the *arrêté* of 27 May 2013 detail the requirements for the labs and their staff in order to be allowed to perform PGx testing. On top of the **basic accreditation** required for all labs in France, labs performing PGx testing need an **additional authorization for genetic testing of the ‘Agences régionales de santé’ (ARS)**, which mainly

evaluate whether the necessary infrastructure for genetic testing is present and conform. The ARS are the regional health authorities in France responsible for the regional management of the national health system.²⁷⁹ The final requirement for being allowed to perform PGx testing is for the lab to hold the **ISO15189 accreditation**, which is issued and controlled by the Comité français d'accréditation (COFRAC). Any lab in France meeting the abovementioned requirements is allowed to perform PGx testing, including private labs.

Important to note is that French legislation forbids all genetic testing outside the health care context (e.g. DTC testing).^{276, 280} The French legislators even introduced a fine of €3750 in their penal code for consumers ordering a (pharmaco)genetic test outside the health care setting.^{51, 281, 282} According to the annual report of Agence de la Biomédecine (ABM), summarized in appendix Table 53, 52 labs performed PGx testing in 2022.^{276, 283, 284} **Each year labs are obliged to deliver the volumes on a test-level to ABM.**^{276, 283}

The regulation also dictates rules related to the **staff** performing pharmacogenetic tests.²⁸⁴ In addition to general educational requirements, the staff has to possess a **license for pharmacogenetics**, issued by ABM and valid for five years. The license is based on training and experience (including research) in the field of (pharmaco)genetics (no particular educational degree is foreseen). In 2023, 44 French practitioners had a specific license for pharmacogenetics and 75 for HLA genotyping, of which 5 hold a license for both pharmacogenetics and HLA genotyping.²⁸⁵

^{mm} The Bioethical Legislation of 29 July 1994 “*Loi no 94-654 du 29 juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal (1)*”, specifically “*Titre VI Médecine prédictive et identification génétique*”.

ⁿⁿ *Décret n° 2008-321 du 4 avril 2008 relatif à l'examen des caractéristiques génétiques d'une personne ou à son identification par empreintes génétiques à des fins médicales.*

^{oo} *Arrêté du 27 mai 2013 définissant les règles de bonnes pratiques applicables à l'examen des caractéristiques génétiques d'une personne à des fins médicales (Hors diagnostic prénatal).*



In addition to the required accreditations and authorizations, several labs have obtained a recognition as reference lab for a specific PGx test. The *arrêté du 15 juillet 2021 fixant la liste des laboratoires de biologie médicale de référence* contains the various reference centres for each of the laboratory tests, including the various PGx tests. Any lab can request to become a reference centre, but no additional budget is foreseen. There is no limitation on the number of reference centres for a specific test. Every reference lab receives the recognition for five years after which the recognition is re-evaluated.^{280, 286}

7.3.2 Which tests are (recommended to be) performed for which drug-gene interactions?

The Réseau Francophone de Pharmacogénétique (RNPGx) is an association providing PGx guidance on which tests to perform and includes therapeutic recommendations (see chapter 0), though this is not necessarily disseminated or endorsed by the French health authorities. In France, there is only a legal obligation for knowing the DPD enzyme status of patients before starting a treatment with 5-fluoropyrimidines. Interestingly, HAS and the French National Cancer Institute (INCa) recommend to perform phenotyping instead of genotyping the DPYD gene.^{68, 280, 287} In addition, for some PGx tests there is a clear recommendation, e.g. for abacavir (HLA-B*5701) and eliglustat (CYP2D6).^{280, 288-290} Interesting to note is that, while these tests are categorized as 'recommended', one may be subject to legal sanctions if the recommendation is not followed.²⁹¹

The French legislation formulates a set of requirements which have to be met before a PGx is allowed to be performed.²⁷⁶ First, PGx tests are restricted to a limited number of indications for a specific drug: (1) prevention of serious adverse drug reactions, (2) choice of most appropriate therapeutic option, or (3) dose adjustment of a specific drug.^{162, 276} This means that a **preemptive test without primary indication** (e.g. panel test in the healthy general population) is currently **illegal**. In addition, the *arrêté* stipulates that a PGx test is only allowed to be performed if the **clinical validity and utility of the test has been demonstrated by multiple publications** in peer-

reviewed journals or when the test is **recommended in professional guidelines** (such as CPIC, DPWG, RNPGx) if the test is not recommended or mandated by the SmPC. This evidence should be available a posteriori (when COFRAC inspection requests clinical rationale for the test). Laboratories are free to choose which professional guidelines to follow or provide the evidence themselves using peer-reviewed journal articles.^{280, 291} The primary aim of the RNPGx is to provide this evidence to potential prescribers and labs with this obligation in mind.²⁸⁰ In practice, the implication of this legislation is that labs actively evaluate the requests for pharmacogenetics and can disagree with the prescribing physician. When in disagreement with the prescribing physician, the lab can refuse to carry out the test and/or recommend a more appropriate test for the indication. Labs are free to choose which technique (e.g. NGS, sanger sequencing, micro array, etc.) they use to analyse the samples. In practice, the cost of the technique and the reimbursement rate/funding often determine which technique is used. For example, the labs receive €78.3 for the analysis of UGT1A1*28 (see later), for which it is currently not possible to perform NGS.²⁸⁰

The annual reports of ABM also shed more light on the volumes of PGx testing in France (see Table 32 for volumes of most frequently performed PGx tests and appendix Table 53 for the evolution in national volumes of PGx tests). Globally, the number of tests has increased gradually over the years from 20 425 tests performed in 2012 to 32 298 tests in 2018 after which the volume decreased substantially towards 24 245 tests in 2022.^{292, 293} In addition to the COVID pandemic, this decline can be explained by the national guideline^{pp} on DPD testing where phenotyping is recommended over genotyping combined with a specific nomenclature code to receive reimbursement for DPD phenotyping.¹¹⁴ Most of the labs follow the recommendation, but not all (e.g. when equipment/infrastructure is not present in the lab).²⁹²⁻²⁹⁴ When not taking into account the DPYD tests due to the change in DPYD testing guidelines, a continued increase in the pharmacogenetic testing volumes can still be observed. Most of the PGx tests performed are reimbursed (see later).

^{pp} Guideline produced by the HAS, in collaboration with ANSM and INCa.

**Table 32 – Volumes* of most frequently performed PGx tests in France**

		2020	2021
Toxicity of fluorouracil derivatives	DPYD	7283	5248
	TYMS	3	3
Toxicity of abacavir	HLA-B	3953	4031
Toxicity and dose adaptation of azathioprine or 6-mercaptopurine	TPMT	3637	3681
	NUDT15	122	178
Dose adaptation of tacrolimus	CYP3A5	1919	1880
	CYP3A4	1491	1378
Toxicity of irinotecan	UGT1A1	4283	3133
Toxicity and dose adaptation of antidepressants or antipsychotics	CYP2C19	491	607
	CYP2D6	799	565
	CYP3A5	305	437
	CYP3A4	305	437
	CYP2C9	192	273
	CYP1A2	142	173
	UGT1A1	0	155
	ABCB1	157	155
	CYP2B6	56	2
	CYP1A2	226	331
Toxicity or non-response of clozapine	ABCB1	0	63
	MTHFR	189	344
Dose adaptation of methotrexate	TPMT	10	5
	TPMT	22	226
Toxicity of cisplatin	TPMT	22	226
Susceptibility to undesired effects of mercaptopurine	ITPA	69	104
	NUDT15	0	95
Resistance to clopidogrel	CYP2C19	138	136
	P2RY12	54	48

* Reimbursed and non-reimbursed volumes in number of tests for most frequently performed PGx tests. The full table is available in the reports of Agence de la Biomédecine.²⁹²

²⁹³ Data of 2022 was not shown due to sub-optimal data quality and different classifications compared to 2020 and 2021.



7.3.3 Communication

The French legislation states that the prescriber has to be able to deliver complete and comprehensible information to the patient before the prescription of the test and obtain a **written signed informed consent** of the patient (as for any genetic test).^{276, 284, 295} The informed consent is often part of the lab ordering form and has to be sent to the lab performing the test.

After conducting the test and interpreting the test results, the lab only delivers the results to the prescribing physician. French legislation prohibits labs from sending the results directly to the patient or other health professionals.²⁷⁶ At the moment clinical pharmacologists do not have an additional role related to PGx, however educational programs to obtain the title and degree of pharmacologist exist in France (Master, PhD, formations spécialisées transversales).

A turnaround time of five and ten days has been reported,²⁸⁷ but in practice this is often longer (up to 30 days or more for some tests).²⁹¹ There are no specific pharmacogenetic consultations or input from pharmacologists foreseen in transferring the message to the patient.

Currently, PGx test results are stored as a PDF-file in the EHR, which does not allow to trigger pop-ups when a physician prescribes a drug for which the patient carries a known actionable variant.²⁸⁷ HAS, in collaboration with Agence nationale de sécurité du médicament et des produits de santé (ANSM), published a drug-indexed decision support system (SAM) on its website in 2021 which enables prescribers to integrate an automated alert message into their prescribing software packages when 5-fluorouracil (5-FU) or capecitabine is being prescribed.^{296, 297} However, there is no obligation for the prescribing software's publishers/editors to integrate these messages in their systems, which hampers implementation.²⁹¹

7.3.4 How is pharmacogenetics funded & reimbursed?

Before 2016, there was a substantial lack of public funding for PGx in France. In 2016, this situation changed due to the inclusion of several PGx tests in the complementary list of biological tests for which partial funding is available.¹⁶² Since then, the funding and reimbursement of PGx has been extended substantially over the years. There are three ways of reimbursing PGx in France.

The **official French nomenclature** currently only contains one PGx code, for the HLA-B*5701 gene in view of an abacavir prescription. A tariff of €52 (200 B) corresponds to the code and is fully reimbursed to the labs by the French national health insurance. Another code in the nomenclature is foreseen for phenotyping the DPD enzyme.

Besides the official nomenclature funded via the national health insurance, a selection of PGx tests in France is funded via two channels of the ministry of health:

The **RIHN (référentiel des actes innovants hors nomenclature)** lists innovative acts outside the nomenclature of biology and anatomopathology. The funding is conditional on the deliverance of a prospective and comparative collection of data to validate the clinical efficacy and the clinical and health-economic usefulness of these innovative procedures. The gathered data will facilitate their subsequent evaluation by HAS to be included in the official nomenclature. RIHN has a closed budget (research envelope). Reimbursement of the acts on the RIHN list is **limited to 40% to 60% of the tariff**.^{280, 298} At the time of writing this report, HAS was in the process of evaluating the sequencing and analysis of one or more gene panels by NGS in post-natal constitutional genetics (particularly in the fields of pharmacogenetics, oncogenetics and rare diseases). RIHN code N350, which is currently used for pharmacogenetic panel analyses, is part of this HAS evaluation. HAS will assess the clinical utility of these procedures in routine care for defined indications. Depending on the outcome of the HAS assessment, the procedure (in this case the panel test) may or may not be included in the official nomenclature. An inclusion in the official nomenclature would mean the procedure is covered by the French national health insurance.²⁹¹



A third source of funding of PGx is the **complementary list** of acts outside the official nomenclature and RIHN. The complementary list is made up of acts and procedures which are no longer considered to be innovative acts, but still await an evaluation by HAS to be included in the official nomenclature. Similar to RIHN, the acts on the complementary list are reimbursed to the labs **for 40-60% of the tariff**.^{291, 298} The tariffs of the acts on the complementary list range between €32.4 and €153.9.

As discussed above, the acts listed in the RIHN and the complementary list are only funded for 40-60%. According to the consulted experts, this amount generally covers the expenses made by the labs.²⁸⁰ Any expenses made above this amount are paid by the prescribing hospital, also when the test is sent to another lab for analysis as this lab will invoice the test back to the prescribing hospital which can request funding from the closed envelope.²⁹¹

The tests included in the official nomenclature, RIHN and the complementary list are reimbursed to every lab authorized to perform PGx testing (see 7.3.1), including private labs.^{162, 280, 291}

Table 33 summarizes the funding and reimbursement of the various (partially) reimbursed pharmacogenetic tests in France.



Table 33 – Reimbursement of genotyping and phenotyping per source of funding in France

Code	Title	Gene(s)	Drug(s)	Tariff 2023 (100%)	Reimbursement
1. Nomenclature					
1.A. Pharmacogenetic testing (genotyping) in nomenclature*					
1691	Recherche allele HLA-B*5701	HLA-B*5701	Abacavir	€52 (200 B)	100%
1.B. Phenotyping in nomenclature					
0500	Dépistage d'un déficit en dihydropyrimidine deshydrogenase	DPD	5-fluoro-pyrimidines	€31.2 (120 B)	Not refundable at 100%
2. RIHN					
N903	Fluorescent simplex DNA PCR and automatic sequencer analysis	Generic	Generic	€37.8	40-60%
N350	Forfait high-throughput sequencing (NGS) < 20 kb	Generic	Generic	€882.9	40-60%
3. Complementary list					
3.A. Pharmacogenetic testing (genotyping) in complementary list					
M101	Genotyping cytochrome P450 3A5 for adjustment of the dose of a treatment with tacrolimus in transplantations	CYP3A5	Tacrolimus	€78.3	40-60%
M103	Genotyping TPMT for the adjustment of the dose of a treatment consisting of a drug with thiopurine	TPMT	Azathioprine & Mercaptopurine	€110.7	40-60%
M104	Genotyping UGT1A1 for the adjustment of the dose of treatment consisting of irinotecan	UGT1A1	Irinotecan	€78.3	40-60%
M118	Genotyping of cytochrome P450 2D6 as part of a prescription for eliglustat or tamoxifen	CYP2D6	Eliglustat & Tamoxifen	€78.3	40-60%
G301	Testing for the presence or confirmation of the absence of an HLA allele (restricted list of prescription indications)*	HLA	Not disclosed	€47.25	40-60%
3.B. Phenotyping in complementary list					
J103	TPMT activity	TPMT	Not disclosed	€67.5	40-60%
3.C. Other relevant tests in complementary list					
N906	Detection of punctual mutations using Sanger	Generic	Generic	€153.9	40-60%

Source: ^{280, 287, 298-300}. The value of B is fixed at €0.26 for 2023 in Arrêté du 26 janvier 2023.³⁰¹ HAS considers testing for genotypic resistance to antiretroviral drugs also as PGx testing (and two codes are included in the official Nomenclature). * The restricted list of prescription indications could not be retrieved. A French expert HLA disclosed using the codes 1180 (€98.8) and 1181 (€182) from the official nomenclature to receive reimbursement for HLA genotyping until G301 is added in the nomenclature.



7.3.5 What are the remaining challenges for pharmacogenetics?

The publication of Barin-Le Guellec et al. and the local expert in France formulated four main challenges for PGx in France.^{280, 287} A first challenge to be addressed is to **reduce the knowledge gap**, for example by incorporating the PGx topic into the basic and continued education of future physicians and pharmacists. In addition, more patient education on the topic will be necessary for PGx testing to become embedded and (cost-)effective in the French health care system. Efforts are underway to include clinical pharmacists and pharmacologists in the communication process with patients regarding PGx. Additionally, the experts deem **pharmacogenetic counselling** sessions useful for further implementation and correct interpretation of PGx testing in the future.^{280, 287}

The second major challenge is related to the **communication and storage of test results**. The infrastructure to share patient results with other health care professionals exists in France, but is unfortunately rarely used.²⁸⁰ There is a risk the communication of test results to the patients is done without proper interpretation.²⁸⁷ In case a PGx passport would be handed out to the patient, the patient decides who is allowed access to the test results. In this scenario, an additional consultation would be required to hand over the passport and explain the implications.²⁸⁰ Pharmacists could be engaged, though currently lack the knowledge to expand responsibility.²⁸⁰

According to Barin-Le Guellec et al., an additional challenge to the widespread adoption of PGx in the French health care system is the **funding and reimbursement**. While some tests have been added to the nomenclature, which warrants full reimbursement, there are still tests not eligible for reimbursement and tests which are only partially funded (e.g. RIHN and complementary list).²⁸⁷

The research field is moving towards panel testing. Due to legal restrictions preventing a full preemptive panel test in healthy individuals, the **semi-preemptive approach** with a panel test initiated when a first drug is put forward.²⁸⁰

7.4 Switzerland

In Switzerland, PGx testing is regulated in the Federal Law on Human Genetic Analysis of 1 December 2022 (nr. 810.12) and the Ordonnance on Human Genetic Analysis of 3 March 2023 (nr. 810.122.1). The Federal Law regulates the general framework for human genetic testing, while the Ordonnance lists the exceptions to the Federal Law with their own corresponding regulatory frameworks. The Federal Law applies to PGx as it is part of the category “human genetic testing for medical purposes with the aim of determining the effects of a particular therapy”. However, “pharmacogenetics” is not explicitly mentioned in the Federal Law. The Ordonnance defines pharmacogenetics as “genetic analyses of characteristics influencing the effect of drugs”.

7.4.1 Who is entitled to prescribe and perform pharmacogenetic tests?

While other genetic analyses (e.g. for predisposition for a disease) are only allowed to be prescribed by either physicians with a specialization in human genetics or a federal postgraduate in the field to which the analysis belongs (e.g. BRCA1 only by oncologists; Art. 20, Federal Law on Human Genetic Testing³⁰²), the Ordonnance of March 2023 makes an exception for PGx and states that **any physician** is authorized to prescribe PGx (Art. 5, Ordonnance on Human Genetic Testing³⁰³). The recently introduced Ordonnance even includes specific clauses which enable **pharmacists, dentists, and chiropractors** to prescribe PGx tests (not reimbursed however).³⁰³ Despite the lack of reimbursement, the role of pharmacists in PGx (genotyping & phenotyping) is expected to increase in Switzerland in the upcoming years.³⁰⁴ Physicians with a specific specialization in clinical pharmacology and toxicology (i.e. **clinical pharmacologists**) conduct patient consultations with the aim of optimizing the drug treatments of patients. They are not involved in the laboratory analyses themselves, but are specialized in the interpretation of test results as well as formulating the therapeutic recommendations. The clinical pharmacologists work as a second line service, meaning both in- and outpatients require a referral by other specialists or general practitioners.³⁰⁵



Article 28 of the Federal Law states that any lab executing cytogenetic or molecular genetic analyses needs the permission of the Federal Council of Human Genetics, which also defines the criteria to which the staff in the lab has to comply.³⁰² In addition, article 9 of the Ordonnance states that the labs performing PGx testing need the appropriate accreditations from the Swiss Accreditation Service, which applies the ISO standards (i.e. ISO15189 for medical laboratories).³⁰³ The five university hospitals in Switzerland all have a lab conducting PGx tests as well as one general hospital which acts like a university hospital. While they perform the highest volumes of PGx tests, a handful of private labs also performs PGx. In total, not more than 20 labs conduct PGx testing in Switzerland.³⁰⁵ Direct-to-consumer (DTC) genetic testing for medical purposes (including PGx) without a prescription by one of the aforementioned health professionals is currently prohibited by Swiss legislation.^{302 305}

7.4.2 Which tests are (recommended to be) performed for which drug-gene interactions?

The Swiss Society of Clinical Pharmacology and Toxicology (SSCPT) has been assigned by the Swiss Federal Office of Public Health to draft and maintain a list of gene-drug-pairs as part of the Swiss List of Analyses which regulates the reimbursement of laboratory investigations by the Swiss health insurance companies (see 7.4.4).³⁰⁶

Unfortunately, no public data on the national volume of PGx tests performed in Switzerland is available. The university hospitals of Geneva (Hôpitaux Universitaires Genève), which are responsible for the highest volume of PGx tests, disclosed having performed approximately 1000 PGx tests since 2017, which translates to roughly 200 tests/year.³⁰⁵

Local experts disclosed that labs more often opt to perform a **PGx panel** instead of single-gene testing when a PGx test for one (or more) gene-target(s) is requested. However, only the results of the requested gene-

targets are communicated to the prescriber and billed to the patient or health insurance as panels are currently not reimbursed in Switzerland (see section 7.4.4). The results of the panel test are being reused in case another gene-target is requested in the future for the same patient, at which point the results of that specific gene-target are communicated and billed^{qq, 305, 307} With regard to the interpretation of the test results and the recommendations on the drug treatment, the clinical pharmacologists use all available professional guidelines (i.e. CPIC in which the SSCPT is represented, DPWG, RNPXG, etc.) and systematically review the latest literature. In Switzerland, there are no rules or obligatory guidelines on which technique should be used for which PGx tests.³⁰⁵

7.4.3 Communication

As pharmacogenetics falls under the Federal Law on Human Genetic Analysis of 1 December 2022 (nr. 810.12), obtaining a signed **written consent** from the patient before testing is obligatory.³⁰²

The lab staff reports the test results to the prescriber, either by inputting them in the hospital Electronic Health Records (EHR) or via e-mail or letter. Currently, Switzerland does **not have a national EHR yet**. Instead, every hospital has its own EHR and can share the PGx data with health professionals based in the same hospital. In some regions, the hospitals can also share data with physicians based in the same city. By integrating the results in the EHR, there is also the possibility of using the PGx information in decision support tools (e.g. automated pop-ups) to guide and/or warn the prescribers who have access. However, the use of these PGx-driven decision support tools is not yet widespread in Switzerland. Initiatives are being taken on the national level to improve data sharing and interoperability between EHRs of different hospitals (i.e. Swiss Personalized Health Network) and on the hospital level to develop PGx-driven decision support tools.

