



T4.3 Pharmacogenomics

PROPHET Expert Workshop: Integrating Pharmacogenomics into Healthcare Systems

Amsterdam UMC/VUMC



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Deliverable Abstract
As part of the PROPHET (Personalised Prevention Roadmap for Future Healthcare) project, a European expert workshop was held in Amsterdam on 21 January 2025, bringing together 58 participants, including 14 speakers, to discuss the integration of pharmacogenomics testing into healthcare systems. The workshop focused on three main areas: evidence, acceptability, and integration. The PROPHET framework was presented as a comprehensive approach to guide Pharmacogenomics implementation, going beyond traditional Health Technology Assessment by incorporating Health Impact Assessment and monitoring. This framework aims to evaluate Pharmacogenomics strategies not only for clinical effectiveness but also for their broader societal and economic impact. Key discussions highlighted the importance of strong evidence for Pharmacogenomics testing, including its clinical utility and cost-effectiveness. The workshop also identified challenges such as data access and sharing, interoperability across healthcare systems, and the need for targeted educational initiatives to increase awareness and acceptance of Pharmacogenomics testing among healthcare professionals and patients. The workshop identified five key priorities for advancing Pharmacogenomics adoption: 1) clear policy development and regulatory frameworks, 2) education and training for healthcare professionals, and raising public awareness 3) investment in ICT infrastructure to enable data sharing, 4) robust health economic evaluations to support funding decisions, and 5) harmonisation of national and EU policies. Overcoming barriers such as reimbursement issues, policy misalignment, and regional differences will require coordinated efforts between stakeholders including policymakers, healthcare providers, and industry stakeholders to ensure Pharmacogenomics becomes a standard part of personalised medicine, ultimately reducing adverse drug reactions.





Keywords

Personalised prevention, personalised medicine, expert workshop, pharmacogenetics, pharmacogenomics, adoption, diagnostic test, PGx, pharmacogenomic testing, pharmacogenetic passport, DPYD, clinical implementation, PROPHET framework, HTA, HIA

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Table of Acronyms

5-FU	5-Fluorouracil
ADR	Adverse Drug Reaction
CDSS	Clinical Decision Support Systems
CPIC	Clinical Pharmacogenetics Implementation Consortium
CRC	Colorectal Cancer
DNA	Deoxyribonucleic Acid
DPD	Dihydropyrimidine dehydrogenase enzyme
<i>DPYD</i>	<i>Dihydropyrimidine dehydrogenase gene</i>
DPWG	Dutch Pharmacogenetics Working Group
EC	European Commission
EHRs	Electronic health records
EMA	European Medicines Agency
ELSI	Ethical, Legal, and Social Issues
EU	European Union
EUnetHTA	European network for Health Technology Assessment
FP	Fluoropyrimidines
GPs	General Practitioners
HCP	Healthcare Professional
HIA	Health Impact Assessment
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratios





ICT	Information and Computer Technology
MLPA	Multiplex Ligation-dependent Probe Amplification
NCDs	Noncommunicable diseases
NGS	Next-Generation Sequencing
NHS	National Health System
NICE	National Institute of Health and Clinical Excellence
OMOP	Observational Medical Outcomes Partnership
PCPs	Primary Care Practitioners
PGx	Pharmacogenetics/Pharmacogenomics
PharmGKB	Pharmacogenomics Knowledge Base
PM	Personalised Medicine
PP	Personalised Prevention
PROPHET	Personalised Prevention roadmap for the future Healthcare
PV	Pathogenic Variant
QALY	Quality Adjusted Life Years
SOC	Patient and social aspects
SmPC	Summary of Product Characteristics
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing





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Executive Summary

Pharmacogenomics (PGx) has the potential to personalise healthcare, improve drug safety, and reduce adverse drug reactions (ADRs). As part of the [PROPHET](#) project (Personalised Prevention Roadmap for Future Healthcare), a European expert workshop was held in Amsterdam on 21 January 2025, bringing together 58 participants, including 14 speakers, from healthcare, policy, pharmacogenomics, and patient organisations. The hybrid-format workshop focused on the integration of PGx testing into healthcare, addressing evidence, acceptance, and integration to support its adoption across healthcare systems.