^{qq} As an illustration, Appendix 5.4 shows an example of the composition of a PGx panel in the University Hospitals of Geneva.³⁰⁵



To overcome the limitations related to data sharing and the limited use of decision support tools, some hospitals currently hand credit-card size PGx safety cards containing the PGx results to patients.³⁰⁵

In general, the average turnaround time of the ordered (panel) tests is a week but depends on the lab performing the test and the ordered tests. For DPYD, the turnaround time is on average one week, for other tests this may lead up to three weeks.³⁰⁷

Specific reimbursed pharmacogenetic patient consultations with a clinical pharmacologist exist, and are embedded in the care trajectory when the clinical pharmacologist is the prescriber of the test. Other prescribers (not clinical pharmacologists) have the opportunity to discuss the results with a clinical pharmacologist in a reimbursed consultation before communicating to the patient.^{rr}

7.4.4 How is pharmacogenetics funded & reimbursed?

The reimbursement of PGx testing is established in Switzerland since 2017. Like in the Netherlands, the insured first have to pay for a number of health care interventions themselves up to a specific amount (i.e. deductible) before the Swiss mandatory health insurance reimburses the covered procedures. The amount of the deductible can be chosen freely by the citizen and ranges between €300 and €2500^{ss}, with a lower premium to be paid for higher deductibles. After the deductible has been spent, citizens still have to pay 10% of their medical bills out of pocket up to a co-payment of €700 per year.^{305, 308} The billing system for medical and technical interventions in Switzerland is based on the TARMED system, covering approximately 4500 tariff items.^{309, 310}

The Swiss government implemented two reimbursement schemes for PGx depending on the specialization of the prescriber of the test. The first reimbursement scheme consists of **a limitative list of PGx tests** (Table 34) which are reimbursed by the Swiss national health insurance if prescribed

by **any physician** independent of the specialization.³¹¹ The limitative list is routinely revised every year by SSCPT. In this process, the opinion of the Group of Pharmacogenetics and Personalized Therapy (SPT), which is a division of SSCPT dedicated to genetics in pharmacotherapy, is taken into account before and after the SSCPT evaluation. The SSCPT executive committee decides (with at least a majority decision) which proposals will be added to or removed from the limitative list and communicates the decision to the Federal Office of Public Health. The whole process of adding or eliminating a gene-drug pair from the list should not take more than 12 months. The standard operating procedure dictates that the following information should minimally be available on the drug-gene pair before an evaluation to be included in the limitative list is possible:

- Estimates of frequencies of clinically relevant variants in the Swiss population.
- Effect size of clinically relevant variants on pharmacokinetics and – dynamics.
- Recommendations and strength of recommendation by relevant societies in the field (e.g. in the pharmgkb collection, CPIC, and DPWG).
- Estimates of non-genetic concurrent influences on pharmacokinetics and –dynamics.
- Clarity of recommendation if variants have been identified.³¹²
- Knowledge of PGx-guided prescribing by the prescribers of the drug and their guidelines.³⁰⁵

^{rr} For example, the oncologists can tick a box on the request form for DPYD to request an interpretation by a clinical pharmacologist, after which the clinical

pharmacologist provides a detailed consultation to the prescribing oncologist but does not see the patient him-/herself.

^{ss}

A currency exchange rate of 1 CHF = €1 was assumed.



Table 34 – Swiss limitative list of reimbursed PGx tests when prescribed by any physician

Drug	Gene(s)
Abacavir	HLA-B5701
Carbamazepine	HLA-A3101 & HLA-B1502
Thiopurines (azathioprine, 6-mercaptopurine)	TPMT
Fluoropyrimidines (5-fluorouracil, capecitabine)	DPYD
Irinotecan	UGT1A1

The second reimbursement scheme is reserved for physicians with a specialization in clinical pharmacology and toxicology. **Any PGx test prescribed by physician-specialists in Clinical Pharmacology and Toxicology (i.e. clinical pharmacologists)** is reimbursed by the Swiss health insurance if the conditions listed below are met.^{306, 311}

First, the pharmacogenetic test must serve the medical treatment of an illness or its consequences. More specifically, the result of the test must have actionable consequences for the treatment of the patient, in whom the test is performed. Second, costs are only covered if the PGx test is performed for a medication, for which the patient currently has an indication or with which the patient is currently undergoing treatment.^{306, 311} Consequently, **panel testing, as well as full preemptive testing** without indication, is currently **not reimbursed** in Switzerland.^{305, 306} The billing of a PGx test is based on tax points (see appendix 5.4). For example, a PGx test for DPYD costs between €204 and €240, while a more complex test for CYP2D6 costs between €573 and €675 (depending on the canton).³⁰⁷

Pharmacogenetic consultations (including test interpretation) by the clinical pharmacologists are also reimbursed at an average cost of approximately €400. Pharmacogenetic advice to other health care workers (see previously) is billed at €3.8 to €4.43 per minute depending on the canton and is also reimbursed (see appendix 5.4 for the specific codes and tariffs).

7.4.5 Phenotyping

Because genotyping does not always predict the real activity of an enzyme adequately, Swiss university labs perform phenotyping to complement the genotyping. Most of the time it is for analysing the CYP enzymatic/metabolic activity, and/or DPD and/or TMPT enzyme activity. This type of testing is performed in three university hospitals labs, and is considered a form of Therapeutic Drug Monitoring (also reimbursed in this way). Other hospitals may refer their samples to the three university hospitals. Specifically for the CYP enzymes, the Geneva University Hospitals developed the Geneva cocktail, which implies the oral administration of five probe substrates relevant to test the enzymatic activity of five CYP enzymes.³¹³ Every physician can request the test via a sample of dried blood spots and send this to the lab.

7.4.6 What are the remaining challenges for pharmacogenetics?

The communication and storage of PGx could improve, as most hospitals do not use the PGx results in clinical decision support tools within their EHRs. Furthermore, the ongoing development of clinical decision support tools in Geneva could expand to not only alerting prescribers when a patient has an actionable variant for the prescribed drug but also automatically displaying specific dosing recommendations for that particular patient.

The (semi-)preemptive testing is not implemented in Switzerland as it is not eligible for reimbursement at the moment. Local experts argue Whole Genome Sequencing (WGS) is the future for pharmacogenetic testing. WGS will generate a very large amount of data. The challenge exists in how to manage, save, and safeguard all this data and regulate how this data can and should be used.³⁰⁵



7.5 The United Kingdom (England)

While the UK is a world leader in mapping individual genomes and in the development of sequencing technologies, the roll-out of PGx testing is not yet widespread. Several recent initiatives (e.g. report of the Royal College of Physicians and the British Pharmacological Society⁷, pilot studies, etc.)^{29, 314} were launched to make PGx a reality for everyone. As England represents the majority of the UK population, the organization of PGx as well as these initiatives will be described from the perspective of England and NHS England.

7.5.1 *Who is entitled to prescribe and perform pharmacogenetic tests?*

At the moment, the selection of PGx tests currently covered by the NHS is limited to medicines prescribed in the hospital setting and are therefore not relevant for other health care professionals such as GPs or pharmacists (see section 7.5.2). Multiple research projects in the UK are ongoing to expand the list with other PGx tests relevant to other health care professionals (see section 7.5.2). Noteworthy is the recently initiated PROGRESS trial, an observational implementation study that aims to expand the list of covered PGx tests with a selection of tests relevant for GPs which inherently would also lead to an expansion of the “covered prescribers” to GPs and potentially other health care professionals (e.g. pharmacists) as well.^{29, 315} More information on the PROGRESS trial is available in Appendix 5.5.

In the UK, all labs are allowed to conduct PGx testing if they have the required accreditation (i.e. ISO15189) issued by the United Kingdom Accreditation Scheme (UKAS)^{tt} and have the necessary equipment. This means that both public and private labs are allowed to conduct PGx. Moreover, direct-to-consumer (DTC) testing is also allowed, though in practice the volumes of PGx tests performed by private labs and those of DTC testing are considered very low as these tests are not covered by the NHS.³¹⁵ However, over the past years, more and more critical voices on DTC genetic testing have brought forward the potential disadvantages of this kind

of testing for both the health care system (e.g. people seeking explanations of their DTC results within NHS, substantial NHS costs of confirming or refuting DTC testing results, etc.) and the patient (e.g. false reassurances, false worrisome results, etc.). For example, in 2021, the House of Commons Science and Technology Committee advocated for a more strict regulation on DTC genetic testing in the UK based on an evaluation of the potential benefits and risks of DTC genetic testing.³¹⁶ In addition, the Royal College of General Practitioners (RCGP) and the British Society for Genetic Medicine (BSGM) recently issued a position statement recommending that “health professionals should exercise caution when asked to offer, or provide, clinical expertise about the results of direct-to-consumer genetic or genomic testing”.³¹⁷ As the focus of this report is on reimbursed testing within the NHS, we refer to the original sources for more information.

To organize NHS genomic testing in general (also including PGx), NHS England reconfigured all genomic testing facilities into **seven regional genomic laboratory hubs (GLHs)** with the aim of consolidating and enhancing the genomic testing capacity and capability.⁷ Each GLH can consist of multiple labs collaborating as a GLH. In addition to the GLHs, the currently recognized HLA labs remain authorized to perform all HLA PGx tests with coverage from NHS England. The HLA labs need an accreditation by UKAS and the European Federation of Immunogenetics (EFI).³¹⁵ In 2023, 21 HLA labs in England conducted PGx testing.³¹⁸

7.5.2 *Which tests are (recommended to be) performed for which drug-gene interactions?*

As there is no official professional association providing own guidelines or recommendations, some medical specialist organizations have included PGx in their guidelines, e.g. for DPYD and TPMT.^{319, 320} However, local experts confirmed that the UK is undertaking initiatives to develop recommendations and guidelines specifically for the situation and context of the UK.³¹⁵ **Testing guidance** is given via the **reimbursement legislation** with NHS listing which PGx tests are covered.³¹⁵ In 2015, the NHS initiated a process of shaping a National Genomic Test Directory for England. The

^{tt} More information on <https://www.ukas.com/>



purpose of developing the directory was to establish a **limitative list of genomic tests** covered by NHS in England and performed by the GLHs. The directory, first published in 2018 and updated annually, details which tests are covered, for which patients, and which technology should be used. Since 2020, the scope of the list expanded and now also includes a selection of pharmacogenetic tests. The overarching directory consists of a directory for rare and inherited diseases and a directory for cancer, in both of which PGx tests were included.³²¹ Table 35 summarizes the limited selection of PGx tests included in the directory and covered by NHS. Three PGx tests are included in the directory for cancer: DPYD, TPMT, and NUDT15.³²² NHS England (together with the NHS organizations in Scotland, Wales and Northern Ireland) covered DPYD genetic testing in 2020, making routine testing for the four DPYD variants available in patients planned to receive fluoropyrimidine treatment.⁷ Both TPMT and NUDT15 genotyping are included in the directory as part of the chemotherapy regime for childhood acute lymphoblastic leukaemia (ALL). However, while TPMT genotyping is currently covered by NHS, TPMT phenotyping is performed more often in the UK.³²³ The remaining PGx tests in the National Genomic Test Directory are part of the directory for rare and inherited diseases.³²² In view of the new NICE guideline on clopidogrel, possibly recommending genotyping CYP2C19 after ischaemic stroke or transient ischaemic attack, there might be an addition to the National Genomic Test Directory in the near future.²¹⁵

The directory is updated every year or can be adapted ad-hoc during the year (e.g. due to relevant NICE evaluation). The annual update is overseen by the Genomics Clinical Reference Group (Genomics CRG) which is supported by three working groups (i.e. working group on cancer, working group on rare diseases, and working group on pharmacogenetics).

Table 35 – PGx tests covered by NGS in the UK (NHS England)

Genes	Indication
National Genomic Test Directory (Genomic Laboratory Hubs) *	
DPYD	Patient planned to receive fluoropyrimidine treatment
TPMT	Patients with a confirmed diagnosis of acute lymphoblastic leukaemia and proposed treatment involving purine analogue based drugs
NUDT15	Patients with a confirmed diagnosis of acute lymphoblastic leukaemia and proposed treatment involving purine analogue based drugs
MT-RNR1	Aminoglycoside exposure risk to hearing loss
UGT1A1	Gilbert syndrome (Irinotecan)
HLA testing (HLA labs) **	
HLA-B5701	Patients planned to receive abacavir treatment
HLA-A3101	Patients planned to receive carbamazepine treatment
HLA-B1502	
HLA-B5801	Patients planned to receive allopurinol treatment
HLA-B1502	Patients planned to receive phenytoin treatment

Source^{315, 322, 324}. * In National Genomic Testing Directory there is also the target *VKORC1*; *GGCX* used for diagnosis of vitamin K-dependent clotting factor deficiency, which might also be used for PGx ** For HLA testing no official list of covered PGX tests is publicly available. The selection is based on country expert communication.



The annual update follows a **standardized stepwise approach**. First, the working groups will carry out a full evidence review to evaluate the clinical and scientific basis for the proposal. Second, the working groups together with the GLH partnership board draft **an impact assessment evaluating the clinical utility and analytic validity**, the **cost-effectiveness**, and the **workforce required to perform the testing**. In a third step, an assessment will be carried out to estimate the impact of the changes on patients and the public with engagement of relevant patient groups. Based on the evidence review, the impact assessment and the public engagement, the working groups draft recommendations to Genomics CRG to support or not to support the proposal. Next, Genomics CRG prioritizes the proposals based on the following criteria:

- Evidence of patient benefit and clinical utility, including if the proposal meets an unmet medical need (e.g. severity of avoided adverse events);
- Strength of scientific and clinical evidence supporting the proposal;
- Financial implications of implementation (cost saving, cost neutral, cost pressure, level of investment required);
- GLH resources required to implement the proposal and technical feasibility of implementation;
- Confidence that overall benefits to patients and/or clinical pathways would be realized upon implementation;
- Alignment to an NHS England and NHS Improvement clinical priority area.

Based on this prioritization, Genomics CRG drafts recommendations to the Genomics Programme Board. In December of every year, the updated directory is published by NHS England with the purpose of achieving full implementation by April of the next year.³²⁵

As shown in Table 35, HLA testing is not included in the National Genomic Test Directory but is also being covered by NHS for four drugs.³¹⁸ Testing for HLA-B*5701 in view of abacavir prescription has been mandatory and embedded in routine care in the UK since 2005, which is in line with the SmPC of the drug. HLA testing for carbamazepine, allopurinol or phenytoin is also covered by NHS.^{315, 326} While HLA testing prior to abacavir treatment is embedded well in standard care with considerable volumes of tests as a consequence, the HLA tests for the other three drugs are currently rarely used. HLA testing is kept out of the directory as the directory was specifically developed for the GLHs and HLA testing is (allowed to be) performed in other labs and settings than the GLHs.^{315, 324}

With regard to the testing strategy, the predominant approach in the UK is **reactive testing** where patients are tested for genetic variations related to the drug they are taking or being prescribed at that moment in time. Full and semi-preemptive testing, while legally allowed, are generally not performed in the UK and currently do not fall under NHS coverage.^{29, 322}

However, the ongoing **PROGRESS study** is testing the feasibility of a semi-preemptive panel testing strategy in primary care. When a study participant is prescribed or needs a change in one of the drugs classified in one of the four predefined medication classes^{uu}, a panel test is conducted for the following gene-targets: CYP2C19, CYP2D6, CYP2C9, and SLCO1B1. Within the trial, the CPIC recommendations are applied to adjust the treatment if necessary. Additional information on the PROGRESS study is summarized in appendix 5.5. In addition, the Royal College of Physicians and British Pharmacological Society also advocates for more panel testing in the future.⁷

^{uu} Selective Serotonin Reuptake Inhibitors [citalopram, escitalopram, fluvoxamine, paroxetine, sertraline], Tricyclic Antidepressants (prescribed for pain or depression) [amitriptyline, clomipramine, doxepin, imipramine,

nortriptyline, trimipramine], Statin Therapy [atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin], Proton Pump Inhibitors [esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole].



7.5.3 Communication

In the UK, the patient is **not obliged to sign a written informed consent** prior to PGx testing. However, the prescriber does have to register a consent to the treatment (of which the PGx test is part) in his/her notes. In case of Whole Genome Sequencing, on the other hand, a signed informed consent form is mandatory before the test is allowed to be performed.³¹⁵

After analysis, the lab generates a report with the genotype and how this connects with national and international guidelines. Most of the time, labs base their therapeutic recommendations on the international CPIC guidelines, though some UK specific guidance is available for some targets.^{319, 320}

Both the test results as well as the recommendations are sent to the prescriber in a PDF format. The average turnaround time varies between three and sixteen days but is highly variable depending on the requested test as well as the lab performing the test. For example, DPYD genotyping takes approximately three days in one GLH but takes seven days in another.^{327, 328}

The majority of prescribers are based in hospitals and therefore store the test results as a PDF in the EHR of the hospital. This means that, at the moment, no automated clinical decision support systems based on pharmacogenetic test results are available and/or used in the UK. In addition, due to the **scattered EHR landscape in the UK** with a multitude of providers, this implies that other hospitals do not have direct access to the test results. In other words, repetitive testing of the same gene-targets is not actively avoided.³¹⁵ Some recently initiated NHS-funded studies aimed to improve data sharing on a national level and developing a centralized genomic database. Within the PROGRESS study, for example, an IT solution has been set up so GPs could have access to the information (in a first step this is via a standalone interface that will need to be logged on, but later the aim is to introduce it in the EHR). In addition, there is an ongoing NHS study which aims to develop a centralized genomic database which allows saving, sharing, and reusing PGx results nationally.³¹⁵

7.5.4 How is pharmacogenetics funded & reimbursed?

All tests included in the National Genomic Test Directory, in which most pharmacogenetic tests are included, are covered by NHS England and are therefore free at the point of delivery as well as a limitative selection of HLA tests (see Table 35). All other tests are not covered by NHS and are therefore at the expense of the patient or local clinical service.³²⁹ In addition, PGx tests included in the National Genomic Test Directory **have to be performed in a GLH** in order to be eligible for NHS coverage. In other words, tests performed in private labs as well as DTC testing are at the expense of the patient. With regard to the testing strategy, NHS coverage only applies to **reactive testing** in which patients are tested for genetic variations related to the drug they are being prescribed at that moment in time or when serious adverse drug events appear.³¹⁵ Finally, the patient has to meet either the **test eligibility criteria** listed in the National Genomic Test Directory or the eligibility criteria related to the covered HLA tests.³²²

The tests listed in the National Genomic Test Directory are funded on a national level by NHS England and NHS Improvement. This means that referring trusts are not charged for the tests as long as the eligibility criteria are met.³²⁹ Every year, NHS England and NHS Improvement reserve a percentage of the budget for implementing the updates to the directory. The total budget for the directory is determined on an annual basis.³²¹ The majority of HLA labs is funded by NHS, except for one which is funded by charity.³¹⁸

7.5.5 What are the remaining challenges for pharmacogenetics?

The remaining challenges for pharmacogenetics in the UK are described elaborately in the 2022 report of the Royal College of Physicians in cooperation with the British Pharmacological Society and were summarized in Table 36.

**Table 36 – Challenges related to PGx implementation in the UK (NHS England)**

Challenges	Sub challenges and strategies
Selection of pharmacogenetic tests	- Centralised selection of key drug-gene pairs - Specification of clinical indications each selected drug-gene pair - Determine impact on testing volumes - Pharmacogenomic services will need to be agile and able to work at pace to include newly discovered gene–drug pairs into the NHS National Genomic Test Directory, but also refine the list or recommendations of existing gene–drug pairs based on evidence generated.
Clinical service	- Fit in existing clinical pathways - Access to expertise in pharmacogenetics for prescribers - Services should include standards for test turnaround times, flexibility in the type of technology used depending on the gene–drug pair, and standards for reporting, storing and incorporating test results in the electronic healthcare record - A PGx test should be considered equivalent to a liver function test and should therefore not need genetic counselling services to be provided
Consent	National standardised recommendations for consenting to PGx testing
Genotyping strategies	- Shift more towards panel testing when pharmacogenetic information is the primary indication for testing - Reuse the results of the panel test for future prescribing (semi-preemptive approach) - Use point-of-care (POC) testing when pharmacogenomic results are required rapidly and testing is reactive – e.g. for warfarin, clopidogrel or aminoglycosides - Ensure the test turnaround time is congruent with the chosen patient pathways
Laboratories	- GLHs should remain the main platform for PGx, but evaluation necessary of ability to use local NHS labs - Provide laboratories the freedom to decide which specific technology, platform and analytical workflow to use to deliver panel testing, based on local experience and expertise, test turnaround time and cost, ensuring the highest quality assurance standards
Clinical decision support	- Develop pharmacogenetic guidelines and recommendations tailored to NHS - Develop coding for genetic variants for incorporation into EHRs - Build inter-connected systems that enable access to community-based services as well as other hospitals to access clinically relevant PGx information - Work towards developing clinical decision support systems that can be used in all healthcare settings, focused not only on pharmacogenomics, but also on other advances in medicine
Funding	Centralised funding is required for nationwide equitable implementation
Prescriber knowledge & education	- Critical to upskill prescribers in pharmacogenetics - Comprehensive education and training package aimed at all sectors of healthcare to improve the skills of the workforce - Integrate pharmacogenetics in education of future workforce
Patient engagement, perspectives, and managing expectations	- Patient representatives should be involved throughout the implementation of PGx - Add relevant pharmacogenomics text to NHS online guidance about medical conditions and treatments for patients and the public

**Clinical governance**

- Encourage audits of local pharmacogenomic services and quality improvement programmes to spread and affirm best practice, share learning, and iteratively improve service delivery
- Improvement of the recording of treatment response (e.g. efficacy, ADRs, adherence, reasons for changing therapy, patient reported outcome measures) in clinical notes and coding to improve measures of outcome and impact

Research

- Conduct collaborative, inclusive and multidisciplinary research to transition towards a learning health care system that provides equitable, clinically and cost-effective, accessible and acceptable care
- Collaboration between health care, academia and the life sciences industry

Source: ⁷.



7.6 Comparison of reimbursement lists

Table 37 shows for which medicines and related genes PGx testing is reimbursed in France, Switzerland and the UK (England). In the Netherlands, the DPWG does publish a list of recommended PGx tests on behalf of the Dutch pharmacist association, but this list is not enforced legally, nor used as a general restriction in the reimbursement of the test.

Dutch health insurers can choose freely (not) to use the DPWG list as a guideline on which targets to reimburse. The selection of France is not exhaustive due to the partial reimbursement of generic codes and NGS panels due to the abovementioned HAS evaluation.

Table 37 – Comparison of reimbursement lists

Medicine	France (Nomenclature + complementary list + RIHN)	Switzerland (Swiss List of Analyses)	UK (England) (National Genomic Testing Database + HLA targets)
Abacavir	HLA-B5701 (nomenclature)	HLA-B5701 All physicians	HLA-B5701
Azathioprine	TPMT (in complementary list)	TPMT All physicians	TPMT + NUDT15 Patients with a confirmed diagnosis of acute lymphoblastic leukaemia
Mercaptopurine	TPMT (in complementary list)	TPMT All physicians	TPMT + NUDT15 Patients with a confirmed diagnosis of acute lymphoblastic leukaemia
Capecitabine	Phenotyping in nomenclature DPYD genotyping advisable in the absence of phenotyping	DPYD All physicians	DPYD
Fluorouracil	Phenotyping in nomenclature DPYD genotyping advisable in the absence of phenotyping	DPYD All physicians	DPYD
Irinotecan	UGT1A1 (in complementary list)	UGT1A1 All physicians	UGT1A1
Carbamazepine	Not specifically mentioned, but possible to receive reimbursement via general codes	HLA-A3101 & HLA-B1502 All physicians	HLA-A3101 & HLA-B1502
Tacrolimus	CYP3A5 (in complementary list)		
Eliglustat	CYP2D6 (in complementary list)		
Tamoxifen	CYP2D6 (in complementary list)		
Allopurinol	Not specifically mentioned, but possible to receive reimbursement via general codes		HLA-B5801
Aminoglycosides			MT-RNR1

**Phenytoin**

Not specifically mentioned, but possible to receive reimbursement via general codes

HLA-B1502

Note: The selection of France is not exhaustive due to the partial reimbursement of generic codes and NGS panels. This selection reflects the explicitly reimbursed tests.