Achieving this integration requires a structured approach that goes beyond clinical assessments to include broader societal, economic, and policy considerations. The PROPHET framework was developed to guide this process, ensuring that personalised prevention strategies such as PGx are implemented effectively, equitably, and sustainably.

The aim of this workshop as part of Task 4.3 of the PROPHET project was to lay the groundwork for adopting the PROPHET framework for assessment of pharmacogenomics in different health systems and strengthen the capacity for PGx testing implementation among policymakers and health authorities.

PROPHET Framework: Beyond Health Technology Assessment, including Health Impact Assessment and Monitoring

The PROPHET framework extends traditional Health Technology Assessment (HTA) by integrating Health Impact Assessment (HIA), offering a more comprehensive and multidimensional approach to evaluating personalised prevention strategies, and monitoring subsequent innovations. The PROPHET Framework aligns with the new [European HTA regulation](#), which may be applicable to genetic and genomic tests in the future.

It was noted that while the European HTA Regulation primarily focuses on clinical effectiveness and safety, non-clinical dimensions such as acceptability and economic impact are left to national HTA bodies. However, such dimensions could be assessed in a more structured, multidimensional way within HIA. HIA uses a participatory approach, ensuring stakeholder engagement, including patients and citizens incorporating equity considerations. The discussion highlighted that HIA could enhance service delivery by addressing equitable access and considering the broader impact of personalised prevention approaches on citizens and patients, healthcare organisations and healthcare systems.

How exactly to integrate HIA and HTA remains an open question, with suggestions to inspire national HTA/HIA initiatives and the establishment of a European network or body to harmonise such initiatives and ensure a more coordinated approach to broader impact assessments.

Session 1: Evidence

The first session of the workshop centred around evidence, which is crucial for the implementation of PGx testing. For PGx tests to be integrated into clinical practice, strong evidence on their clinical utility and cost-effectiveness is essential. Two case studies were presented: *DPYD* testing and the PGx pass. *DPYD* testing, mostly performed as a single-gene test, is well-established in clinical practice, particularly in oncology, to identify individuals who may experience severe toxicity when treated with fluoropyrimidine-based chemotherapy. It is supported by clinical guidelines and reimbursement pathways, making it a strong example of a successful pharmacogenomics application. In contrast, the





PGx pass, a pre-emptive multi-gene test, is still in its early stages of implementation, with ongoing evaluations of its clinical utility and cost-effectiveness in various implementation scenarios.

The workshop also addressed the challenges of data sharing and integration for PGx testing, focusing on the need for interoperable systems that can store and share pharmacogenetic data across different healthcare settings, such as hospitals and primary care or pharmacies. Real-world data and health technology assessments (HTA) were discussed as tools for demonstrating the effectiveness and economic viability of PGx tests. However, there is ongoing debate about which combinations of genetic variants should be tested to maximise the cost-effectiveness of PGx testing, particularly in the case of *DPYD* testing.

Session 2: Acceptability

The second session focused on the acceptance of PGx testing, emphasising the importance of education and engagement to foster support among healthcare professionals, patients, and the public. Educational initiatives, including e-learning, professional training, and public awareness campaigns, were identified as key enablers. The Estonian Biobank's *My Genome Portal* illustrated how direct access to pharmacogenetic reports can enhance engagement and understanding. Patient representatives highlighted the value of incorporating real-world experiences into policy and guideline development to bridge the gap between theory and practice. To strengthen acceptance, clear and accessible educational resources, standardised clinical guidelines, and active involvement of healthcare professionals and patient organisations were recommended. Addressing these factors will facilitate the integration of PGx testing into routine care, supporting informed decision-making and improving patient outcomes.

Session 3: Integration

The third session focused on the integration of PGx testing into clinical workflows and national and international policies, highlighting both facilitators and barriers. Integration at the national and international levels was discussed in the first panel, which examined how contextual and regional differences shape PGx implementation. Spain was presented as a success story due to strong government support, national regulations, and reimbursement policies, while ICT infrastructure challenges remain a barrier. Finland's biobank model demonstrated the benefits of pre-emptive PGx testing but highlighted difficulties in integrating data into electronic health records. The Netherlands showcased the role of pharmacists in implementation, underscoring the importance of stakeholder engagement. A key takeaway was that PGx integration extends beyond the test itself and requires robust ICT infrastructure, clear regulatory frameworks, and awareness among healthcare professionals and the public.