Key points**General**

- Reimbursement criteria rather than legislation shapes the implementation of PGx. However, France and Switzerland have a clear legal framework for PGx.

Which gene-targets are eligible for reimbursement?

- In France, Switzerland, and the UK a well-defined assessment is conducted before a specific PGx test can be included on a defined list of reimbursed gene-drug targets.
- PGx tests are foreseen in every reimbursement list analysed for: abacavir, azathiopurine, mercaptopurine, irinotecan, carbamazepine, fluorouracil and capecitabine. However, in France, for the latter two only the phenotyping test is included in the official Nomenclature.
- The UK has the most restrictive list in terms of number of drug-gene pairs.
- Switzerland has a stepped system with on the one hand the limitative list with PGx tests for 7 medicines available to all physicians, and on the other hand a wider range of PGx tests when requested by a physician-specialist in clinical pharmacology and toxicology.

Who prescribes PGx?

- In all examined countries, the highest volumes of PGx tests are prescribed by specialist physicians (e.g. oncologist).
- In Switzerland and the Netherlands, patients requiring complex drug treatment optimisation can be referred to physicians specialised in clinical pharmacology.

- In primary care in the Netherlands PGx tests can be ordered by officina pharmacists (and the order signed later by the GP for reimbursement). Recently introduced legislation in Switzerland allows pharmacists, dentists and chiropractors to order PGx (without reimbursement). In the UK, PGx tests in first line setting are currently being evaluated in a research setting.

Centralisation of PGx testing labs?

- In the examined countries, the labs performing PGx testing need (local) recognitions, licenses, and the ISO15189 accreditation.
- HLA is in most countries performed in dedicated HLA labs, separated from the genetics labs.
- In the UK there is a centralisation of reimbursed PGx testing in 7 genomic laboratory hubs. In the other countries there is no centralisation.
- France is the only country where the national volumes of PGx are systematically collected and publicly disclosed.

Reactive or (semi-)preemptive testing?

- In none of the examined countries the (semi-)preemptive PGx testing strategy is currently reimbursed by national health insurance.
 - In France, PGx panel testing with a medical indication is under evaluation by HAS and therefore partial and conditional funding is available.
 - In the Netherlands, only supplemental health insurance plans reimburse semi-preemptive testing under specific conditions.

How are PGx results communicated and stored?



- Only in Switzerland and France patients are required to sign an informed consent before PGx testing is allowed.
- In the Netherlands and Switzerland patients can participate in a consultation session with a physician-specialist in clinical pharmacology.
- In the Netherlands, multiple clinician, hospital and pharmacist guidelines indicate the contra-indications as the designated place to store PGx information in the EHR. Information in the contra-indications can be consulted by other physicians and pharmacists via a national platform after the explicit consent of the patient.
- In none of the other countries, nationally developed platforms are used to store PGx information outside the research setting, hampering both the (re)use and clinical decision support based on known PGx (panel) information.
- In France, the government offers prescribers a software add-in which alerts them to order DPYD testing when 5-fluorouracil (5-FU) or capecitabine is being prescribed.
- In the Netherlands, all DPWG information is available in the drug repository (*G-standaard*). Prescribers' and pharmacists' software can link the PGx information in the contra-indications with DPWG information in the drug repository enabling automated decision support (if available in the respective software).
- In the other countries, initiatives related to the use of PGx information-driven decision support systems is limited to individual hospitals or health care providers.

8 FINANCIAL ACCESS TO GENETIC TESTING IN BELGIUM

The reimbursement of (diagnostic) testing in Belgium is organised via nomenclature codes on specific lists, each with its own requirements/access criteria. For genetic testing there are several lists: article 33 which currently includes PGx,⁴⁷ article 33bis which is a mix of germline and somatic testing,¹³¹ article 33ter on companion diagnostics focused on somatic mutations,¹³² and article 24 including some genetic tests for HLA typing in view of haematopoietic stem cell transplantation.¹³⁴

In regard to financial accessibility, the article 33 list is the most restrictive, permitting reimbursement for tests only when conducted by the eight CHGs.

There is the potential rise in demand for PGx testing, perhaps driven by the introduction of new medications explicitly highlighting it in their drug labels (e.g. mavacantem, siponimod, eliglustat), or by the growing need of clinicians and patients to know the reasons behind inefficacy or side effects (e.g. psychotropic medications) in order to adapt the therapy. Therefore, it is interesting to learn how the other RIZIV-INAMI lists are conducted and whether they can form an inspiration for PGx. Specifically, in the realm of panel testing, a noteworthy development is a pilot project initiated in 2019, and aiming at testing a novel reimbursement strategy that involves providing a fixed fee per panel.

8.1 Article 33bis

Article 33bis of the nomenclature was created in 2007 to cover the genetic tests for cancer diagnosis and prognosis with the focus on searching for acquired genetic aberrations. Nowadays the list has a wider scope and includes molecular biological tests to also search for constitutional/germline genetic mutations e.g. in the context of (stem cell) transplantation, coagulation diseases such as factor V Leiden, prediction of Rhesus antigen problems, non-invasive prenatal 'NIPT' test.



Each nomenclature code has its own fee. The reimbursement fees are proposed by the Technical Council and accepted by the *Verzekeringscomité-Comité de l'assurance*.

The labs performing tests on the art 33bis list need to have the ISO15189 accreditation (or equivalent) for these tests and need to participate in internal and external quality controls (for example an audit by Sciensano). The HLA typing in article 33bis is reserved for the HLA laboratory that has a valid EFI certificate for the organ transplant category and has a Eurotransplant Tissue Typing Programme formally linked to an accredited transplant centre.

Table 38 – Examples of nomenclature codes and their fees listed in article 33bis

Code	Description	Fees (honorarium) at 1/1/2024
587016 - 587020	Detection of a mutant factor V, type Leiden, with a molecular biological technique	€90.63
587031 - 587042	Detection of a mutant factor II (G20210A) with a molecular biological technique	€90.63
587053 - 587064	Genotyping of fetal RH1 on blood from a RH:-1 (RhD negative) mother	€251.75
565611 - 565622	Prenatal detection of trisomy 21 by means of a molecular biological method on a blood sample from the mother from the 12th gestational week	€274.61
555354 - 555365	Determination of the loci HLA-A and/or B and/or Cw and/or DR and/or DQ and/or DP in an organ transplant candidate, by a method of molecular biology, by locus (maximum 5, which indicates that five times this fee can be charged if 5 loci are genotyped)	€100.70

^{vv} Article 33ter of the Royal Decree of 14 September 1984 on molecular biological testing of human material in acquired diseases associated with a pharmaceutical specialty.

8.2 Article 33ter – “RIZIV interpretation of CDx”

Since 2018, a specific article 33ter list^{vv} has been set up for companion diagnostics (CDx), which lists those molecular tests for acquired somatic mutations that predict whether a patient will benefit from a treatment with a targeted medicine. At the moment, the companion diagnostic tests in article 33ter are focused on **oncological** biomarkers which are specifically mentioned in the **drug label**, and the focus is on biomarkers which predict the possible **effectiveness** of the drug.

The RIZIV-INAMI worked out a reimbursement policy via a **coupled procedure** to link the procedure for reimbursement of the **tests** (article 33ter of the nomenclature and a chapter VIII-c with a list of pseudocodes with specific biomarker/indication combinations) to the procedure for the reimbursement of the **medicine** (chapter VIII-b of the reimbursed medicines). This means that tests are only reimbursed when they are prescribed in the context of a potential reimbursement for a medicine listed in chapter VIII-b of the list of reimbursed drugs. Within RIZIV-INAMI, this coupled reimbursement procedure is supervised by the CDx platform, which is a permanent working group incorporating two separate commissions: the Commission for the Reimbursement of Medicines and the council responsible for the nomenclature (Medical Technical Council).

Unlike the article 33bis list where each test has its own nomenclature and its own fee, article 33ter has general nomenclature codes for six broad categories of tests with a corresponding fee (Table 39). For technical reasons (different diagnostic rules), a distinction is made between a diagnostic test and a follow-up test. These diagnostic and follow-up tests each have their own general nomenclature codes but have corresponding fee.



The general nomenclature codes in article 33ter reflect different "**levels of complexity**" of the tests. The "complexity levels" depend on the type of test and the frequency with which the test is performed:

1. Tests classified as level 1 detect an acquired point mutation. This is usually a simple PCR (polymerase chain reaction) test.
2. Level 2 tests are more labour intensive or require more analytical work, such as analysis of a few exons and screening for deletions and translocations.
3. Level 3 includes the most complex analyses, such as some HIS (in situ hybridisation) tests on tissue, but also complex mutation and deletion analyses.

Those general nomenclature codes do not give much detail on which biomarker has been tested and for which indication. Therefore, specific pseudocodes were created (listed in chapter VIII-c of the reimbursed medicines). This pseudocode also needs to be reported which makes it possible to know exactly how often the tests are carried out, for which indication and at which stage of the disease. Examples of pseudonomenclature codes can be found in Table 40. Both the list of medicines and the list of biomarkers may be amended each month by the Minister of Social Affairs.

**Table 39 – General nomenclature codes and their fees listed in article 33ter (companion diagnostic)**

Code	Diagnostic test	Code	Follow-up test	Fees (honorarium)* at 1/1/2024
594016-594020	Screening for an acquired molecular abnormality with predictive value of therapeutic response to a pharmaceutical product listed in chapter VIII of the Royal Decree of 1 February 2018 by means of a molecular biological method in the diagnostic phase	594031-594042	Screening for an acquired molecular abnormality, as a follow-up to the therapeutic response to a pharmaceutical product listed in chapter VIII of the Royal Decree of 1 February 2018 by means of a molecular biological method	€100.70
594053-594064	Screening for an acquired molecular abnormality with predictive value of therapeutic response to a pharmaceutical product listed in chapter VIII of the Royal Decree of 1 February 2018 by means of a molecular biological method in the diagnostic phase	594075-594086	Screening for an acquired molecular abnormality, as a follow-up to the therapeutic response to a pharmaceutical product listed in chapter VIII of the Royal Decree of 1 February 2018 by means of a molecular biological method	€166.15
594090-594101	Screening for an acquired molecular abnormality with predictive value of therapeutic response to a pharmaceutical product listed in chapter VIII of the Royal Decree of 1 February 2018 by means of a molecular biological method in the diagnostic phase	594112-594123	Screening for an acquired molecular abnormality, as a follow-up to the therapeutic response to a pharmaceutical product listed in chapter VIII of the Royal Decree of 1 February 2018 by means of a molecular biological method	€221.54

* Honorarium includes the RIZIV-INAMI share and the patient share. For non-preferential patients who are not hospitalised, a co-payment of 15% is required with a maximum of €8.68 per test, for all tests in article 33ter. No co-payment is required for preferential patients, whether or not they are hospitalised, and for non-preferential patients who are hospitalised.

**Table 40 – Examples of pseudonomenclature codes specific for an indication and gene-target linked to a reimbursed drug**

Pseudocode*	Description	Code art 33ter / Level	Reimbursed drug**
Solid Tumours			
594252 – 594263	Analysis of HER2 gene amplification in primary metastatic adenocarcinoma of the stomach or oesogastric junction	594090 – 594101 (Level 3 diagnostic)	Trastuzumab
594274 – 594285	Analysis of RAS gene mutation status in primary metastatic colorectal carcinoma	594053 – 594064 (Level 2 diagnostic)	Cetuximab, panitumumab
594451 – 594462	Analysis of HER2 gene amplification in metastatic breast cancer	594090 – 594101 (Level 3 diagnostic)	Trastuzumab, lapatinib, pertuzumab
595195 - 595206	Detection of human leukocyte antigen (HLA) A*02:01 in non-resectable or metastatic uveal melanoma	594090 – 594101 (Level 3 diagnostic)	Tebentafusp
Haematological cancer – diagnostic phase			
594495 – 594506	Screening for the BCR/ABL1 gene (Philadelphia chromosome) in chronic myeloid leukaemia	594053 – 594064 (Level 2 diagnostic)	Imatinib, nilotinib, dasatinib, ponatinib
594510 – 594521	Screening for mutations in the kinase domain of the BCR/ABL1 gene (Philadelphia chromosome) in therapy-resistant chronic myeloid leukaemia	594090 – 594101 (Level 3 diagnostic)	Imatinib, nilotinib, bosutinib, dasatinib
594591 – 594602	Screening for TP53 mutation in chronic lymphatic leukaemia requiring treatment	594090 – 594101 (Level 3 diagnostic)	Imburvica®, Zydelig®
594635 – 594646	Screening for translocation of the t(15;17) PML-RARa gene in acute promyelocytic leukaemia	594053 – 594064 (Level 2 diagnostic)	Vesanoid®, arseentrioxide
Haematological cancer – follow-up phase			
594753 – 594764	BCR/ABL1 (Philadelphia chromosome) gene screening for monitoring of Ph+ chronic myeloid leukaemia or acute lymphoblastic leukaemia	594075 – 594086 (Level 2 follow-up)	
594871 – 594882	Screening for t(15;17) translocation of the PML-RARa gene in monitoring acute promyelocytic leukaemia	594075 – 594086 (Level 2 follow-up)	Arseentrioxide

* Pseudonomenclature codes available in lists of medicines reimbursed by RIZIV-INAMI in chapter VIII-c. ** The info on the reimbursed medicine is available in a list VIII-b.



The requirements to obtain a reimbursement for a companion diagnostic test in the article 33ter are:

1. The specific biomarker must have been prescribed in the context of a potential reimbursement for a pharmaceutical listed in chapter VIII-b of the list of reimbursed drugs and the biomarker should be listed in chapter VIII-c (pseudocodes) of the list of reimbursed drugs;
2. For each biomarker billed, both the general nomenclature code of the test (article 33ter) and the specific pseudonymenclature code linked to the test in chapter VIII-c must be mentioned on each relevant document;
3. The test must have been prescribed in the context of a multidisciplinary consultation, oncological or other;
4. Requirements regarding the prescription details: name patient, name prescriber, date of sample and the clinical question stating the specific condition;
5. Based on the clinical data, the clinical biologist/geneticist/anatomopathologist may carry out the most appropriate tests or refuse to carry out the prescribed tests at all;
6. Registration of the tests performed and test result (not the raw data) in the Predictive tests for a therapeutic response (PITTER) database by the lab receiving the sample;
7. The lab needs to have an ISO15189 accreditation (or equivalent accreditation) for the test performed, as well as take part in external and internal quality control.

The legislation states that no cumulation of an art 33bis and art 33ter code for the same indication can take place. For the same indication (pseudocode), only one test can be charged.

8.3 NGS panel testing in pilot projects

In order to harmonize NGS testing practices in Belgium and to have a controlled introduction of NGS within routine clinical diagnostics, a pilot project in 10 NGS networks (linking more than 100 hospitals to 30 labs performing NGS panel testing) was set up in 2019.⁵⁴ It is limited to oncology, focussing on NGS panel tests for analysing somatic mutations for solid tumours and haematological conditions.

A specific convention (article 56 §1) between the RIZIV-INAMI and 10 NGS networks enabled the reimbursement of NGS panel tests. The NGS panel test should be performed on tumour material (exceptions are possible) and for each indication there is **a minimum of specific genes and regions determined** for sequencing (for example for metastasis colorectal carcinoma at least BRAF, KRAS and NRAS should be included in the panel). The Verzekeringscomité of RIZIV-INAMI decides upon the selection of genes, and can seek advice from a commission on personalised medicine ComPerMed.³³⁰ Moreover, Belgian practice guidelines to provide generic, platform independent, recommendations for targeted next generation sequencing tests to detect acquired somatic mutations in DNA, in (haemato)-oncology were published in 2017.³³¹ While the focus is on somatic mutation, there is the possibility to identify germline variations. Therefore, there is the requirement to include a CHG in the NGS network to help manage germline findings.

It was agreed upon that for a NGS panel test each centre receives a fixed amount of **€350** for **DNA sequencing** (annual indexations resulted in €363.28 in 2022) and **€550** for **RNA sequencing** (€559.95 in 2022). In practice, the panels have several gene-targets which are reimbursed via the art 33bis or art 33ter nomenclature. The instruction is to keep invoicing these specific nomenclature codes, as these will be supplemented by surcharges to reach the maximum fixed amount for NGS panel tests (€350 or €550). If the codes from article 33bis or 33ter are used, a patient co-payment can be charged as stipulated in the nomenclature (no extra supplements are allowed).



The lab performing the NGS panel test should have an ISO15189 accreditation from Belac (or equivalent) for NGS analyses in oncology or genetics and participate in the quality program of Sciensano.

The **registration** of the test and the test result are a condition for reimbursement (a specific platform was designed via healthdata.be but as of July 2023 the reporting should go via an excel file).

Importantly, this pilot project will be converted into a **new convention from 1 July 2024**.

9 GENERAL DISCUSSION

With approximately 90% to 99% of the population carrying at least one actionable gene variant that could potentially influence (future) pharmacotherapy, the potential for pharmacogenetics (PGx) as a discipline is high.^{24, 213} However, not all conditions necessary for a widespread implementation of PGx testing are currently met. On one hand, there are the technical prerequisites of the laboratories, specifically regarding the capability to detect all relevant PGx variations accurately and present the findings consistently. On the other hand, there are prerequisites for implementing these advancements in the clinical field. At the moment, a mismatch exists, where technological progress (with panel testing) is moving forward, but the practical application in clinical settings lags behind.

A clinician needs to know for which medications PGx testing is relevant, i.e. would impact therapy choice or dosing (clinical utility - actionability). Several sources exist (see chapter 3), and based on these, a whole series of lists with selected drug-gene pairs have been drafted.³⁹ The selection criteria for these lists vary depending on the intended purpose. The content and broadness of these lists logically changes whether the goal is to showcase recommendations on gene-drug interactions in the context of preemptive testing, to make a list of 'must test' medications, or to guide reimbursement.

Moreover, recommendations produced by experts specialised in PGx are often not reflected in clinical practice guidelines of medical specialties. Additionally, when addressing the desirability of reimbursement of PGx for certain drug-gene combinations, health care payers may not only want to see proof of effectiveness but also cost-effectiveness in a routine care setting. Since this report was commissioned by the National Health and Disability Insurance (RIZIV-INAMI), this health care payer perspective was incorporated into the study.



9.1 Need for clear definitions

How broad is the definition of pharmacogenetics and which gene-drug variants are included within this definition? There is consensus a gene variant that may be a PGx target must stem from constitutional (germline) alterations. But confusion arises when some germline variants are the culprit of a disease, and identification of this germline variation is considered necessary for (reimbursement of) treatment, or when the drug is a targeted therapy.

For example, the targeted therapy 'ivacaftor' is a CFTR-gene modulator and is therefore only indicated in cystic fibrosis patients carrying certain CFTR mutations. The identification of HLA-DR2 or HLA-DQB1*0602 for the diagnosis of narcolepsy is requested before reimbursement of 'modafinil', as is the identification of HLA-A*02:01 for the targeted medication 'tebanesafusp' in patients with metastatic uveal melanoma.

While some use a broad interpretation of PGx including testing for targeted medications, this study adopts a more limited definition of PGx. Specifically, it excludes testing aimed at diagnosing diseases or determining the suitability of targeted drugs (e.g. ivacaftor).

This PGx definition overlaps with the definition of companion diagnostics (CDx) (see Figure 1). In Europe, the IVDR regulation, sets, for the first time, a legal definition for CDx and this includes some PGx tests which are considered "essential" for the safe and effective use of certain drugs.⁵³ Another group of PGx tests which inform dosing decisions (not really considered "essential") are not considered CDx according to the EMA definition.¹⁷ In the Belgian reimbursement context however, the term 'CDx' is limited to molecular tests used in oncology for targeted medications (article 33ter nomenclature), leaving germline testing out of scope, and therefore excludes overlap with PGx.

Also the lack of common definitions for the terms reactive and preemptive testing, depending on the source consulted, evokes confusion.

Most experts refer to preemptive testing when instead of conducting a targeted test for a specific medication, a more comprehensive panel test is used. Consequently, the information used to inform therapy decisions for the medication for which the panel is launched is essentially reactive, while all

the other information within the panel, stored in medical files, pertains to the preemptive approach (this approach is defined in our report as a semi-preemptive approach). Full preemptive testing, i.e. in a population that does not need a particular medicine was considered out of scope as this could be considered population screening. However, repurposing clinical whole exome/genome sequencing data for PGx also classifies as a preemptive approach. In such a case, the whole exome/genome was analysed in the context of a (rare) disease diagnosis (mostly paediatric population), and the data is then re-analysed with bioinformatics tools to identify relevant variants in PGx genes.²² Several research projects on repurposing are ongoing (In Belgium MyPgx pilot at UZBrussel/VUB, in the Netherlands MijnDNAmedicatiepas at LUMC and Amsterdam UMC).

9.2 Evidence on PGx, and testing in particular

There is a wealth of literature on PGx, but that does not automatically equate to a wealth of strong evidence. To address this problem, consortia, such as CPIC, RNPGx and the DPWG provide the much-needed structure to organise the PGx literature (see chapter 3). Can we simply rely on those sources and their categorisation of evidence?

A first observation is that there is a difference in purpose between guidelines that give information on the strength of the association between a variant and an outcome (safety or effectiveness) and give therapeutic recommendations (change dose, change therapy) (CPIC), and guidelines that go further and also give recommendations on whether or not to test (DPWD, RNPGx, CPNDS). In this report we focused on **testing recommendations** rather than therapeutic recommendations.

A second observation is the existence of inconsistencies among these sources, which is a result of their respective methodologies. There are differences in the selection of drugs with strong testing recommendations between different dedicated PGx consortia (see Table 9). Also the selection of drug-gene tests in reimbursement lists of different countries differs (see Table 37).



9.2.1 Effectiveness

A fundamental and widely adopted strategy among all consortia is the **appraisal of available evidence**, though this is done in various ways (see chapter 3).

An RCT comparing PGx guided treatment to usual care without PGx testing, is the gold standard for assessing the effectiveness of PGx testing. As the difference in effectiveness and safety is driven by a small subgroup having the genetic variant of interest, a huge sample size may be needed to demonstrate the effectiveness of PGx testing. For abacavir, the effectiveness could be shown in the PREDICT-1 RCT (n=1956) with the HLA-B*57:01 variant present in over 5% of the population.²³⁰ For variants that concern only a few percent of the population or less, it is more expensive and more challenging to conduct an RCT, since it should include a few thousand patients. It was not possible in this report to check all available evidence for each drug-gene pair. PGx testing for clopidogrel was used as a case study because of its potential budget impact. And in the chapter on economic literature, we highlight the effectiveness data on which the cost-effectiveness studies were based.

There are not many **RCTs available where PGx testing was the intervention** under study. The medical domains informed by RCTs with PGx testing as the intervention are cardiovascular disease, psychiatric disorders, autoimmune diseases, and HIV.³³² Notably, the cardiovascular domain hosts the most substantial studies in terms of both quantity and participant inclusion. Many studies are pilot or feasibility studies and are often lacking patient-relevant outcomes.^{332, 333}

As expected, for most drug-test pairs the absolute effect size for patient-relevant outcomes is very small when tested in a randomised trial with PGx testing as intervention versus no PGx testing. The bulk of the evidence is based on **associations between a certain gene variant and an (surrogate) outcome** (indirect evidence).

For some drugs, testing has been recommended in absence of RCT data (e.g., fluoropyrimidines and DPYD testing and siponimod and CYP2C9 testing). A review from 2022³³⁴ showed that existing evidence for DPYD is mainly based on showing associations between variants and adverse events

(11 studies) with one Dutch study (n=1103) comparing PGx guided treatment with historical control.²⁴⁸ However, when a variant is reasonably linked to a potentially life-threatening adverse drug reaction, it is considered unethical to assign patients randomly to a standard care group. Recently, a good quality systematic review on CYP2C19 testing for clopidogrel in patients with stroke and TIA concluded that testing is likely effective, although no good quality RCTs were available and the conclusion was mainly based on cohort studies showing a significant association between a variant and cerebrovascular events.¹⁸⁹ This indicates that observational studies are deemed acceptable if they involve a substantial and consistent volume of studies or patients (e.g., for clopidogrel: 20 cohort studies and 5 post-hoc analyses of RCTs not studying PGx as intervention). The strength of evidence required for the clinical implementation of PGx testing is highly debated. Some argue that PGx is held to a higher standard than other laboratory tests (e.g. renal and liver function) routinely incorporated into prescribing decisions without RCT evidence, and also compared to therapeutic drug monitoring (TDM) for which conflicting evidence on clinical effectiveness exists.³³² On the other hand, relatively new medications such as siponimod and mavacamten have explicit recommendations to genotype in the drug label, to guide dosing, without any clinical study with PGx testing as the intervention.¹⁴³

Ongoing and recent research

The PGx research continues as several large scale RCTs with PGx as the intervention are ongoing (see chapter 4.3). In February 2023, the results of the European PREPARE study were published.²⁶ This study compared the occurrence of clinically relevant ADR in a group of patients with PGx panel testing and those without. Given the hypothesis that the impact of PGx testing is mainly expected in patients with actionable drug-gene variants, the primary analysis focused on this subgroup of patients (22.4% of the whole included population), as analysis of the whole population might dilute the effect. Indeed both analyses, i.e. the one limited to the patients with an actionable gene variant, and the one on the whole cohort, are relevant. However, in the PREPARE a similar reduction in ADR was noted in the subgroup without actionable variants as compared to the subgroup with actionable variants; there was thus no dilution of the effectiveness. This implies that other reasons should be considered to explain the reduction in



self-reported ADRs.²⁰⁹ For practical and logistical reasons, this study was cluster randomized, essentially meaning that each country had one period where PGx-guided therapy was done for all recruited patients, and one period with no PGx testing (no randomization on patient level). Moreover, each country recruited patients in different medical domains (UK, Slovenia, and The Netherlands in primary care, Greece in psychiatry, Italy in oncology, and Spain in cardiology). Consequently, drawing conclusions from the PREPARE study is challenging (see chapter 0). Gradually the country-specific results are published, focusing on the economic evaluation.^{216, 224, 226} The clinical effectiveness, however, is either not reported (Spain) or very limited (Italy, Greece).

9.2.2 Other criteria relevant to consider

In addition to the appraisal of the evidence, expert consortia highlight **other criteria** to guide testing recommendations.

The **severity of the outcome** determines the clinical impact (a potentially life-threatening hypersensitivity reaction is not judged to have the same clinical impact as lack of antidepressant effect. A standardised severity scale, such as Common Terminology Criteria for Adverse Events, can help to classify the adverse events (see Table 8 in chapter 3).

Diagnostic test criteria are also considered useful (sensitivity, specificity, positive predictive value, negative predictive value, and **number needed to genotype** NNG).^{158, 159} More specifically this last metric, which is a variant on “number needed to treat (NNT)” has been included in the methodology of the Dutch DPWG consortium (see Table 8 in chapter 3). Both the **outcome of interest** and the **baseline risk**, which depends on the variant frequency, are important to consider in this metric. NNG for hypersensitivity reaction to abacavir ranges from around 40 in white race, to 400 in black race.¹⁵⁹ When mortality is the outcome of interest, Van der wouden and coauthors calculated NNG of around 300 for CYP2C19 testing for clopidogrel to around 5000 for DPYD and fluoropyridines.¹⁶⁰ Importantly, the quality of the data on which the NNG is based should be considered as small changes in assumptions on absolute risk differences will be reflected in large NNG differences.

The need for consensus on the necessary parameters for establishing clinical utility for PGx tests has been the object of recommendations (e.g. in Italy (C_17_notizie_3270_listaFile_itemName_0_file.pdf (salute.gov.it))

9.2.3 The drug label

The information on the **drug label** should guide whether or not to test. Indeed, it is an important source of information, but here too discrepancies were observed. First of all it depends on the manufacturer providing the information, and the assessor who defines whether the information is clinically relevant, **without a transparent and reproducible process** in place that leads to the inclusion of such information from a solid evidence base. The result is that some drugs have PGx information in the label while others not, and it is not necessarily based on high quality evidence. For some drugs, the testing requirement is explicitly stated in the drug label: abacavir, siponimod, mavacantem and eliglustat (see chapter 4.1.5). While there are EMA guidelines in place, the formulation and location of the PGx information (i.e. the section in the drug label where this info appears) is also not standardised.¹⁴⁴

9.3 From evidence to clinical implementation

The reasons why some drug–gene pairs have been implemented in clinical practice, whilst some have not, are manifold and complex.

9.3.1 Clinical practice guidelines

Clinical practice guidelines from medical professional organisations greatly influence the adoption of new practices across therapeutic areas. Most clinicians (outside of PGx implementers) are currently unaware of the dedicated PGx guidelines or are not convinced of the clinical utility in their field.¹⁷⁷ Although we did not consistently check all available clinical practice guidelines from professional organisations, the incorporation of PGx guided therapy appears limited.



Illustrative is the case of CYP2C19 testing before clopidogrel administration; this is considered 'essential' by both the Dutch DPWG and the French RNPx,¹⁵⁷ but the European Society of Cardiology guideline states that the benefit of platelet function testing or genetic testing remains unclear in acute coronary syndrome.¹⁸⁷ For the indication on cerebrovascular disease, NICE is in the process of formulating guidance (expected to be published in May 2024).²¹⁵

With regard to thiopurines and TPMT testing, current clinical practice guidelines include recommendations on assessing TPMT activity, but they do not specify whether this should be done by genotyping or phenotyping. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO) recommended in 2014 to test prior to treatment (when available).⁶⁰ The American College of Gastroenterology states that a TPMT activity test before start of thiopurines should be considered (strong recommendation, low level of evidence).⁶¹ The NICE guideline on Crohn's disease also recommends testing TPMT activity.⁶² Despite the low level of evidence, TPMT testing is thus recommended by the medical professional organisations, which resulted in higher uptake of PGx testing among clinicians (in Belgium the second most performed PGx test).

9.3.2 Alternatives available

This discrepancy between PGx guidelines and clinical practice guidelines highlights that medical professional organisations also consider other testing approaches, for example **phenotypic tests** assessing the enzymatic activity to guide pharmacotherapy (see chapter 3.6). Clinicians might be more comfortable monitoring the patient with TDM or phenotypic testing options (such as platelet function tests in case of clopidogrel), as these approaches reflect not only the genetic makeup but also other factors which are important in the activity of the drug (e.g. drug interactions). The drawback of the latter approach is that it requires the patient to already be on the therapy, which is considered an *a posteriori* approach (increased risk of toxicity). Moreover, while DNA is stable and samples for genotyping can thus easily be transported in routine practice, enzymatic activity and drug levels in blood are more unstable with often strict pre-analytical and storage requirements. As many of these phenotypic tests are not available in all labs, it can be

logistically challenging to organize efficient transport of such samples to the referral laboratory.

As mentioned above, the genetic makeup of an individual is just one factor among many **non-genetic factors** that interact with the safety and effectiveness of a medication.¹ Medical professional organisations such as Dutch General practitioner organisation, and the Dutch Psychiatrist organisation recommend to first check other potential risk factors (such as smoking, comorbidities, nutrition, adherence, etc.) after which PGx testing is one of the options besides prescribing a different drug to the patient and TDM.²⁵⁵ The concept of phenoconversion and interaction of co-medication on enzyme status has been highlighted in several papers,^{9, 11} and might render the phenotypic approach a preferred option among clinicians as it integrates more variables. However, experts argue that PGx and phenotypic testing or TDM are complementary and not alternative testing approaches.³³⁵

9.3.3 Logistical challenges

Logistical factors such as test availability and turnaround time also play a role.^{7, 336} Are there enough labs offering PGx tests? Is referral of samples to larger laboratories organized efficiently? Are testing volumes for PGx sufficiently high to allow efficient batch testing? Some countries have centralized (reimbursed) PGx testing, such as the UK (the seven Genomic Laboratory Hubs, GLH). In France and the Netherlands, a larger number of labs offer reimbursed PGx testing, respectively 52 (2022) and 19 labs (2024). In Switzerland the bulk of testing is done in the 5 university labs (and 1 non university lab), but some private labs also offer PGx. The turnaround time is highly dependent on the requested test and the lab performing the test (e.g. methodology used by the lab, capacity, expertise, etc.), and also the availability of labs in the country. The lowest turnaround times reported are those for DPYD testing (2 days in the Netherlands,²⁶⁹ 5 days in the Belgian Genetic Tests Database, BGTD). In research settings, such as the PREPARE trial, panel test results were available within 7 days, and in the PROGRESS study 10 working days.



9.3.4 Knowledge gap

Lack of PGx knowledge has been cited by many as a barrier to PGx implementation.^{32, 337} The development of guidelines requires collaboration and coordination between medical specialists and dedicated PGx experts to create a well-supported multidisciplinary guideline. In this era of personalised drug, educational efforts are needed to train clinicians,⁷ though educating all prescribers is not always considered a priority for implementation.³³⁸ For clinicians, it is necessary to know who to test, when and what to test, and what to do with the test results, emphasising the importance of **clear protocols and clinical practice guidelines**.¹¹⁹ PGx-based research or clinical trials automatically increase the participating clinicians' knowledge. Moreover, this **research** allows “**early adopter**” institutions to extend their influence and knowledge dissemination to clinicians in neighbouring areas.³³⁹

There is also a role for **clinical decision support at the point of prescribing**. Ideally, prescribers should receive an automated alert when prescribing a drug for which evidence-based testing recommendations and therapeutic recommendations are available. In France, HAS offers a drug-based decision support tool since 2021 which can be integrated in prescription software and sends an alert to prescribers to test for DPYD when they prescribe fluoropyrimidines. In the Netherlands, the DPWG recommendations are available to prescribers via the national drug repository (“G standaard”). Both examples are national initiatives, meaning they are made accessible to all prescribers, but also that the recommendations are agreed upon on a national level. In Switzerland and Belgium, PGx-driven decision support systems in electronic health records (EHRs) are being developed at the hospital level. However, a nationally shared decision support system implementing evidence-based PGx guidelines would improve consistency of care.

As seen in the Netherlands and in Switzerland, there is a role for specialised consultations with **clinical pharmacologists**, as experts on pharmacotherapy, including PGx. In Switzerland and the Netherlands, patients requiring optimisation of their drug treatment, e.g. because of adverse events or a suboptimal effect, can be referred to physicians with a degree in clinical pharmacology (e.g. a psychiatric PGx policlinic Parnassia group in the Netherlands). In Switzerland, clinical pharmacologists even

have extended prescribing rights with regard to PGx tests, and other physicians can consult them for their expertise when needed (specific reimbursement foreseen). Also in Spain, clinical pharmacology is embedded, with several (university) hospitals having a Pharmacogenetics unit, staffed with a multidisciplinary team and the option for clinical pharmacogenetic consultations.³⁴⁰ There is a close collaboration between the medical geneticist who generates a molecular report and the clinical pharmacologist who elaborates a patient report. It is important to emphasise that clinical pharmacologists are not solely focused on genetic testing; they also have expertise in and access to alternatives, such as phenotyping, TDM, and consider the impact of other factors such as smoking on drug response. In Belgium, such consultations with a clinical pharmacologist for optimisation of drug therapy do not yet exist. However, the legal groundwork for an educational programme in clinical pharmacology for physicians, as well as the recognition of “*physician - clinical pharmacologists*”, has been established with the publication of the Royal and Ministerial decrees on September 4, 2023.³⁴¹ The UK report on *Personalised Prescribing* also highlights the need for prescribers to have access to expertise in pharmacogenetics.⁷ In the Mayo-Baylor RIGHT 10K Study, Mayo Clinic's pharmacists with additional training in PGx, were engaged to provide electronic consultations with the physicians.³⁴²

9.3.5 Funding gap

In general, **lack of reimbursement** has also been cited as a barrier for implementation.¹¹⁹ And while there is a wealth on economic literature (see chapter 5), the uncertainty about the clinical benefit cascades down to the economic evaluations.³⁴³ As stated earlier, evidence on the clinical effectiveness of PGx testing issued from RCTs with PGx as the trial intervention is scant and there are only a few RCTs to which the economic evaluations referred to populate their model. The results of the cost-effectiveness analyses are thus highly uncertain.

The reimbursement contexts of four countries were analysed, revealing differences in the selection of drug-gene indications eligible for reimbursement (see Table 37 in chapter 7). The UK, where full reimbursement is provided once a test is included in the National Genomic Testing database, has the most restrictive list. In France, full reimbursement of PGx is only guaranteed for one drug-gene target (abacavir) which is



included in the official nomenclature. For many other targets, only partial reimbursement is foreseen in a research envelope context. In Switzerland there is a tiered system with a limited selection of drug-gene targets (five medication groups and six gene-targets) available to all prescribers, and extended prescriber rights for clinical pharmacologists. In all of the aforementioned countries, there is a **formal and standardised procedure** for selecting the drug-gene pairs eligible for reimbursement.

9.3.6 *Communication with the patient and between health care practitioners*

Informed consent is universal, although its implementation in practice varies. In Belgium, the UK, and the Netherlands, written informed consent prior to genetic testing is not mandatory, unlike in France and Switzerland where it is legally required. However, ambiguity arises when multiple genes are tested using (whole genome) sequencing, potentially leading to incidental findings and findings of unknown significance, in which case genetic counselling may be needed. This highlights the need for clear national guidelines on implementing informed consent for PGx testing. Experts argue that a PGx test is equivalent to renal or liver function testing to guide prescribing decisions, and therefore should not routinely require genetic counselling services.⁷ Other experts, however, stress the importance of genetic counselling for all genetic tests.³⁴⁴ Based on our findings and current clinical practice in Belgium, expert input (e.g. clinical pharmacologist or clinical geneticist) might be necessary for some complex cases, variants of unknown significance or incidental findings, but routine genetic counselling for each PGx test may not be necessary.

In this report we focus on the process where a physician orders the PGx tests, however we are aware Direct-To-Consumer tests are also an option as it becomes more accessible via online ordering. While the volumes of DTC testing are generally considered to be low, societies in various countries warn for the potential disadvantages of this kind of testing on the health care system and individual patients.^{48, 262, 316, 344} Patients might go to their GP or pharmacist asking for clarification (or confirmation) of received DTC reports, the clinical validity of the tests is often low or unknown, which could induce increased costs.

Communication and data-sharing of PGx information between laboratory and prescribers took on different forms in different countries, but generally lacks an automatic incorporation of the PGx info in a **shared EHR**, which is accessible to all relevant prescribers nationwide. Most often, local solutions are developed, limited to a hospital or group of hospitals working with the same IT. In the Netherlands, the PGx results are inserted in the EHR as a contra-indication (e.g. similar to an allergy). Communication and data sharing is particularly important for results of panel testing, as the added value of the preemptive approach is only possible when this information is safely stored and accessible to all relevant health care practitioners for future prescriptions, necessitating data availability across organisational boundaries.³²⁴

A work-around for the shared storage approach, pursued by some of the (hospitals in the) examined countries, and seen in research context (PREPARE study), is handing the patient a PGx passport in the format of a credit card-size card or an app containing the known PGx information (not the raw data) of the patient.²⁶⁶ While useful as a temporary solution until the technological infrastructure is in place, it should be noted that the PGx passport has drawbacks in terms of privacy, patient safety, and effectiveness. The technological infrastructure should therefore be developed further to ensure safe storage and reusability of test results (and potentially also the raw data which might be relevant when new variants have actionable information).

What is the role of **pharmacists**? In the Netherlands, pharmacists already have a prominent role in PGx implementation, based on their knowledge and involvement in many research projects.³³⁸ In the Netherlands, DTC companies also find their way through sales in pharmacies.²⁶³ The Royal Pharmaceutical Society in the UK published a position paper clarifying their future leader role in PGx, including identifying eligible patients, ordering PGx tests and providing advice.³⁴⁵ In France, they also see potential for the pharmacist in addition to their expertise on drug-drug interactions and allergies.³⁴⁶ In several USA implementation projects (RIGHT study in the Mayo clinic) the hospital pharmacists were responsible for electronic consultations and communication of recommendations to the prescribers, but additional PGx training was necessary.³⁴²



9.4 Panel testing

Panel testing has been cited by many experts as the way to implement PGx. Instead of a targeted test focused on the information specific for the drug prescribed (which is currently mostly done), a panel test simultaneously analyses various gene variants from a single sample, providing also information for future prescriptions. Laboratories are already using the panel technology in a reactive way, for example when entire genes, multiple codons and/or more (rare) variants need to be analysed. Panels are available or being developed, either based on NGS technology (e.g. Sophiagenetics in collaboration with RNPGx), or microarray technology (ThermoFisher, Illumina - UZBrussels/VUB 'My PGx' pilot project in research context). While validation of several panel technologies is underway, a combination of testing approaches for PGx is still often used in the lab.

Furthermore, experts have emphasized the importance of **standardizing the selection of genes and variants**, to be included in the panel, **taking into account ethnicity**, and regular **updates**. International consortia are involved in providing this information, but a full overview for all relevant genes and variants is not available yet. The Association for Molecular Pathology Clinical Practice Committee's Pharmacogenomics aims at defining a minimum panel of variant alleles (tier 1) and an extended panel of variant alleles (tier 2) that will aid clinical laboratories when designing assays for PGx testing. At the moment they have recommendations for CYP enzymes and TPMT and NUDT15.³⁴⁷

A panel test evidently offers more information, so if the **cost of a panel** were roughly equivalent to that of a single-gene test, there would be little reason not to opt for panel testing over single-gene testing. However, complex multigene panels can easily be twice as expensive as single-gene tests (priced between \$100 and \$500 depending on the testing company and platform).³² Moreover, the added value of the preemptive approach of the panel test which could justify a higher reimbursement fee, remains uncertain.³² Follow-up time of studies on panel testing is too short to gather information on potential benefits for future prescribing (which may well be

many years in the future), therefore no (cost-)effectiveness data is available for this approach (1 hypothetical study²¹).

Our international comparison showed that in none of the examined countries the (semi-)preemptive PGx testing strategy is currently reimbursed by national health insurance. However, at the time of writing this report, HAS is evaluating whether NGS gene panels in post-natal constitutional genetics (particularly in the fields of pharmacogenetics, oncogenetics and rare diseases) should be included in the official nomenclature (full reimbursement). In the Netherlands, only supplemental health insurance plans reimburse semi-preemptive panel testing under specific conditions. **Implementation of panel tests in Europe is currently in research phase** (UK-PROGRESS study^{ww} in primary care, Personalised therapeutics study in Leiden University Medical Centre, etc). In the US, panel testing is performed mainly on an institutional level.^{24, 25}

Panel testing (especially with sequencing technology) may present more **ethical issues** than single-gene testing. Variants of unknown significance in other genes than those initially targeted for prescription may be detected of which the clinical implications for the patient are unclear; moreover, knowledge of these variants may not necessarily be desired by the patient. Therefore, informed consent will be needed before panel testing can be performed and reporting of variants, especially those of unknown significance, has to be done carefully.

In addition to the uncertainty around (cost-)effectiveness of the preemptive approach, organisational challenges hamper the practical roll-out of preemptive panel testing.

^{ww} PROGRESS - Study to assess the rollout of a genetic-guided prescribing service in UK General Practice - <https://www.isrctn.com/ISRCTN15390784>



The following **organisational challenges** first need to be addressed:

- Guidelines on the practical organization of informed consent for panel tests and rare variants.
- Guidelines on reporting: should only clinically validated variants be reported? Should there be a direct link with PGx therapeutic recommendations (lower dose, change therapy...)? How to report rare variants for which no recommendations exist? Ideally reporting of variants of unknown significance is standardized across healthcare facilities.
- Integration of the information in the (electronic) patient record to allow data availability across organisational boundaries.

9.5 The Belgian situation

Our survey results on the number of PGx tests together with the incident users of the relevant drugs (based on the national database with reimbursed medication) showed good uptake for certain PGx tests. However, interpretation is not straightforward (see 2.2.5).

Comprehensive volume data together with details on the indication to tests are key for a solid interpretation of PGx implementation. France is the only country, among those studied, where the national volumes of PGx are systematically collected and publicly disclosed.

For other aspects on implementation, such as the conduct of pilot studies and the existence of specialised PGx centres, Belgium does not yet reach the level of The Netherlands, Switzerland. Various academic centres and hospitals are committed to PGx research and its potential implementation as demonstrated by various master theses,³³⁻³⁷ publications³⁸⁻⁴² and pilot projects (MyPGx: the fight against medication failure' at the UZ Brussel hospital).

9.5.1 Access to PGx

From the prescriber's viewpoint, the list of available reimbursable drug-gene targets is rather broad when compared to other countries (see further limitative list).

A limitation is more likely to be observed within the laboratories, where the tests are conducted. Reimbursed PGx testing, like many other germline genetic tests in Belgium, is **confined to the 8 CHGs**. In practice this means that **every prescriber** can send a sample together with the clinical question to one of the 8 CHGs and it is the medical geneticist of the lab who decides whether a genetic test and which technology is appropriate. If all prescribers are aware for which drugs a PGx might be indicated and reimbursed, and which labs conduct specific PGx tests and refer their samples accordingly to these CHGs, access is assured. However, the long turnaround time of PGx has been stated as an issue (see 2.2.5), where some clinicians ask the test as part of the diagnostic workup of a patient, and eventually might not even use the test result, as another therapy has already been launched. This also explains the higher number of tests compared to new drug users.

Each of the eight CHGs offers PGx testing, although for some, the focus is limited to a single target. In Belgium, the CHG at UCL St Luc currently offers the most comprehensive range of PGx services, and is also a referral point for other CHGs.

The access to reimbursed PGx testing is not completely consistent for HLA targets. There is the example of abacavir: when done in a HLA lab which has no affiliation with a CHG, the test is not reimbursed. HLA is an important target for PGx, and expertise in this area primarily resides within HLA laboratories. This distinction between HLA and other PGx targets is also seen in the other examined countries (UK, France, Switzerland), though reimbursement is assured.

Our report showed that some PGx targets, relevant in oncological therapy (DPYD, UGT1A1, TPMT, SLCO1B1), are included in some oncological somatic panels run at clinical biology or anatomopathological labs. For these panels, the extraction of DNA is based on tumour tissue, which is not the ideal sample to perform PGx (see chapter 3.3.2).³⁴⁸ We were unable to offer a thorough summary of the extent of this practice as not all contacted labs



responded to our survey. Reasons for including such targets in somatic panel tests could be that some have strong confidence in the technical feasibility to reliably detect germline PGx targets, or it could signify that access to PGx is currently deemed too restricted, or logistically not optimal.

9.5.2 A Belgian reimbursement list – limitative list

There are some unclear and inconsistent points in the limitative list^{xx} concerning PGx indications. While genes and their variants are listed, there is often no connection with available drugs. Currently the list entails both indications for which there are strong recommendations to test, but also where the evidence is less clear. An update of the limitative list is necessary. Moreover, the establishment of the current Belgian limitative list lacks **transparency**. The process of selecting PGx targets for inclusion in the limitative list is not clear: is it based on the level of evidence, or on clinical need? Another question arises regarding the **extensiveness of this list**: should it solely encompass PGx targets backed by strong evidence, which are essential for testing, or should there also be room for more exploratory options? For instance, clinical pharmacologists in Switzerland have a broader range, while in France, certain generic codes are covered by research budgets.

Considering the various consortia and countries offering testing recommendations, it prompts the question of whether a country should formulate its own list. However, it is not the ambition of guidelines such as CPIC to be overly prescriptive. Individual institutes or health care systems should consider it an informational resource to build and strategize their own integration of PGx.³²⁴ Moreover, guidelines are no reimbursement lists, and the particular context of a country is important. For example in some countries phenotyping is much more implemented (France – DPYD, UK – TPMT). In France, Switzerland and England, a structured procedure is put in place to evaluate whether a certain PGx test indication is eligible for reimbursement by the national health insurance. This can be a cumbersome process, as many variables are taken into account (see chapter 3), which of course requires an organisation to take on this task (e.g. the Swiss Society

of Clinical Pharmacology & Toxicology, the HAS in France). One of the variables considered in the UK are the financial implications of implementation, e.g. to be able to determine the impact of testing volumes on the budget. The budget impact analysis as explored in chapter 6 is an example of this.

9.5.3 Technologies – Quality assurance

While the majority of PGx tests in the 8 CHGs are single gene tests based on PCR methodology, some labs use ISO accredited NGS panels for specific targets (in a reactive way). Several labs are in the process of validating panel technologies for identifying a wide array of PGx targets (micro-array, NGS short or long read panels), though these are currently still in the process of validation.

With regard to quality assurance of the 8 CHGs, the rules set out by legislation are not very explicit, creating ambiguity on interpretation of some rules (see chapter 0). An artefact is that the CHGs are not subjected to the same quality assurance regulations as the clinical biology and anatomopathological labs. **Harmonization of quality monitoring** of CHGs is of importance to ensure the quality of care. Quality improvement projects can be carried out across the whole chain of PGx, from identifying patients eligible for testing, optimising laboratory processes, incorporating results into each hospital's electronic health record system, to improving patient medication reviews. It should be the role of local institutions (clinical governance) and competent authorities (RIZIV-INAMI, Sciensano, FPS) to encourage and support service audits and quality improvement programs in order to disseminate and affirm best practices, share learning and iteratively improve service delivery. A structured system for monitoring quality of PGx should be put in place, with high and uniform quality standards, while encouraging innovative research and allowing the labs to choose the appropriate technology, platform and workflow for their context.

^{xx} The limitative list contains all the indications for reimbursable genetic testing in the 8 CHGs (around 600), including several indications for PGx.



9.5.4 Reimbursed Fees

At the moment, for PGx in Belgium, two standardised fixed fees based on technical and intellectual complexity are used. Most of the tests are targeted, focused on identifying a limited number of variants, and are around €170 (€185.18 in 2024). For the more complex pharmacogenes, or when it is necessary to have a more agnostic approach (e.g. identify a rare variant), sequencing including NGS panels, are used, which corresponds to a fee of around €400 (€426.41 in 2024). These fees include the sampling, the test, the work of the lab staff and the reporting to the prescriber.

Important to note is that currently a reorganization of the entire Belgian fee schedule (nomenclature) is foreseen to make it more transparent and standardized, by using an activity based costing approach. In this fast evolving part of medicine, technological advances will lower costs, requiring regular updates of the fee schedule.

The use of a limited number of codes with fixed fees comes with a drawback, as these codes, designed for numerous indications, lack specificity. These codes, declared and systematically collected at the national level, serve as valuable claims data for monitoring, and are frequently used as an information source in various studies. The lack of specific nomenclature codes per PGx indication hampers automatic data-collection. For companion diagnostics (CDx), the issue is tackled by requiring distinct **pseudocodes** for each CDx, enabling precise tracking of the frequency of tests, the specific indications for which they are conducted.

9.5.5 Next steps

Implementation of PGx is not straightforward, encompassing many barriers.³³⁷ In those countries/institutes where an active research environment is cultivated including **clinical trials and implementation initiatives**, the expertise is being built for a PGx rollout. Often barriers are being tackled alongside the conduct of pilot studies. However, sharing PGx data across institutions, between primary care and hospitals, between

regions is important, therefore a **national IT solution with clear reporting guidelines** should be installed.

Once the specific requirements for a (semi-)preemptive testing approach are established, large randomised pragmatic trials could be launched aimed to assess the effectiveness of PGx-informed future prescriptions and therapy adjustments, and to evaluate costs including those for storing data.

9.6 Limitations

- This study was not focused on identifying the gene variants. Therefore, not much information on variants or the prevalence is included. The starting point was not to create a test (panel) that contained all relevant variants, or an IT pipeline that detects the necessary variants.
- The current implementation in Belgium was assessed via survey to the labs. The prescriber viewpoint was not explored in this study. Ideally, to identify the need for PGx testing, in each medical specialty the place of PGx should be defined. However, this was not feasible in the timespan of this study.
- The volumes focused on what is within the reimbursement, i.e. the volume in the 8 CHGs. However, there is a small indication of what is done outside the 8 CHGs, though this is not exhaustive – merely an indication. The volumes are self-reported through a survey.
- Ideally for every gene-drug pair a thorough evaluation of the evidence should be considered before cost-effectiveness can be assessed. This was not feasible in the timeline of this report.
- This study did not dig into detail into all the barriers for implementation, for example did not check all the available IT solutions currently being developed, the ethical and medico-legal aspects of PGx testing.



■ APPENDICES

APPENDIX 1. BELGIAN SITUATION

Appendix 1.1. Information on the laboratoria

Table 41 – The eight Centres for Human Genetics

Centre of Human Genetics (CHG)
Centrum Menselijke Erfelijkheid, KUL
Centrum Medische Genetica - UZ Antwerpen
Centrum voor Medische Genetica - VUB
Centrum Medische Genetica - Gent
Centre de génétique humaine – Institut de pathologie et de génétique (IPG)
Centre de Génétique médicale - Cliniques Universitaires Saint-Luc UCL
Centre de Génétique Humaine - ULB
Center for Human Genetics Liège pathology institute - CHU Sart-Tilman Liège

Table 42 – Contacted labs, other than the CHGs

HLA labs
UCL, Molecular Biology (HLA & HHI) - part of the Laboratoires Cliniques Universitaire Saint-Luc)
HILA Laboratory, Rode Kruis, Vlaanderen
HLA Laboratory Division of Laboratory of Hematology, AZ Sint Jan Brugge-Oostende AV Campus Brugge
HLA Laboratory, CHU Dinant Godinne
HLA Laboratory, Hôpital ERASME – part of the Laboratoire hospitalier universitaire de Bruxelles - universitair laboratorium Brussel (LHUB-ULB)
HLA Laboratory, Centre Hospitalier Universitaire de Liège

Universitair Ziekenhuis Brussel, HLA and Molecular Hematology

Other labs in NGS network*

Pathologische ontleedkunde UZ Leuven	
Jessa Ziekenhuis-Klinisch laboratorium	
Laboratoriumgeneeskunde, AZ Sint-Jan	Also HLA lab
Pathologische Anatomie, AZ Sint-Jan	
AZ St-Lucas	
Laboratorium voor Klinische Biologie UZ Gent	
Laboratoriumgeneeskunde, AZ Delta	
pathologische anatomie, UZA	
CellCarta	
klinische biologie, UZA	
klinische biologie, ZNA	
klinische biologie, AZ Klina	
Anapath IPG	
Laboratoires Cliniques Universitaire Saint-Luc (CUSL)	Also HLA lab
Laboratoires Cliniques CHU Liège	Also HLA lab
Laboratoires CHR Citadelle (vanaf 16 maart 2021)	
UZ Brussel - labo anatomo pathologie	
UZ Brussel - labo voor klinische biologie	Also HLA lab
Bordet - Service d'anatomie pathologie, cytologie et cytogénétique	
Erasmus laboratoire d'anatomie pathologie	
Laboratoire hospitalier universitaire de Bruxelles - universitair laboratorium Brussel (LHUB-ULB)	Also HLA lab
Klinisch laboratorium, AZ Groeninge	
Klinisch laboratorium, AZ Maria Middelaes	

There are ten NGS network having a convention with RIZIV-INAMI. Each network has at least 1 centre for human genetics (they are not displayed in this section).



Appendix 1.2. Survey

Below you can find the survey addressed to the eight centres of human genetics (CHGs). the survey addressed to the non-CHGs labs is available upon request.

KCE is undertaking a study on pharmacogenetic testing. A first step is to understand the current Belgian situation. Therefore we launch a survey for which we solicit your input.

This survey has some more general questions to understand which labs are performing pharmacogenetic tests.

If you indeed perform pharmacogenetic testing there will be a second survey (link at the end of this survey).

Section A: Introduction

For reference, here is the list of pharmacogenetic tests (as compiled by the college for human genetics and included in the RIZIV – INAMI limitative list).

If you are performing pharmacogenetic testing on targets not available on the RIZIV – INAMI limitative list, you can also indicate this in the survey further.

A1. Are you responding in the name of a centre for human genetics?
This is a question help text.

Yes ☐

No ☐

A2. For which genetic centre are you answering?

Centrum Medische Genetica - UZ Gent ☐

Centrum Medische Genetica - UZ Antwerpen ☐

Centrum Medische Genetica - UZ Brussel VUB ☐

Centre de Génétique Humaine - Erasme UIB ☐

Centre de Génétique-Institut de Pathologie et de Génétique (IPG) ☐

Centre de Génétique Médicale UCL ☐

Centrum Menselijke Erfelijkheid - KUL ☐

Centre de Génétique Humaine - CHU Sart Tilman ☐

A3. For which lab are you answering?

A4. RIZIV – INAMI number of the lab:

A5. Please enter your name (first name last name):

A6. Please enter the head of the lab's name (first name last name):

A7. Please enter the head of the lab's email address:

A8. Did your lab/centre perform pharmacogenetic testing in 2021 or 2022?

Yes ☐

No ☐

**Section B: Part one - Overview testing**

Below you can find the Limitative list of tests reimbursed by RIZIV-INAMI when performed in one of the 8 centres of human genetics. For some gene targets, there are already in the RIZIV – INAMI list more than one test (e.g. VKORC1, or DPYD, only the single nucleotide polymorphism or sometimes the full sequencing of exons). Even if you are not one of the 8 centres for human genetics, it is possible that you are performing these test for patients without the RIZIV – INAMI reimbursement.

If your lab/centre is performing pharmacogenetic testing on targets not available on the RIZIV – INAMI limitative list, you can also indicate this in the survey below.

For 5-Fluorouracil (5-FU), capecitabine and tegatar phenotype testing of the enzyme dihydropyrimidine dehydrogenase (DPD) is also possible/recommended, through the measurement of uracil and dihydrouacil/uracil ratio in plasma samples.

B1. Can you indicate which pharmacogenetic targets on the RIZIV – INAMI list your lab/centre is testing in clinical setting in 2021 or 2022 at germline level (not specific to tumour tissue/ctDNA)? If you are performing pharmacogenetic testing on tumour tissue (biopsy, ctDNA), please specify which gene targets and whether you are able to capture germline information (in 'any remarks on the sample').

- | | |
|--|--------------------------|
| Transport protein ABCB1 | ☐ |
| Metabolism/biotransformation CYP2B6 | ☐ |
| Metabolism/biotransformation CYP2C19 | ☐ |
| Metabolism/biotransformation CYP2C9 | ☐ |
| Metabolism/biotransformation CYP2D6 | ☐ |
| Metabolism/biotransformation CYP3A4 | ☐ |
| Metabolism/biotransformation CYP3A5 | ☐ |
| Transport protein SLCO1B1 | ☐ |
| Metabolism/biotransformation (Gilbert/irinotecan sensitivity) UGT1A1 | ☐ |
| Abacavir hypersensitivity HLA5701 | ☐ |
| Vit K antagonist sensitivity VKORC1 (2 SNPs) | ☐ |
| Vit K antagonist resistance VKORC1 (exons) | ☐ |
| Clopidogrel resistance PON1 | ☐ |
| Dihydropyrimidine dehydrogenase deficiency (5-fluorouracil toxicity) DPYD (exons) | ☐ |
| Dihydropyrimidine dehydrogenase deficiency (5-fluorouracil toxicity) DPYD (4 variants) | ☐ |
| Response to antiviral (Hep C) IL28B | ☐ |
| Narcolepsy HLA-DQB1 | ☐ |
| Thiopurine S-Methyltransferase deficiency TPMT | ☐ |
| Thiopurine S-Methyltransferase deficiency TPMT + NUDT15 (exons) | ☐ |



- | | |
|---|--------------------------|
| Susceptibility to pancreatitis induced by thiopurine immunosuppressants HLA-DQA1-HLA-DRB1 | ☐ |
| Celiac disease HLA-DQ2-HLA-DQ8 | ☐ |
| Butyrylcholinesterase deficiency BC11F | ☐ |
| Mitochondrial non-syndromic sensorineural deafness with susceptibility to aminoglycoside exposure hot spot mutation MT-RNR1 | ☐ |

B2. Any remarks on tests on this RIZIV – INAMI list?

B3. Did your lab/centre perform other (not on the list) pharmacogenetic testing in 2022?

- Yes ☐
- No ☐

B4. Please list the gene target-indication that is not included in the limitative list.

B5. Did your lab perform the pharmacogenetic tests on tumour tissue/ctDNA?

- Yes, we perform primarily on tumour tissue/ctDNA ☐
- No, we perform primarily on blood, saliva ☐

B6. Any remarks on the sample on which the pharmacogenetic test is run?



LimeSurvey



B7. In the near future, 2023-2024, is your lab planning on (adding extra) pharmacogenetic testing for clinical or research purpose?

B8. Is your lab performing this phenotyping test?

Yes ☐
No ☐

B9. Is the phenotyping of DPD done preferably over the genotyping?

Yes, most of the times we perform the phenotyping standard and only in rare cases we add the genotyping ☐
Most of the time we perform both on the same patient, a combination of phenotyping and genotyping ☐
No, we primarily do the genotyping, and only in rare cases we do a phenotyping ☐

B10. What is the number of phenotyping tests for dihydropyrimidine dehydrogenase deficiency in 2022?

B11. At the moment no nomenclature reimbursement is foreseen for this phenotyping test. What is the amount charged to the patient? (in EUR)

B12. Are there other phenotyping tests (other than DPD) which are done in your lab/centre and which are linked to pharmacogenetic testing?

LimeSurvey



B13. Any remarks?

Thank you for filling in these general questions on pharmacogenetic testing!

If you are performing pharmacogenetic tests at germline level, we kindly ask you to fill in part 2 of this survey:

Go to part 2



For each “pharmacogenetic test” we would like to understand the indication and technology used in addition to the volume.

If your lab offers multiple methods of testing the same gene target (e.g. targeted or combined in a panel, e.g. TMPT and TPMT + NUDT15), each specific test requires a separate entry.

If you have pharmacogene targets that are not (yet) in the limitative list and not (yet) in the Belgian Genetic Tests database, you will also be able to give the technical information in this survey.

Section A: Per pharmacogene target information

A1. Are you responding in the name of a centre for human genetics?

Yes ☐

No ☐

A2. Your center for human genetics is the following:

This is a question help text.

Centrum Medische Genetica - UZ Gent ☐

Centrum Medische Genetica - UZ Antwerpen ☐

Centrum Medische Genetica - UZ Brussel VUB ☐

Centre de Génétique Humaine - Erasme ULB ☐

Centre de Génétique-Institut de Pathologie et de Génétique (IPG) ☐

Centre de Génétique Médicale UCL ☐

Centrum Menselijke Erfelijkheid - KUL ☐

Centre de Génétique Humaine - CHU Sart Tilman ☐

A3. For which lab are you answering?



A4. Please select the pharmacogene target that your lab is testing (and for which you will give input in the subsequent questions).

For a pharmacogene target which is not in this list, please select "A test not in the RIZIV-INAMI limitative list" (last option) and specify which target/test.

If you are testing pharmacogene targets in panels, please select one pharmacogene target and specify further whether it is run in a panel and which other pharmacogene targets are run simultaneously.

Transport protein ABCB1 (565390-565401) ☐

Metabolism/biotransformation CYP2B6 (565390-565401) ☐

Metabolism/biotransformation CYP2C19 (565390-565401) ☐

Metabolism/biotransformation CYP2C9 (565390-565401) ☐

Metabolism/biotransformation CYP2D6 (565456-565460) ☐

Metabolism/biotransformation CYP3A4 (565390-565401) ☐

Metabolism/biotransformation CYP3A5 (565390-565401) ☐

Transport protein SLCO1B1 (565390-565401) ☐

Metabolism/biotransformation (Cilbert/Irinotecan sensitivity) UGT1A1 (565390-565401) ☐

Abacavir hypersensitivity HLA5701 (565390-565401) ☐

Vit K antagonist sensitivity VKORC1 (2 SNPs) (565390-565401) ☐

Vit K antagonist resistance VKORC1 (exons) (565390-565401) ☐

Clopidogrel resistance PON1 (565390-565401) ☐

Dihydropyrimidine dehydrogenase deficiency (5-fluorouracil toxicity) DPYD (exons) (565456-565460) ☐

Dihydropyrimidine dehydrogenase deficiency (5-fluorouracil toxicity) DPYD (4 variants) (565390-565401) ☐

Response to antiviral (Hep C) IL28B (565390-565401) ☐

Narcolepsy HLA-DQB1 (565390-565401) ☐

Thiopurine S-Methyltransferase deficiency TPMT (565390-565401) ☐

Thiopurine S-Methyltransferase deficiency TPMT + NUDT15 (exons) (565456-565460) ☐

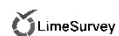
Susceptibility to pancreatitis induced by thiopurine immunosuppressants (HLA-DQA1-HLA-DRB1, 565390-565401) ☐

Celiac disease HLA-DQ2-HLA-DQ8 (565390-565401) ☐

Butyrylcholinesterase deficiency BCHE (565471-565482) ☐

Mitochondrial non-syndromic sensorineural deafness with susceptibility to aminoglycoside exposure hot spot mutation MT-RNR1 (565390-565401) ☐

A test not in the RIZIV-INAMI limitative list ☐



A5. Which mutations/variations are checked with the test?

A6. Is the test limited to this specific pharmacogene or is it tested in a panel with other targets?

specific pharmacogene ☐

in a panel ☐

A7.

Which other targets?

Please add information on the panel.

If the panel contains several pharmacogene targets, you can describe it the first time and give it a name; in the subsequent iterations, you can skip the description if you give the name of the panel.

A8. Which methodology/technique is used for the test? (e.g. Sanger, real-time PCR, NGS)



A9. How is the test developed?

in-house ☐

commercial kit or panel with CE mark ☐

in-house modified kit or panel ☐

Other ☐

Other

A10. From which commercial company?

A11. What is the turnaround time of the test?

A12. Did your lab/centre participate in External Quality Assessment for this test in 2021 or 2022?

Yes ☐

No ☐

A13. Why was there no EQA?

A14. Please specify the EQA(s).



A15. Did you update the Belgian Genetic Tests Database including the information which mutations/variants are checked, whether the test is part of a panel or limited to the pharmacogene target?

Yes ☐

No ☐

A16. For testing this pharmacogene target, what is the indication? (name of medications, condition, etc. If not known please indicate so)

A17. Annual volume of this specific pharmacogenetic test.

If you don't know, please indicate it in the textbox.

If you run panels for this pharmacogene in combination with other pharmacogenes, you can indicate how many times the panel is run.

Total number of tests performed in lab in 2021 (n)

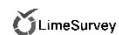
Number of tests invoiced to RIZIV-INAMI in 2021 (n) + specify which nomenclature code used

Total number of tests performed in lab in 2022 (n)

Number of tests invoiced to RIZIV-INAMI in 2022 (n) + specify which nomenclature code used

A18. Any remarks on volume?

A19. What is the proportion of tests for which the result for the pharmacogene cannot be interpreted or give no result? (n %)



A20. If known, please give the main reasons for not being able to interpret or have results (poor sample, etc.).

A21. Are there other tests (enzyme testing, etc.) that are needed to complement this pharmacogenetic test for clinical interpretation?

Yes ☐

No ☐

A22. Please specify which ones.

A23. Regarding turnaround time, do you wait until you have a minimum number of samples before running the test?

Yes ☐

No ☐

Sometimes ☐

A24. Is a change expected in method/technique over the next 2 years?

Yes ☐

No ☐

A25. Please specify.



A26. Who are the main prescribers (specialty) for this pharmacogene/test?
Can you quantify in percentages?

A27. Please indicate when the test is performed.

Before the first prescription ☐

Close to the first prescription ☐

During the treatment with the medication ☐

Unknown ☐

Other ☐

Other

Thank you for your contribution.

If you have more pharmacogenetic tests performed at germline level, you need to repeat this survey as we are interested in the volume per test.

Repeat the survey



APPENDIX 2. TECHNIQUES AND METHODS FOR PHARMACOGENETIC TESTING

Table 43 – Overview of techniques used for PGx targets and the quality assurance in the eight CHGs

CHG Lab	Gene-target	Method technique	Accreditation/EQA	TAT (max)
Gent	HLA B*5701 (abacavir)	NGS	no info	6 weeks
Gent	Vit K antagonist resistance VKORC1 (exons)	NGS	no info	8 weeks
Gent	DPYD (4 variants)	bi-directional Sanger	EQA 2021, 2024 DPD GenQA	2 weeks
Gent	Butyrylcholinesterase deficiency BCHE	NGS	no info	3 months
CHUliège	DPYD (4 variants)	PCR based	ISO 15189 + EQA: 2022 pharmacogenetic panel EMQN	5 days
CHUliège	TPMT (*2, *3A, *3B, *3C)	Real-time PCR	ISO 15189 + EQA: 2022 pharmacogenetic panel EMQN	2 weeks
CHUliège*	HLA-DQA1-HLA-DRB1	PCR based	no info	15 days
CHUliège*	HLA5701 (abacavir)	PCR based	ISO 15189	2 weeks
CHUliège	UGT1A1 (*1, *6, *28, *36, *37)	PCR based	no info	3 weeks
CHUliège	MTHFR c.677C>T and c.1298A>C	NGS	EQA 2015	
VUB	HLA B*5701 (abacavir)	targeted PCR in HLA lab, in second line NGS in CHG	ISO 15189	unknown
VUB	MT- RNR1 (aminoglycosides)	NGS	no info	
KUL	DPYD (4 variants)	bi-directional Sanger + MLPA	ISO 15189 + EQA: 2022 DPD GenQA	7 days
KUL	DPYD (exons)	no info in BGTD	no info in BGTD	
KUL	UGT1A1 (*28 homozygote)	PCR based	ISO 15189	8-13 weeks
KUL	TPMT (*2, *3B, *3C)	real-time PCR	ISO 15189	2-3 weeks
UCL	DPYD (4 variants)	QF-PCR	ISO 15189 + EQA: 2022 DGKL/RfB	10 days
UCL	DPYD (exons)	NGS - panel test	ISO 15189 + EQA: 2022 DGKL/RfB	3 weeks
UCL	UGT1A1 (*28, *36, *37, *6)	HRM and real-time PCR	EQA: 2022 DGKL/RfB	2 weeks
UCL	TPMT (5 variants)	real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	TMPT + NUDT15 (exons)	NGS - panel test	ISO 15189 + EQA DGKL/RfB	10 days
UCL	SLCO1B1(*5,*15,*37)	real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	CYP 3A5 (*3, *6)	real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	CYP2C9 (*2, *3)	real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	CYP2D6 (full gene sequencing + pseudogene and CNV analysis)	NGS - panel test	ISO 15189 + EQA DGKL/RfB	3 weeks
UCL	CYP2C19 (*2, *3, *17)	real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks



UCL	CYP3A4 (*22)	real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	CYP2B6 (*9, *11, *18)	real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	VKORC1 (2 SNPs)	Real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	VKORC1 (all exons)	NGS – panel test	ISO 15189 + EQA DGKL/RfB	3 weeks
UCL	antiviral (Hep C) IL28B	real-time PCR	EQA: 2020 DGKL/RfB	2 weeks
UCL	ABCB1 (2 variants)	Real-time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	MTHFR c.677C>T and c.1298A>C	real time PCR	ISO 15189 + EQA DGKL/RfB	2 weeks
UCL	NAT2 at least *4 (wild-type), *5, *6, *7 and *14	NGS	external comparison with other lab	
UCL*	HLA B*5701 (abacavir)	No info		
UCL	A panel with 41 pharmacogenes	NGS		
UZA	DPYD (4 variants)	bi-directional Sanger	no info in BGTD (but in accreditation scope via check BELAC dossier)	2 weeks
UZA	MT-RNR1 hot spot	bi-directional Sanger	ISO 15189 (till 2023-11-08))	2 months
IPG	TPMT	NGS	EQA: 2021: Molecular genetics 03-set06- INSTAND e.V.	15 days
IPG	MT- RNR1 (hot spot)	Bi-directional Sanger - NGS	EQA: 2020 mtDNA Metabolic disorders -EMQN	20-60 days
IPG	UGT1A1 (homozygote*28)	bi-directional Sanger	no info	15 days
ULB	UGT1A1 (homozygote *28)	PCR based	no info	2 months
ULB	TPMT	real-time PCR	ISO 15189	3 weeks

Source: Belgian Genetic Tests database and survey, * indicates that the HLA analysis is done in the HLA lab linked to the CHG hospital.



Table 44 – Quality criteria mentioned in reimbursement legislation (nomenclature) in Dutch

Article 33 – genetic testing in the 8 centres for human genetics

§ 6. Het laboratorium voldoet aan de volgende kwaliteitseisen

- 1) in bezit van ten laatste 1ste januari 2014 van de **accreditatie ISO 15189**, of alle andere accreditatie die voldoen aan een gelijkwaardige Europese of internationale laboratoriumnorm, **voor minimum 80 % van de uitgevoerde verstrekkingen**. Voor de verstrekkingen waarvoor geen accreditatie bestaan, levert het laboratorium het bewijs van opvolging van een intern systeem van kwaliteitscontroles;
- 2) het laboratorium levert **elke jaar het bewijs van deelname aan interne en externe kwaliteitscontroles** die voldoen aan nationale of Europese of internationale kwaliteitsnormen;
- 3) tot het bekomen van de accreditatie bedoeld onder 1° levert het laboratorium het bewijs van het oprichten van een systeem van kwaliteitscontroles.

§ 7. De erkende centra voor antropogenetica zijn ertoe gehouden een uniform jaarlijks activiteitenrapport met overzicht van de uitgevoerde genetische onderzoeken op te maken.

§ 8. Een jaarlijks rapport van de kwaliteitscoördinator met opgave van resultaten van de interne en externe kwaliteitscontroles en van de acties ondernomen in het kader van kwaliteitsbewaking wordt aan het onder § 7 vermelde rapport toegevoegd.

§ 9. Elke in § 2 bedoelde laboratorium houdt een register bij waarin per indicatie de ervoor uitgevoerde nomenclatuurverstrekkingen zijn genoteerd.

§ 10. De centra voor antropogenetica stellen een « Handboek voor een diagnostische op puntstelling.

Artikel 33bis – molecular biological tests on human genetic material

2bis° Het laboratorium moet voor wat betreft de moleculaire diagnostiek van hematologische aandoeningen die in rubriek B worden vermeld, een

register houden + bewijs van accreditatie voor de uitgevoerde verstrekkingen.

3° De verstrekkingen moeten uitgevoerd zijn in een laboratorium dat een **ISO 15189 accreditatie of een accreditatie** volgens een gelijkwaardige laboratoriumnorm bezit voor de uitgevoerde verstrekkingen.

4° Het laboratorium moet het bewijs kunnen voorleggen van **deelname aan interne en externe kwaliteitscontroles** die voldoen aan nationale of internationale kwaliteitsnormen.

5° Het laboratorium verbindt zich ertoe zich vanaf 1 augustus 2007 te onderwerpen aan de **controles** uitgevoerd door het Wetenschappelijk Instituut Volksgezondheid (WIV).

Specifically for nomenclature codes on molecular techniques for **HLA loci in the context of transplantation** there is the prerequisite to geldig **EFI-certificaat** voor de categorie orgaantransplantatie en over een Eurotransplant Tissue Typing Program dat formeel gelinkt is aan een erkend transplantatiecentrum én over een ISO15189-certificaat te beschikken.

Artikel 33ter – molecular biological test on human material in acquired diseases associated to a medicine (companion diagnostics)

6° De vergoeding van de verstrekkingen is eveneens afhankelijk van de **registratie** van de uitgevoerde testen en het testresultaat

7° De verstrekkingen moeten uitgevoerd zijn in een laboratorium dat voldoet aan de volgende kwaliteitsvereisten:

- a) het laboratorium moet zelf een ISO 15189 accreditatie bezitten en voor de uitgevoerde verstrekkingen moet het ook een ISO 15189 accreditatie bezitten of een accreditatie volgens een gelijkwaardige laboratoriumnorm;
- b) het laboratorium moet het bewijs kunnen voorleggen van deelname aan interne en externe kwaliteitscontroles die georganiseerd of gecoördineerd worden door Sciensano;



- c) het laboratorium dient zich te onderwerpen aan de controles uitgevoerd door Sciensano.

Artikel 32 – pathological anatomy

§ 8 - 5. De verstrekkingen worden uitgevoerd in overeenstemming met criteria betreffende kwaliteit zoals bepaald in het koninklijk besluit van 5 december 2011 betreffende de erkenning van de laboratoria voor pathologische anatomie door de Minister tot wiens bevoegdheid de Volksgezondheid behoort.

"§ 10. Om de verstrekkingen 588932-588943 en 588954-588965 (HPV molecular test) te mogen aanrekenen :

- a) moeten deze verstrekkingen uitgevoerd zijn in een laboratorium dat een **ISO 15189 accreditatie**, of een accreditatie volgens een gelijkwaardige laboratoriumnorm bezit voor de uitgevoerde verstrekkingen;
- b) moet het laboratorium het bewijs kunnen voorleggen van deelname aan **interne en externe kwaliteitscontroles** die voldoen aan nationale of internationale kwaliteitsnormen;
- c) dient het laboratorium zich te onderwerpen aan de controles uitgevoerd door Sciensano."

Article 24 – clinical biology: No explicit mention of quality criteria in nomenclature

Article 24bis – molecular biological analysis on genetic material of micro-organisms

2° De verstrekkingen moeten uitgevoerd zijn in een laboratorium dat een **ISO 15189 accreditatie**, of een accreditatie volgens een gelijkwaardige laboratoriumnorm bezit voor de uitgevoerde verstrekkingen."

4° Het laboratorium moet voor de uitgevoerde verstrekkingen het bewijs kunnen voorleggen van deelname aan **interne en externe kwaliteitscontroles** die voldoen aan nationale of internationale kwaliteitsnormen.

5° Het laboratorium moet voor wat betreft de moleculaire diagnostiek van infectieuze aandoeningen, een **register** houden waarin volgende gegevens voorkomen.

6° Het laboratorium dient zich vanaf het in werking treden van dit besluit te onderwerpen aan de **controles** uitgevoerd door Sciensano.



APPENDIX 3. EVIDENCE

Table 45 – Examples of Number Needed to Genotype for selected drug-gene pairs

Drug-gene	Study	Outcome	Frequency carriers in population	Number needed to genotype
Abacavir and HLA-B*5701	RCT with PGx guided treatment compared to usual care (Mallal et al. 2008)	Clinically diagnosed hypersensitivity	5.6 % (Mallal et al. 2008)	29 (reported by Manson et al. 2020)
	RCT with PGx guided treatment compared to usual care (Mallal et al. 2008)	Immunological confirmed hypersensitivity	5.6% (Mallal et al. 2008)	37 (reported by Manson et al. 2020)
	Prospective cohort (n=1877 of which 149 suspected cases (of which 27 likely) and 140 controls) (Rauch et al. 2008)	Clinically diagnosed hypersensitivity	6.0% (Rauch et al. 2008)	41 (reported by Manson et al. 2020)
Fluorourpyrimidines and DPYD (4 variants)	Cross-over RCT ²²⁶ with PGx guided treatment compared to usual care. Both DPYD and UGT1A1 were considered	Adverse event (not specified in paper)		294 (own calculation: 1/0,34%)
	Prospective cohort with PGx guided treatment compared with historical control (Hendricks 2017)	Severe toxicity (grade ≥3)	7.7% (Hendricks et al. 2019)	114 (own calculation: 1/0,88%)
	Van der wouden et al 2022: The risk is extracted separately for a group with no PGx test (with data from Meta-analysis Meulendijks et al 202), and a group PGx tested (based on five cohort studies).	Mortality (extrapolated from grade ≥ 3 fluoropyrimidine induced toxicity)	Frequencies of phenotype* based on Dutch sample	4863 (reported by Vanderwouden et al. 2022)
Clopidogrel and CYP2C19	Van der wouden et al. 2022: The risk is extracted separately for a group with no PGx test (with data from Meta-analysis Sorich et al. 2014), and a group PGx tested (based on two cohort studies Lee et al. 2018 and Cavallari et al. 2018).	Mortality (extrapolated from MACE)	Frequencies of phenotype* based on Dutch sample	287 (reported by Vanderwouden et al. 2022)

* Frequency of phenotype (two alleles known) is not the same as carrier status, where the identification of 1 allele is sufficient.

**Table 46 – Results of literature search on systematic reviews for pharmacogenetic testing and clopidogrel**

Author	Title	Information
Cardiovascular		
Kuno et al 2023	Short-Term DAPT and DAPT De-Escalation Strategies for Patients With Acute Coronary Syndromes: A Systematic Review and Network Meta-Analysis.	SR + Network MA analysing different strategies of which guided selection is 1 arm. A sensitivity analysis on genotyping is available (2 RCTs POPular Genetics and TAILOR-PCI included)
Kang et al 2023	Dual antiplatelet therapy de-escalation in acute coronary syndrome: an individual patient meta-analysis	SR + MA compare de-escalation versus standard antiplatelet therapy. All de-escalation strategies were combined as 1 strategy. No sensitivity analysis on genotyping (only RCT “POPular Genetics” included)
Patti et al 2022	Safety and Efficacy of Selective, Clopidogrel-Based Strategies in Acute Coronary Syndrome: A Study-Level Meta-analysis	MA comparing de-escalation strategies and guided selection. Both genotyping and platelet function were combined, but no separate info on genotype guided (2 RCTs POPular Genetics and TAILOR-PCI included)
Tavenier et al 2022	Guided and unguided de-escalation from potent P2Y12 inhibitors among patients with acute coronary syndrome: a meta-analysis.	SR + MA comparing guided versus nonguided de-escalation. Both genotyping and platelet function were combined. Only RCT “POPular Genetics” included because TAILOR-PCI and RAPID Gene study focus on guided escalation
Kuno et al 2022	Comparison of Unguided De-Escalation Versus Guided Selection of Dual Antiplatelet Therapy After Acute Coronary Syndrome: A Systematic Review and Network Meta-Analysis.	Network MA comparing guided selection and unguided de-escalation. A sensitivity analysis on genotyping is available (2 RCTs POPular Genetics and TAILOR-PCI)
Malik et al 2022	Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Randomized Clinical Trials.	SR + MA including 7 RCTs (TAILOR-PCI, POPular Genetics, Pharmaclo, and IAC PCI and three pilot studies with surrogate outcomes)
Yamani et al 2022	Does individualized guided selection of antiplatelet therapy improve outcomes after percutaneous coronary intervention? A systematic review and meta-analysis.	SR + MA comparing guided versus standard antiplatelet therapy. Both platelet function tests as genotyping were considered in the guided. There were 5 RCTs on genotyping (POPular Genetics, TAILOR-PCI, Pharmaclo, IAC-PCI, and ADAPT-PCI, of which only the two first have low risk of bias)
Xie et al 2022	Effect of CYP2C19 genetic polymorphism on the pharmacodynamics and clinical outcomes for patients treated with ticagrelor: a systematic review with qualitative and quantitative meta-analysis.	Not discussed as the focus is on ticagrelor
Galli et al 2022	Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials.	SR + MA comparing guided versus potent antiplatelet therapy. Both platelet function tests as genotyping were considered in the guided. There were 3 RCTs on genotyping (POPular Genetics, TAILOR-PCI, Pharmaclo)
Biswas et al 2022	Effects of the CYP2C19 LoF allele on major adverse cardiovascular events associated with clopidogrel in acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis.	No full text – focus on carrier status



Tang et al 2022	Genotype-Guided Antiplatelet Therapy Versus Standard Therapy for Patients with Coronary Artery Disease: An Updated Systematic Review and Meta-Analysis.	SR + MA comparing genotyped antiplatelet versus usual care. 11 RCTs were included (POPular Genetics, TAILOR-PCI, Pharmaclo, IAC-PCI, and ADAPT-PCI, Onside test, Rapid Gene, Tam 2017, Zhang 2020, Alrubais 2021, Shi 2021)
Jafrin et al 2021	Risk of stroke in CYP2C19 LoF polymorphism carrier coronary artery disease patients undergoing clopidogrel therapy: An ethnicity-based updated meta-analysis.	Investigates the association of the carrier status (CYP2C19) with stroke risk in clopidogrel treated patients. Does not investigate the intervention of genotyping
Biswas et al 2021	Risk of major adverse cardiovascular events of CYP2C19 loss-of-function genotype guided prasugrel/ticagrelor vs clopidogrel therapy for acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis.	Investigates the best antiplatelet in terms of safety and efficacy in patients with a loss of function carrier status . Does not investigate the intervention of genotyping
Galli et al 2021	Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis.	SR + MA comparing guided versus potent antiplatelet therapy. Both platelet function tests as genotyping were considered in the guided. There were 5 RCTs on genotyping (POPular Genetics, TAILOR-PCI, Pharmaclo, IAC-PCI, and ADAPT-PCI, of which only the two first have low risk of bias)
Nazir et al 2021	A meta-analysis of efficacy and safety of genotype-guided versus standard of care treatment strategies in selecting antiplatelet therapy in patients with acute coronary syndrome.	SR + MA comparing genotyping versus standard of care. 2 RCTs (POPular Genetics, Pharmaclo) and 1 cohort study was included
Cerebrovascular		
Bristol Technology Assessment group 2023	Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE: Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack	SR with three research questions. The first RQ focuses on analysing the intervention "genotyping" including 2 RCTs (Chinese). The third RQ focuses there are more studies on checking the association between gene status (carriers or non-carrier) and recurrence (20 observational and 5 post-hoc analyses of RCTs)
Cargnin et al 2023	Impact of CYP2C19 Genotype on Efficacy and Safety of Clopidogrel-based Antiplatelet Therapy in Stroke or Transient Ischemic Attack Patients: An Updated Systematic Review and Meta-analysis of Non-East Asian Studies	SR + MA including 8 observational studies on the association of the carrier status
Yan et al 2022	Relationship between CYP2C19*2, *3 gene polymorphism and the recurrence in ischemic stroke patients treated with clopidogrel in China: A meta-analysis.	SR + MA including 9 observational studies in China on the association of the carrier status
McDermott et al 2022	The role of CYP2C19 genotyping to guide antiplatelet therapy following ischemic stroke or transient ischemic attack.	Narrative review including cohort studies and retrospective analyses of large RCTs
Collette et al 2021	Clinical importance of testing for clopidogrel resistance in patients undergoing carotid artery stenting-a systematic review.	Investigates the relationship of clopidogrel resistance with thromboembolic outcomes after coronary artery stenting. Does not investigate the intervention of genotyping.
General		



Morris et al 2022	Cost Effectiveness of Pharmacogenetic Testing for Drugs with Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines: A Systematic Review.	A systematic review of the economic literature
Huang et al 2022	Clinical non-effectiveness of clopidogrel use for peripheral artery disease in patients with CYP2C19 polymorphisms: a systematic review.	SR on the use of clopidogrel in peripheral artery disease, including four observational studies
Lopez et al 2023	Role of genetic polymorphisms in clopidogrel response variability: a systematic review.	Non systematic narrative review
Zhang et al 2021	Genotype-guided antiplatelet treatment versus conventional therapy: A systematic review and meta-analysis.	SR + MA comparing genotyping versus standard. 8 RCTs (POPular Genetics, Pharmaclo, IAC-PCI, and ADAPT-PCI, Roberts 2012, Tam 2017, Tomaniak 2017, Yu 2017) and 7 cohort studies were included.
Pereira et al 2021	Effect of CYP2C19 Genotype on Ischemic Outcomes During Oral P2Y12 Inhibitor Therapy: A Meta-Analysis	investigates the association of the carrier status (CYP2C19) but does not investigate how this carrier status should be determined (the genotyping is not the intervention)
Valeria et al 2021	The need of a multicomponent guiding approach to personalize clopidogrel treatment.	No full text

Search string in Pubmed: (pharmacogen OR genotype OR guided) AND (clopidogrel OR antiplatelet OR "P2Y12") – filter systematic review and from 2021 onwards.*

**Table 47 – Cochrane risk of bias tool (RoB 2) – version cluster-randomised trials²¹⁰ of PREPARE study²⁶**

Domain of risk of bias	Score and rationale
Randomisation process	High risk of bias as the randomization occurred before participants were recruited and lack of concealment of allocation sequence introduces selection bias. Every country had their own recruitment pool (in the Netherlands this was very broad via the pharmacies, whereas in Italy it was the oncology department). The risk of baseline imbalance is limited due to the crossover design and capping inclusion of any individual index drug at 10% of all drugs in both the intervention and control groups. However, the addition of recruiting centres during the study to ensure sufficient patient enrolment might have led to differences in type of medications prescribed with respect to crossover. At baseline, statistically significant differences between intervention and control were observed in the global health score and number of comedications.
Effect of assignment to the intervention	Some concern of bias as every participant was aware of the received intervention. The primary analysis on which the results were based does not take into account the patients lost-to-follow-up (no intention to treat analysis, therefore no appropriate analysis to estimate the effect of assignment to the intervention).
Effect of adhering to the intervention	High risk of bias. There was no information on possible other interventions during the trial. The main intervention was the transfer of the DWPG recommendations to the prescribing physician. In around 70% the recommendations were followed. But the analysis was not done taking into account patients for whom the recommendations were implemented and resulted in a change in dose/therapy.
Missing outcome data	Low risk of bias. 52 [1.6%] of the study group and 47 [1.3%] of the control group withdrew consent after group assignment. 367 [11.0%] in the study group and 285 [7.9%] in the control group were lost to follow-up. Lost to follow up means that there are no data available on ADR at 4 weeks or 12 weeks. Considering missing outcome per country (cluster): Most patients completed the 12-week follow-up period, with the proportions ranging from 1038 (84.3%) of 1232 in Italy to 1213 (91.8%) of 1321 in Greece.
Measurement of the outcome	High risk of bias. The outcome was binary: the incidence of an adverse drug reaction attributed to the prescribed drug in the 12-weeks follow-up. ADRs were self-reported, though a trained physician or pharmacist from the local study team assessed severity and causality of the ADR with a standardized method, Common Terminology Criteria for Adverse Events (CTCAE) and Liverpool Causality Assessment Tool (LCAT), respectively. However none of them was blinded.
Selection of the reported result	High risk of bias. Deviations from the statistical plan were done in 2022. Originally it was foreseen to analyse the primary endpoint in each country using logistic regression, since each country acts as its own control. These seven logistic regressions were foreseen to be combined to a meta-analysis. However in the final analysis all countries were combined, and country was used as a factor. In Slovenia and Austria, the PGx guided group reported more ADR compared to the non guided PGx. No clear intention-to-treat analysis with the primary outcome was shown.



APPENDIX 4. ECONOMIC LITERATURE

Appendix 4.1. Search strategy for the economic literature

Databases were searched in 08/2023.

Appendix 4.1.1. INAHTA HTA database

The international HTA database provides free access to bibliographic information about ongoing and published health technology assessments commissioned or undertaken by HTA organisations internationally. The HTA database started in 1996 under the responsibility of the Centre for Reviews and Dissemination (CRD) from the University of York, England. In 2018 this responsibility was taken over by the International Network of Agencies for Health Technology Assessment (INAHTA). In 07/2019, the database records were imported from the CRD platform to the new INAHTA platform, and in 06/2020 the new platform was launched.

The search with the MeSH term "Pharmacogenetics"[mh] on the international HTA database of INAHTA (<https://www.inahta.org/hta-database/>) provided 20 references, of which 9 were published after 2010.

Appendix 4.1.2. Medline

Date	31/08/2023		
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to August 31, 2023>		
Search Strategy	1	Economics/	27 507
	2	exp "Costs and Cost Analysis"/	265 995
	3	Economics, Dental/	1921
	4	exp "Economics, Hospital"/	25 739
	5	Economics, Medical/	9253
	6	Economics, Nursing/	4013
	7	Economics, Pharmaceutical/	3109
	8	Letter/	1 227 317

9	Editorial/	662 110
10	8 or 9	1 889 181
11	*Pharmacogenetics/	6876
12	*Pharmacogenomic Testing/	565
13	1 or 2 or 3 or 4 or 5 or 6 or 7	314 753
14	11 or 12	7325
15	13 and 14	240
16	15 not 10	224
17	limit 16 to yr="2010 -Current"	141

Appendix 4.1.3. Embase

Date	30/08/2023		
Database	Embase		
Search Strategy	#1	'economic evaluation'/exp/mj	75 771
	#2	'cost-effectiveness':ab,ti	106 080
	#3	'cost-utility':ab,ti	9417
	#4	'cost-minimization':ab,ti	2136
	#5	'economic evaluation':ab,ti	16 350
	#6	#1 OR #2 OR #3 OR #4 OR #5	152 677
	#7	'pharmacogenomics'/exp	13 976
	#8	'pharmacogenetic testing'/exp	2161
	#9	#7 OR #8	15 671
	#10	#6 AND #9	298
	#11	#10 AND ([editorial]/lim OR [letter]/lim)	7
	#12	#10 NOT #11	291
	#13	#12 AND [2010-2023]/py	257
	#14	#13 AND [medline]/lim	152
	#15	#13 NOT #14	105

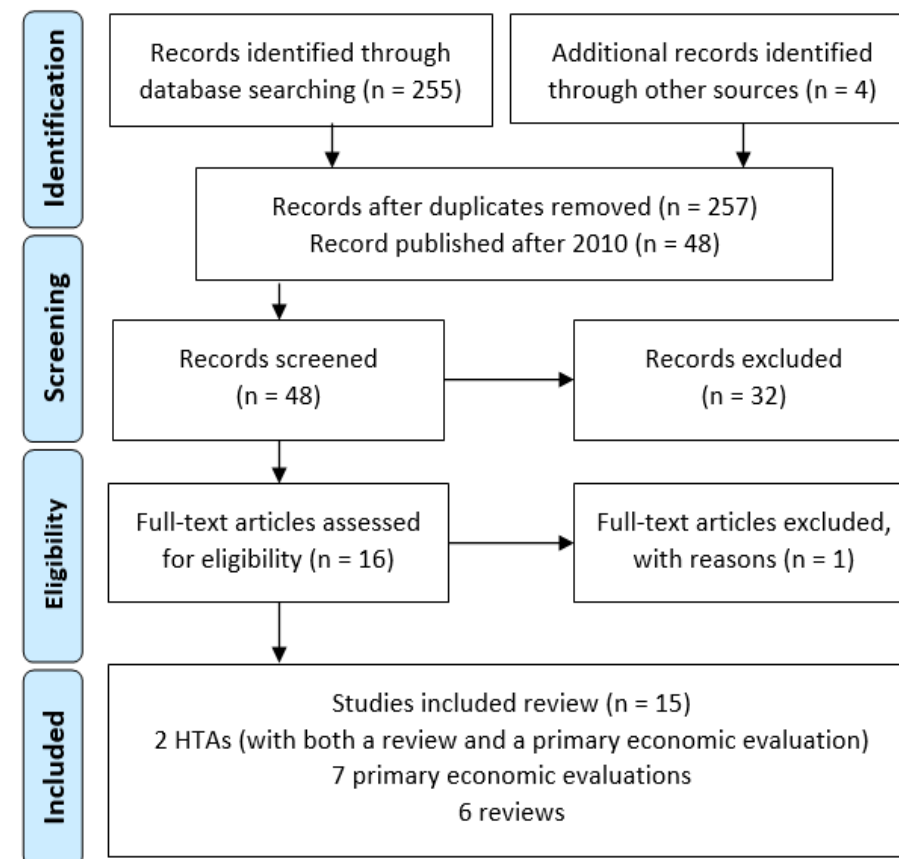


Appendix 4.1.4. Results of the search strategy

	Number of references identified
Database searches	
- INAHTA	9
- Medline	141
- Embase	105
- Total	255
Other sources (HTA websites)	4
Duplicates	2
Total	257
- Publication date since 2021	48

References published between 2010 and 2023.

Figure 9 – PRISMA flow diagram of the economic search strategy





Appendix 4.2. Economic evaluations covered in the reviews

	Morris et al. 2022	Turongk-aravee et al. 2021	Kamil et al. 2022	Bristol TAG HTA 2023	Lim et al. 2021	Young et al. 2023	Karam-peris et al. 2021	Ontario Health Quality 2021
Literature search time up to:	6/2021	10/2019	6/2020	8/2022	6/2020	1/2023	8/2020	1/2020
Total number of references reviewed:	108	59	18	5	3	19	18	4
Anticoagulants (warfarin) and CYP2C9/VKORC1	16	14	18	0	3	0	0	0
1 Ng SS, Nathisuwan S, Phrommintikul A, et al. Cost-effectiveness of warfarin care bundles and novel oral anticoagulants for stroke prevention in patients with atrial fibrillation in Thailand. <i>Thrombosis Research</i> 2020, 185:63-71.			x					
2 Abdullaev SP, Mirzaev KB, Sychev DA: Comparative clinical and economic evaluation of pharmacogenetic testing application for dabigatran in patients with atrial fibrillation. <i>Terapevticheskii Arkhiv</i> 2019, 91:22-27.			x					
3 Moloney E, Craig D, Holdsworth N, Smithson J: Optimising clinical effectiveness and quality along the atrial fibrillation anticoagulation pathway: An economic analysis. <i>BMC Health Services Research</i> 2019, 19:1007.			x					
4 Kim DJ, Kim HS, Oh M, et al. Cost effectiveness of genotype-guided warfarin dosing in patients with mechanical heart valve replacement under the fee-for-service system. <i>Appl Health Econ Health Policy</i> . 2017;15(5):657-67.	x	x						
5 Martes-Martinez C, et al. Cost-utility study of warfarin genotyping in the VACHS affiliated anticoagulation clinic of Puerto Rico. <i>P. R. Health Sci. J.</i> 2017;36(3):165-172.	x							
6 Verhoef TI, Redekop WK, Langenskiold S, et al. Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden. <i>Pharmacogenomics J.</i> 2016;16(5):478-84.	x	x	x					
7 Janzic A, Kos M: Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control. <i>Pharmacoeconomics</i> 2015, 33:395-408.			x					
8 Mitropoulou C, Fragoulakis V, Bozina N, et al. Economic evaluation of pharmacogenomic-guided warfarin treatment for elderly Croatian atrial fibrillation patients with ischemic stroke. <i>Pharmacogenomics</i> . 2015;16(2):137-48.	x	x	x					
9 Shiffman D, Perez MV, Bare LA, Louie JZ, Arellano AR, Devlin JJ: Genetic risk for atrial fibrillation could motivate patient adherence to warfarin therapy: A cost effectiveness analysis. <i>BMC Cardiovascular Disorders</i> 2015, 15:1-7.			x					
10 Verhoef TI, Redekop WK, De Boer A, Maitland-Van Der Zee AH: Economic evaluation of a pharmacogenetic dosing algorithm for coumarin anticoagulants in the Netherlands. <i>Pharmacogenomics</i> 2015, 16:101-114.			x					
11 You JH. Pharmacogenetic-guided selection of warfarin versus novel oral anticoagulants for stroke prevention in patients with atrial fibrillation: a cost-effectiveness analysis. <i>Pharmacogenet Genomics</i> . 2014;24(1):6-14.	x	x	x					
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Antiplatelet (clopidogrel, tramadol) and CYP2C19		23	9	0	5	0	0	0	0
27	Micieli A, Singh N, Jahn B, et al. Cost-effectiveness of testing for CYP2C19 loss-of-function carriers following transient ischemic attack/minor stroke: A Canadian perspective. <i>International Journal of Stroke</i> . 2023;18(4):416-425.				x				
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Cardiovascular medication (clopidogrel, warfarin, simvastatin)		2	1	0	0	0	0	0	0
54	Zhu Y, et al. A model-based cost-effectiveness analysis of pharmacogenomic panel testing in Cardiovascular Disease Management: preemptive, reactive, or none? <i>Genet. Med.</i> 2021;23(3): 461–470,	x							
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Psychiatric disorders		11	1	0	0	0	19	18	4
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HIV		11	8	0	0	0	0	0	0
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Auto-immune disease		11	8	0	0	0	0	0	0
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95	Priest VL, Begg EJ, Gardiner SJ, Frampton CM, Gearry RB, Barclay ML, et al. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. <i>Pharmacoeconomics</i> . 2006;24(8):767-81.	x	x						
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Gout - Allopurinol and HLA-B*58:01	10	8	0	0	0	0	0	0
102 Cheng H, Yan D, Zuo X, Liu J, Liu W & Zhang Y. A retrospective investigation of HLA-B* 5801 in hyperuricemia patients in a Han population of China. <i>Pharmacogenet. Genomics.</i> 2018;28(5):117–124.	x							
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110 Dong D, Tan-Koi WC, Teng GG, Finkelstein E, Sung C. Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. <i>Pharmacogenomics.</i> 2015; 16(16):1781-93.	x	x						
111 Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. <i>PLoS One.</i> 2014;9(4):e94294.	x	x						
Epilepsy/neuropathic pain	8	6	0	0	0	0	0	0
112 Yuliwulandari R, et al. Cost-effectiveness analysis of genotyping for HLA-B* 15:02 in Indonesian patients with epilepsy using a generic model. <i>Pharmacogenomics J.</i> 2021;21(4):476–483.	x							
113 Choi H & Mohit B. Cost-effectiveness of screening for HLA-B* 1502 prior to initiation of carbamazepine in epilepsy patients of Asian ancestry in the United States. <i>Epilepsia.</i> 2019;60(7):1472–1481.	x							
114 Chong HY, Mohamed Z, Tan LL, Wu DBC, Shabaruddin FH, Dahlui M, et al. Is universal HLA-B*15:02 screening a cost-effective option in an ethnically diverse population? A case study of Malaysia. <i>Br J Dermatol.</i> 2017;177(4): 1102-12.	x	x						



	Morris et al. 2022	Turongk- aravee et al. 2021	Kamil et al. 2022	Bristol TAG HTA 2023	Lim et al. 2021	Young et al. 2023	Karam- peris et al. 2021	Ontario Health Quality 2021
115 Chen Z, Liew D, Kwan P. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. <i>Neurology</i> . 2016;86(12):1086-94.	x	x						
116 Plumpton CO, Yip VL, Alfirevic A, Marson AG, Pirmohamed M, Hughes DA. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. <i>Epilepsia</i> . 2015;56(4):556-63.	x	x						
117 Tiamkao S, Jitpimolmard J, Sawanyawisuth K, Jitpimolmard S. Cost minimization of HLA-B*1502 screening before prescribing carbamazepine in Thailand. <i>Int J Clin Pharm</i> . 2013;35(4):608-12.	x	x						
118 Rattanavipapong W, Koopitakkajorn T, Praditsitthikorn N, et al. Economic evaluation of HLA-B*15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand. <i>Epilepsia</i> . 2013;54(9):1628-38.	x	x						
119 Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. <i>Neurology</i> . 2012;79(12):1259-67.	x	x						
Cancer (Fluoropyrimidines / irinotecan)	5	3	0	0	0	0	0	0
120 Fragoulakis V, et al. Estimating the effectiveness of DPYD genotyping in Italian individuals suffering from cancer based on the cost of chemotherapy-induced toxicity. <i>Am. J. Human Genet</i> . 2019;104(6):1158–1168.	x							
121 Henricks LM, et al. A cost analysis of upfront DPYD genotype-guided dose individualization in fluoropyrimidine-based anticancer therapy. <i>Eur. J. Cancer</i> . 2019;107:60–67.	x							
122 Murphy C, et al. Cost implications of reactive versus prospective testing for dihydropyrimidine dehydrogenase deficiency in patients with colorectal cancer: a single-institution experience. <i>Dose-Response</i> . 2018;16(4):155932581880304.	x							
123 Cortezoso L, García-González X, García MI, et al. Cost-effectiveness of screening for DPYD polymorphisms to prevent neutropenia in cancer patients treated with fluoropyrimidines. <i>Pharmacogenomics</i> . 2016;17(9):979–984.	x							
124 Deenen MJ, Meulendijks D, Cats A, Sechterberger MK, Severens JL, Boot H, et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. <i>J Clin Oncol</i> . 2016;34(3):227-34.	x	x						
125 Pichereau S, Le Louarn A, Lecomte T, et al. Cost-effectiveness of UGT1A1*28 genotyping in preventing severe neutropenia following FOLFIRI therapy in colorectal cancer. <i>J Pharm Pharm Sci</i> . 2010;13(4):615-25.		x						
126 Gold HT, Hall MJ, Blinder V, Schackman BR. Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 before irinotecan administration for metastatic colorectal cancer. <i>Cancer</i> . 2009;115(17):3858-67.		x						
Aminoglycosides	1	0	0	0	0	0	0	0
127 Veenstra DL, Harris J, Gibson RL, et al. Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes. <i>Genet. Med</i> . 2007;9(10):695–704.	x							
Analgesics	1	0	0	0	0	0	0	0
128 Moretti ME, Lato DF, Berger H, et al. A cost-effectiveness analysis of maternal CYP2D6 genetic testing to guide treatment for postpartum pain and avert infant adverse events. <i>Pharmacogenomics J</i> . 2017;18(3):391–397.	x							
Antifungal	2	0	0	0	0	0	0	0
129 Patel JN, et al. Evaluation of CYP2C19 genotype-guided voriconazole prophylaxis after allogeneic hematopoietic cell transplant. <i>Clin. Pharmacol. Therapeut</i> . 2019;107(3):571–579.	x							
130 Mason NT, Bell GC, Quilitz RE, Greene JN & McLeod HL. Budget impact analysis of CYP2C19-guided voriconazole prophylaxis in AML. <i>J. Antimicrob. Chemother</i> . 2015;70(11):3124–3126.	x							
Hormone replacement therapies	0	1	0	0	0	0	0	0



	Morris et al. 2022	Turongk- aravee et al. 2021	Kamil et al. 2022	Bristol TAG HTA 2023	Lim et al. 2021	Young et al. 2023	Karam- peris et al. 2021	Ontario Health Quality 2021
131 Smith KJ, Monsef BS, Ragni MV. Should female relatives of factor V Leiden carriers be screened prior to oral contraceptive use? A cost-effectiveness analysis. <i>Thromb Haemost.</i> 2008;100(3):447-52.		x						
Multidrug	1	0	0	0	0	0	0	0
132 Brixner D, et al. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. <i>J. Med. Econ.</i> 2015;19(3):213-228.	x							
Pegylated interferon	2	0	0	0	0	0	0	0
133 Blázquez-Pérez A, San Miguel R, Mar J. Cost-effectiveness analysis of triple therapy with protease inhibitors in treatment-naïve hepatitis C patients. <i>Pharmacoeconomics.</i> 2013;31(10):919-931.	x							
134 Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C. <i>Ann. Intern. Med.</i> 2012;156(4):279-290.	x							
Proton pump inhibitor	1	0	0	0	0	0	0	0
135 Lehmann DF, Medicis JJ, Franklin PD. Polymorphisms and the pocketbook: The cost-effectiveness of cytochrome P450 2C19 genotyping in the eradication of <i>Helicobacter pylori</i> infection associated with duodenal ulcer. <i>J. Clin. Pharmacol.</i> 2003;43(12):1316-1323.	x							
Selective estrogen receptor modulator	3	0	0	0	0	0	0	0
136 Wei X, et al. CYP2D6*10 pharmacogenetic-guided SERM could be a cost-effective strategy in Chinese patients with hormone receptor-positive breast cancer. <i>Pharmacogenomics.</i> 2020;21(1):43-53.	x							
137 Wei X, et al. Cost-effectiveness analysis of CYP2D6*10 pharmacogenetic testing to guide the adjuvant endocrine therapy for postmenopausal women with estrogen receptor positive early breast cancer in China. <i>Clin. Drug Investig.</i> 2019;40(1):25-32.	x							
138 Woods B, Veenstra D, Hawkins N. Prioritizing pharmacogenetic research: a value of information analysis of CYP2D6 testing to guide breast cancer treatment. <i>Value Health.</i> 2011;14(8):989-1001.	x							



Appendix 4.3. Reviews of economic evaluations of PGx testing to guide warfarin treatment in cardiovascular diseases

Kamil et al.²¹⁹ reviewed 18 economic evaluations (all model-based) of PGx testing (CYP2C9 and VKORC1) for patients with atrial fibrillation (AF) to determine warfarin dosing or to stratify patients into warfarin or direct-acting anticoagulant (dabigatran, rivaroxaban, apixaban, edoxaban). The results of the studies were heterogeneous, with about half of them concluding that PGx testing is cost-effective (or cost-saving), and the other half not cost-effective (or dominated). Of the parameters contributing most to changes in the studies' results, the (relative) effectiveness of PGx testing was the most frequently cited. The data sources differed greatly for this parameter, with some studies relying on RCT-data (the EU-PACT trials for European-based models, the COUMAGEN trials for the US-based models or meta-analyses) while others were based on observational data or on assumptions. Whatever

the data source for PGx effectiveness data, most studies relied on proxy measures (e.g. days to warfarin maintenance dose) to extrapolate future events and only few of them modelled relative risks of events (in bleeding or in ischemic stroke) obtained from meta-analyses. The cost of PGx testing was another influential parameter. Kamil et al.²¹⁹ concluded that "the economic evaluations to date only partially inform decisions on selecting optimal PGx testing for AF."

Lim et al.²²⁰ reviewed 3 economic evaluations, all model-based, of CYP2C9/VKORC1-testing for warfarin to avoid higher risk of bleeding in patients with venous thromboembolism (VTE). They report that the range of results found in the economic evaluation was so large that it was not possible to conclude on the cost-effectiveness of PGx testing. The parameter most influent on the cost-effectiveness results was consistently reported to be the (relative) effectiveness of testing. The quality of data used for effectiveness was poor as existing trials³⁴⁹ and meta-analysis^{350, 351} were not specific to patients with VTE.

Table 48 – Reviews of economic evaluations of PGx testing to guide warfarin treatment in cardiovascular diseases

Reference	Disease area	Review period	Drug	Gene	# EE	Review main conclusion
Warfarin (26 unique economic evaluations)						
Morris et al.²¹³ 2022, USA	Cardiovascular disease	up to 06/2021	Warfarin	CYP2C9/VKORC1	16	Inconclusive (7 studies CE, 5 not CE, 4 uncertain)
Turongkaravee et al.²¹² 2021, Thailand	Cardiovascular disease	up to 10/2019	Warfarin	CYP2C9/VKORC1	14	Inconclusive (9 studies CE, 4 not CE, 1 uncertain)
Kamil et al.²¹⁹ 2022, USA	Atrial fibrillation	up to 06/2020	Warfarin, acenocoumarol, phenprocoumon	CYP2C9/VKORC1	18	Inconclusive (9 studies CE/CS, 9 not CE/dominated)
Lim et al.²²⁰ 2021, UK	Venous thromboembolism	up to 06/2020	Warfarin, acenocoumarol	CYP2C9/VKORC1	3	Inconclusive (1 study CE, 1 not CE, 1 uncertain)

CE: cost-effective, CS: cost-saving, EE: economic evaluation.



APPENDIX 5. INTERNATIONAL COMPARISON

Appendix 5.1. Interview questions and consulted experts

The interview questions used in the semi-structured interviews with international experts on pharmacogenetic testing are summarized in Table 49. If the interviewee was involved in one or more clinical trials related to the topic of PGx, additional questions were posed to identify the PICO of the respective study as well as to obtain the study protocols and, if already available, the resulting publications. Table 50 lists the contacted international experts in each of the selected countries.

Table 49 – Interview questions used in international comparison

Interview questions and sub-questions used in international comparison
Cluster 1: Prescribers and executers of pharmacogenomic testing
Who is entitled to prescribe a PGx test?
Are general practitioners also allowed to prescribe PGx testing?
Are pharmacists also allowed to prescribe PGx testing?
Do the legally allowed prescribers all have sufficient knowledge on PGx testing?
Which specialties (including GPs) most often prescribe PGx testing?
Who is allowed to execute the PGx tests?
How many labs currently execute PGx testing?
Which requirements/accreditations need to be fulfilled by the labs in order to be allowed to perform PGx testing?
Do you have data on the volumes of PGx tests performed or the amount of patients undergoing a PGx test in your country?
Cluster 2: Trajectory of a PGx test
What is the procedure to obtain a PGx test?
Are there guidelines on which technology/platform should be used: NGS, sanger seq, microarray,...?
When is the test run at the lab (turnaround time)?

To what extent are the patients informed about the results of the test and by whom?

Do patients have to sign an informed consent prior to the PGx test?

What happens with the results of the PGx tests? Are they stored for future use?

Who has access to the results of the PGx tests?

Are clinical decision support tools based on PGx information used in your country?

Is a pharmacogenetic counselling session provided to patients?

Cluster 3: List of drug-gene interactions for which PGx testing is (recommended to be) performed

Does your country have a list of PGx tests which are recommended to be performed and when they are recommended to be performed?

Does your country have legal or reimbursement restrictions on which PGx tests can be performed?

Does your country have specific dosing/treatment recommendations for each of the (recommended) PGx tests?

On which (international) sources are the dosing recommendations based?

What is the methodology used to establish a list of allowed/reimbursed PGx tests?

To what extent is the cost(-effectiveness) taken into account for a DGI to be added on the list?

Cluster 4: Economics- /policy-related

What determines the cost of PGx testing?

How is pharmacogenetics funded & reimbursed?

Which criteria have to be fulfilled for reimbursement?

Is panel testing and preemptive PGx testing reimbursed?

How is repetitive testing avoided?

What are the remaining challenges for PGx in your country?

What are the future prospects/ongoing initiatives/studies with regard to PGx testing in your country?

**Table 50 – List of consulted international experts**

Country	Experts
The Netherlands	Prof. dr. Henk-Jan Guchelaar, Prof. dr. Bart Rijnders, Prof. dr. Roos van Westrhenen, Ilse Verstijnen
France	Cédric Carbonneil, Eunice Low, Stéphanie Malard, Prof. Nicolas Picard, Nadia Squalli
Switzerland	Prof. Caroline Samer, Isabelle Gauchat-Bouchardy
The United Kingdom	Prof. Bill Newman, Prof. dr. Kay Poulton, Prof. Tom Walley

Appendix 5.2. The Netherlands

Table 51 – List of drugs for which a PGx test may be useful for GPs according to NHG guideline²⁵⁵

<i>Cardiovascular medication</i>			
Atorvastatin	Simvastatin	Clopidogrel	Metoprolol
<i>Anti-acids</i>			
Lansoprazole	Omeprazole	Pantoprazole	
<i>Psychiatric medication</i>			
Amitriptyline	Clomipramine	Imipramine	Nortriptyline
Haloperidol	Citalopram	Paroxetine	Sertraline
Venlafaxine			
<i>Other medication</i>			
Allopurinol	Carbamazepine	Flucloxacillin	Tramadol



Table 52 – Prices of PGx tests in the Netherlands

Test	Price range*	Maximal turnaround time [†]	Number of laboratories performing test [‡]
<i>Single-gene tests (NVKC database)²⁶⁹</i>			
ABCB1	€82.50	1 week	1
BCHE	€182.50	1 week	1
CYP1A2	€71.47 – €82.5	1 week – 3 weeks	3
CYP3A4	€63.95 – €82.50	1 week – 4 weeks	4
CYP3A5	€63.95 – €82.50	1 week – 3 weeks	3
CYP2B6	€74.2 – €82.50	1 week	2
CYP2C8	€82.50	1 week	1
CYP2C9	€71.47 – €94.49	1 week – 4 weeks	5
CYP2C19	€71.47 – €216.99	1 day – 4 weeks	9
CYP2D6	€71.47 – €216.99	1 week – 4 weeks	8
DPYD	€66.35 – €311.32	2 days – 1 week	9
HLA-B5701	€63.95 – €82.50	3 days – 2 weeks	4
HLA-B1502	€82.50	1 week	1
SLCO1B1	€82.50	1 week	2
TPMT	€58.66 – €216.99	3 days – 4 weeks	8
UGT1A1	€63.95 – €186.38	3 days – 1 week	4
UGT1A9	€82.50	1 week	1
VKORC1	€63.95 – €82.50	1 week – 3 weeks	3
<i>Panels (not exhaustive)^{275, 352}</i>			
Panel 1 (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, BCHE, TPMT, NUDT15, UGT1A1, UGT1A9, VKORC1, ABCB1, ABCC2, ABCG2, SLCO1B1)	€216.85	/	1
Panel 2 (CYP2C9, CYP2C19, CYP2D6, CYP3A4, VKORC1, SLCO1B1)	€624.50	/	1
Panel 3 (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKORC1, SLCO1B1)	€912	/	1
Panel 4 (Psych: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4)	€542	/	1
Panel 5 (Cardiac: CYP2C9, CYP2C19, CYP2D6, VKORC1, SLCO1B1, ABCB1)	€584.50	/	1
Panel 6 (Pain: CYP2C9, CYP2D6, CYP3A4, OPRM1, COMT)	€552.50	/	1
Panel 7 (Onco: CYP2D6, CYP3A4, CYP3A5, DPYD)	€470	/	1

* The reported prices are the prices of the test itself, excluding any additional cost for ordering the test as this cost can be spread over multiple orders. Reported prices represent publicly available prices without taking into account potential price deals with health insurers. Reported prices are prices of 2023 except for the panels, which represent prices of 2021. † The reported turnaround times may be an underestimation of the true turnaround times in practice. ‡ The number of labs is based on the database of Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde (NVKC). The offer in panels is not exhaustive for the Dutch situation, but offers examples of frequently performed PGx panels in the Netherlands.



Appendix 5.3. France

Table 53 – Evolution of the pharmacogenetic testing activity in France between 2012 and 2022

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022**
Number of individuals tested	-	-	-	18 777	20 147	22 535	33 619	38 091	21 548	18 966	19 412
Number of tests	20 425	25 303	19 596	19 909	23 627	26 458	32 298	29 193	26 262	24 115	24 245
Number of tests per 1 million inhabitants*	311	383	296	299	354	395	481	433	388	356	357
Number of tests (excluding DPYD)	NA	NA	NA	NA	NA	NA	NA	NA	14 265	18 867	NA
Number of tests per 1 million inhabitants (excluding DPYD)*	NA	NA	NA	NA	NA	NA	NA	NA	211	279	NA
Number of labs with pharmacogenetic activity	44	47	53	47	51	54	55	56	56	53	52
Number of labs with solely pharmacogenetic activity	5	5	5	5	5	7	5	5	5	4	NA

Source: Agence de la Biomédecine, Rapport d'activité annuel de génétique postnatale, 2017 & 2022.^{283, 353} * Own calculation. NA=not available. ** In 2022, ABM changed the methodology of collecting the data for RAMS. The quality of the 2022 data is therefore not optimal.



Appendix 5.4. Switzerland

Table 54 – Example of PGx panel used in University Hospitals of Geneva

Genes		
ABCB1	CYP3A4	MTHFR
ABCC2	CYP3A5	NAT2
ABCG2	CYP4F2	NUDT15
ANKK1	DPYD	OPRD1
APOE	F2	OPRK1
CES1	F5	OPRM1
CES2	FLOT1 (HLA-B1502)	POR
COMT	GSTA1	SLCO1B1
CYP1A2	GSTP1	TPMT
CYP2B6	HCP5 (HLA-B5701)	UGT1A1
CYP2C19	HLA-A (HLA-A3101)	UGT1A6
CYP2C8	HTR2A	UGT1A7
CYP2C9	HTR2C	UGT2B15
CYP2D6	INFL4	UGT2B7
CYP2E1	MC1R	VKORC1

Billing example of PGx tests in Switzerland

a PGx test for DPYD

1. DNA extraction (54.9 TP)
2. Pharmacogenetic analysis PCR & SEQ for 1 gene (193.5 TP)

Total: 248.4 TP (€204 – €240).^{307, 354}

More complex PGx test for CYP2D6

3. DNA extraction (54.9 TP)
4. Pharmacogenetic analysis PCR & SEQ for 1 gene, but counted as 2 due to complexity (2x193.5 TP)
5. Pharmacogenetic analysis by real-time nucleoid acid amplification for 1 gene, but counted as 2 due to complexity (2x83.7 TP)
6. Supplement for reporting complex molecular genetic results (90 TP)

Total: 699.3 TP (€573 – €675).^{307, 354}

TP=tax points

Table 55 – Billing of pharmacogenetics in Switzerland^{354, 355}

Code	Label	Tax points	Tariff range*	Maximal number of times to be billed at once
<i>Laboratory</i>				
6001.03	DNA extraction	54.9	€45 – €53	1
6500.56	Pharmacogenetic analysis with PCR & SEQ	193.5	€154 – €186	6 (max. 2 per gene)
6500.50	Pharmacogenetic analysis by real-time nucleoid acid amplification	83.7	€69 – €80	max. 4 per gene (max. 6 for CYP2D6)
6008.09	Supplement for reporting complex molecular genetic results	90	€74 – €86	1
6500.51	Nucleic acid amplification with subsequent amplification or mutation detection using electrophoresis (agarose gel, polyacrylamide)	94.5	€77 – €91	/
6500.53	Nucleic acid amplification using Sequence Specific Primer Polymerase Chain Reaction (PCR-SSP, synonym "ARMS") with subsequent amplification or mutation detection using electrophoresis (agarose gel, polyacrylamide) or fluorescence detection of the specimen	94.5	€77 – €91	/
<i>Pharmacogenetic counselling by clinical pharmacologist[‡]</i>				
JP.00.0010	Initial consultation (per minute, assumption: 5 minutes)	23	€19 – €22	/
JP.00.0020	Consultation (per minute, assumption: 30 minutes)	139	€114 – €133	/
JP.00.0050	Interpretation without presence of patient (per minute, assumption: 30 minutes)	139	€114 – €133	/
JP.00.0040	Consultation to other health care workers without presence of patient (per minute, assumption: 30 minutes)	139	€114 – €133	/

* The reported tariffs are ranges representing the tariff in the canton with the lowest tax point value and the tariff in the canton with the highest tax point value. A currency exchange rate of 1 CHF = €1 was assumed. ‡ These acts and corresponding codes are currently generic and will be replaced by specific codes for pharmacogenetics in 2024.^{305, 354}



Appendix 5.5. The United Kingdom (England)

PROGRESS study (Pharmacogenetics Roll Out – Gauging Response to Service)

Background: The PROGRESS trial is part of a programme of work to introduce pharmacogenetic testing in primary care. A panel of genes with known implications for a range of commonly prescribed medicines has been selected and an informatic solution to help guide prescribing has been developed called the Genomic Prescribing Advisory System (GPAS). This pharmacogenetic testing and advisory system will be implemented at a number of GP practices to establish whether genetic testing can be delivered to support genotype-guided prescribing, in a clinically relevant timeframe and to assess any challenges to implementation.

Outcomes: Implementation: feasibility on large scale, patient & GP acceptance, usefulness, etc.

Design: Pragmatic observational implementation study

Setting: Primary care networks

Medication classes:

- Selective Serotonin Reuptake Inhibitors [citalopram, escitalopram, fluvoxamine, paroxetine, sertraline]

- Tricyclic Antidepressants (prescribed for pain or depression) [amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine]

- Statin Therapy [atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin]

- Proton Pump Inhibitors [esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole]

Panel of genes:

- CYP2C19

- CYP2D6

- CYP2C9

- SLCO1B1

Testing strategy: Reactive PGx testing with planned reuse (referred to as semi-preemptive testing in this report). Panel test at start/change of a drug in one of four pre-defined medication classes.

Recommendations: CPIC

Number of participants: 1450 primary care patients

Timeline: results expected by 2026



APPENDIX 6. BELGIUM REIMBURSEMENT

Table 56 – History of the fees for the general codes of article 33ter of the nomenclature

Code	Start date	1/01/2023	1/06/2022	1/01/2022	1/01/2021	1/01/2020
	End date	-	31/12/2022	31/05/2022	31/12/2021	31/12/2020
594016-594020	Honorarium	€94.95	€90.42	€88.65	€88.01	€87.31
594031-594042	Patient share	€8.68	€8.68	€8.68	€8.68	€8.68
	NIHDI share	€86.27	€81.74	€79.97	€79.33	€78.63
594053-594064	Honorarium	€156.67	€149.20	€146.27	€145.21	€144.06
594075-594086	Patient share	€8.68	€8.68	€8.68	€8.68	€8.68
	NIHDI share	€147.99	€140.52	€137.59	€136.53	€135.38
594090-594101	Honorarium	€208.90	€198.93	€195.03	€193.62	€192.08
594112-594123	Patient share	€8.68	€8.68	€8.68	€8.68	€8.68
	NIHDI share	€200.22	€190.25	€186.35	€184.94	€183.40

Patient share and NIHDI share are reported for an ordinary ambulatory patient. For ordinary hospitalized patients, and for patients entitled to preferential reimbursement, the patient share is €0.



APPENDIX 7. MEDICATION USERS

Appendix 7.1. INCIDENCE OF USERS PER ATC5 CODE

Appendix 7.1.1. Source of data: IMA – AIM

IMA – AIM is a non-profit organisation that manages and analyses information on all reimbursements related to the compulsory health insurance, collected by the Belgian sickness funds on all insured citizens. These data cover all reimbursed services (consultations, pharmaceuticals, diagnostic and therapeutic procedures) and some patient socio-demographic characteristics as well as social security related data to the extent they influence reimbursement.

Appendix 7.1.2. Methodology

Patients selected in the data were those who were delivered at least one of the listed medication defined at the molecule level (ATC5 of the Anatomical Therapeutic Chemical Classification System) in Table 1 for the 2013-2021 period.

PGx testing was identified by the following codes from the healthcare nomenclature (see Table 3 in the main report):

- 565331-565342: Simple molecular analysis to search for a constitutional disease, including DNA extraction, maximum three mutations per gene analysed (Diagnostic rule 10, 11, 18)
- 565390- 565401: Molecular analysis to search for a constitutional disease or to establish an individual genetic profile, for genetic counselling and/or diagnostic purposes, including DNA extraction (diagnostic 10, 11, 18)
- 565456- 565460: Complex molecular analysis to search for a constitutional disease (diagnostic rule 6, 10, 18): level 1
- 565471- 565482: Complex molecular analysis to search for a constitutional disease (diagnostic rule 6, 10, 18): level 2

A patient was considered as having a PGx testing for a medication (ATC5 code) when one of the genetic tests above was invoiced in the healthcare database (GZSS) either up to one year (365 days) before the first delivery of the medication or up to one year (365 days) after the first delivery of the medication (identified in the healthcare database or the Pharmanet database). To calculate incidence, a patient was considered starting a new medication when his or her first delivery happened after 2013. Incidence was calculated per year from 2014 to 2021.



Appendix 7.1.3. Results

Table 57 – Incidence of users per ATC5

ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
A02BC01	omeprazole	0.99%	43 700
A02BC02	pantoprazole	1.23%	254 372
A02BC03	lansoprazole	0.80%	843
A02BC05	esomeprazole	1.08%	34 038
A07AA06	paromomycin	0.75%	938
A08AA62	bupropion & naltrexone	25.00%	< 5
A10BH51	sitagliptin & simvastatin	0.00%	0
A16AX10	eliglustat	30.00%	< 5
B01AA03	warfarin	0.97%	3 965
B01AA04	phenprocoumon	1.07%	4 327
B01AA07	acenocoumarol	1.27%	6 774
B01AC04	clopidogrel	1.13%	34 950
C01BC03	propafenone	0.69%	873
C01BC04	flecainide	0.86%	8 960
C01EB16	ibuprofen	5.24%	97
C07AB02	metoprolol	0.92%	34 523
C07BB02	metoprolol & thiazides	0.43%	54
C07BB52	metoprolol & thiazides, combinations	0.00%	0
C07CB02	metoprolol & other diuretics	0.00%	0



ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
C07FB02	metoprolol & other antihypertensives	0.73%	555
C07FB13	metoprolol & amlodipine	0.00%	0
C07FX03	metoprolol & acetylsalicylic acid	0.00%	0
C07FX05	metoprolol & ivabradine	0.00%	0
C10AA01	simvastatin	0.90%	55 095
C10AA05	atorvastatin	1.25%	58 480
C10AA07	rosuvastatin	1.19%	25 664
C10BA02	simvastatin & ezetimibe	1.33%	1 901
C10BA04	simvastatin & fenofibrate	0.00%	0
C10BA05	atorvastatin & ezetimibe	2.20%	1 901
C10BA06	rosuvastatin & ezetimibe	1.66%	3 153
C10BA08	atorvastatin & omega-3 fatty acids	0.00%	0
C10BX01	simvastatin & acetylsalicylic acid	0.00%	0
C10BX03	atorvastatin & amlodipine	0.00%	0
C10BX04	simvastatin, acetylsalicylic acid & ramipril	0.00%	0
C10BX06	atorvastatin, acetylsalicylic acid & ramipril	0.82%	400
C10BX08	atorvastatin & acetylsalicylic acid	0.00%	0
C10BX11	atorvastatin, amlodipine & perindopril	0.54%	187
C10BX12	atorvastatin, acetylsalicylic acid & perindopril	0.00%	0
C10BX15	atorvastatin & perindopril	0.74%	145



ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
C10BX18	atorvastatin, amlodipine & ramipril	0.00%	0
D04AX01	doxepin	0.00%	0
D11AH01	tacrolimus	0.76%	111
G02CC01	ibuprofen	0.00%	0
J01CF05	flucloxacillin	0.64%	14 269
J01GB01	tobramycin	1.76%	2 407
J01GB03	gentamicin	0.90%	7 031
J01GB06	amikacin	1.40%	24 778
J01RA06	cefepime & amikacin	0.00%	0
J01XE01	nitrofurantoin	0.68%	17 657
J02AC03	voriconazole	2.26%	1 153
J05AE08	atazanavir	15.19%	93
J05AF06	abacavir	14.67%	19
J05AG03	efavirenz	10.58%	23
J05AR02	lamivudine & abacavir	12.55%	134
J05AR04	zidovudine, lamivudine & abacavir	8.76%	8
J05AR06	emtricitabine, tenofovir disoproxil & efavirenz	20.18%	70
J05AR11	lamivudine, tenofovir disoproxil & efavirenz	0.00%	0
J05AR13	lamivudine, abacavir & dolutegravir	30.71%	394
L01BA01	methotrexate	3.01%	3 022
L01BB02	mercaptopurine	25.27%	199



ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
L01BB03	tioguanine	9.22%	101
L01BC02	fluorouracil	2.63%	7 257
L01BC03	tegafur	0.00%	0
L01BC06	capecitabine	6.83%	1 345
L01BC52	fluorouracil, combinations	0.00%	0
L01BC53	tegafur, combinations	0.00%	12
L01CE02	irinotecan	6.05%	2 056
L01XA01	cisplatin	1.16%	6 223
L01XX33	celecoxib	0.00%	0
L02BA01	tamoxifen	2.13%	2 114
L03AB11	peginterferon alfa-2a	5.53%	15
L04AA42	siponimod	35.14%	8
L04AD02	tacrolimus	8.46%	1 480
L04AX01	azathioprine	26.15%	1 410
L04AX03	methotrexate	1.93%	2 836
M01AC01	piroxicam	0.54%	17 350
M01AC02	tenoxicam	0.47%	2 394
M01AC06	meloxicam	0.53%	5 479
M01AC56	meloxicam, combinations	0.00%	0
M01AE01	ibuprofen	0.94%	221 802



ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
M01AE51	ibuprofen, combinations	0.00%	0
M01AE52	naproxen & esomeprazol	0.46%	225
M01AH01	celecoxib	0.58%	9 510
M02AA07	piroxicam	0.54%	488
M02AA13	ibuprofen	0.58%	4 648
M03AB01	suxamethonium	1.07%	21 456
M03AC10	mivacurium chloride	0.70%	35 913
M04AA01	allopurinol	0.96%	26 220
M04AA51	allopurinol, combinations	0.00%	0
N01AB01	halothane	0.00%	0
N01AB04	enflurane	0.00%	0
N01AB06	isoflurane	0.96%	144
N01AB07	desflurane	0.77%	25 289
N01AB08	sevoflurane	1.03%	417 515
N02AA08	dihydrocodeine	1.03%	3 707
N02AA58	dihydrocodeine, combinations	0.00%	0
N02AA59	codeine, combinations excl. psycholeptics	0.89%	9
N02AA79	codeine, combinations with psycholeptics	0.00%	0
N02AJ01	dihydrocodeine & paracetamol	0.00%	0
N02AJ02	dihydrocodeine & acetylsalicylic acid	0.00%	0
N02AJ03	dihydrocodeine & other non-opioid analgesics	0.00%	0



ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
N02AJ06	codeine & paracetamol	0.75%	8 934
N02AJ07	codeine & acetylsalicylic acid	0.00%	0
N02AJ08	codeine & ibuprofen	0.61%	7
N02AJ09	codeine & other non-opioid analgesics	0.62%	23
N02AJ13	tramadol & paracetamol	0.73%	30 540
N02AJ14	tramadol & dexketoprofen	0.00%	
N02AJ15	tramadol & other non-opioid analgesics	0.00%	0
N02AJ16	tramadol & celecoxib	0.00%	0
N02AX02	tramadol	1.09%	416 880
N02BG09	methoxyflurane	0.30%	326
N03AB02	phenytoin	2.15%	1 729
N03AB52	phenytoin, combinations	0.40%	81
N03AF01	carbamazepine	1.70%	3 084
N03AF02	oxcarbazepine	3.33%	181
N03AX09	lamotrigine	2.18%	3 429
N05AD01	haloperidol	0.67%	27 105
N05AF05	zuclopenthixol	0.76%	1 977
N05AG02	pimozide	0.89%	449
N05AH04	quetiapine	0.92%	22 364
N05AX08	risperidone	0.86%	12 213



ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
N05AX12	aripiprazole	1.18%	5 454
N06AA02	imipramine	0.76%	75
N06AA03	imipramine oxide	0.00%	0
N06AA04	clomipramine	1.08%	1 785
N06AA09	amitriptyline	1.21%	11 289
N06AA10	nortriptyline	1.27%	1 204
N06AA12	doxepin	0.87%	187
N06AB04	citalopram	0.81%	4 610
N06AB05	paroxetine	0.96%	9 391
N06AB06	sertraline	0.97%	13 921
N06AB10	escitalopram	0.98%	33 607
N06AX12	amfebutamone / bupropion	0.95%	4 445
N06AX16	venlafaxine	1.12%	12 807
N06AX26	vortioxetine	1.49%	90
N06BA09	atomoxetine	0.77%	171
N06CA01	amitriptyline & psycholeptics	0.00%	0
R02AX02	ibuprofen	0.00%	0
R05DA04	codeine	1.16%	2 317
S01AA11	gentamicin	0.00%	0
S01AA12	tobramycin	0.61%	27 059
S01AA21	amikacin	0.00%	0



ATC5	Name	Proportion of patients with a genetic test (between one year before and one year after medication delivery)	Mean annual incidence in timeframe 2014-2021
S01BC06	piroxicam	0.00%	0
S02AA14	gentamicin	0.00%	0
S03AA06	gentamicin	0.00%	0
V03AF07	rasburicase	1.89%	1 033

Source: IMA – AIM



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