The role of policies in PGx implementation was explored in the second panel, which examined how regulatory and policy frameworks influence the adoption of PGx across Europe. EU-funded initiatives such as [U-PGx](#) and [PROPHET](#) were highlighted as key drivers in advancing PGx integration. However, national differences, such as Italy's decentralised healthcare system, present challenges in aligning drug approvals and genomic testing policies. The discussion emphasised the need for harmonised frameworks at the EU, national, and regional levels, alongside increased investment in ICT infrastructure. Policy alignment remains a challenge due to varying standards of evidence required for decision-making, making the transfer of best practices, as seen in [HEcoPerMed](#), crucial to avoiding duplicated efforts. Engaging policymakers on the economic benefits of PGx was identified as a key strategy, with a focus on cost savings, competitiveness, and productivity. Additionally, addressing drug overuse and ADRs was highlighted as a pressing concern, with Spain providing an example of how PGx





could be leveraged to mitigate rising ADRs. Overall, integrating PGx into healthcare systems requires a coordinated policy approach, investment in infrastructure, and strong collaboration between policymakers, healthcare providers, and industry stakeholders.

Roundtable Discussion

The roundtable discussion identified key challenges, priorities, and actions needed for the sustainable integration of PGx into healthcare systems. Challenges include insufficient reimbursement frameworks, unclear policies, ICT integration barriers, and a lack of education for healthcare professionals and the public. Even where reimbursement exists, organisational and policy gaps hinder uptake. Additionally, disparities in access due to high costs and funding limitations remain a concern.

To advance PGx implementation, five priorities were identified: (1) Policy development and regulatory clarity—establishing clear national roadmaps, reimbursement models, and alignment with EU regulations; (2) Education and training—integrating PGx into medical and pharmacy curricula, providing continuous professional education, and increasing public awareness; (3) Investment in ICT and data infrastructure—ensuring interoperable electronic health records (EHRs) and clinical decision support tools to facilitate real-time use of PGx data; (4) Health economic evaluations—generating strong cost-effectiveness evidence to support funding and policy decisions; and (5) Harmonisation and collaboration—aligning national and EU policies, standardising testing procedures, and facilitating knowledge-sharing to avoid duplication of efforts.

Key recommendations for policymakers include developing structured reimbursement strategies, strengthening regulatory frameworks, and prioritising ICT integration to ensure seamless data exchange. Healthcare providers should receive targeted education, and patient organisations can play an active role in raising awareness and supporting implementation. Standardised data collection and monitoring at the national and EU levels are essential for tracking PGx adoption and outcomes. A coordinated approach between policymakers, healthcare professionals, researchers, and industry stakeholders are crucial to ensure PGx becomes a standard tool for safer, more effective personalised medicine.

Conclusion

In conclusion, the PROPHET PGx expert workshop highlighted the potential for both national and international collaboration in the implementation and integration of PGx across health systems, taking account of regional and national differences. While progress is being made in several countries and national implementation studies are being conducted, there is room for greater exchange of knowledge on what information is crucial for success. The establishment of a dedicated network or body to foster communication, harmonise national/regional and local initiatives, develop key performance indicators and to collect data, and facilitate the sharing of information between stakeholders is vital. Such a network would build on existing efforts such as assessments and implementation research ensuring that countries can learn from one another and align their efforts towards effective PGx testing.

The PROPHET framework, with its capacity to guide the structured assessment and implementation of PGx, provides a foundation for this collective approach. Ongoing engagement among key stakeholders is crucial to support informed and coordinated integration of PGx into healthcare systems.





1.Introduction

This research is part of the PROPHET project: [a Personalised Prevention roadmap for the future HEalThcare](#), to support the definition and implementation of innovative, sustainable and high-quality personalised strategies that are effective in preventing chronic diseases. According to the PROPHET consortium personalised prevention (PP) ‘aims to prevent onset, progression and recurrence of diseases through the adoption of targeted interventions that consider the biological information, environmental and behavioural characteristics, socio-economic and cultural context of individuals. This should be timely, effective and equitable in order to maintain the best possible balance in lifetime health trajectory’ (1). PP should not substitute traditional prevention but can complement prevention by leveraging the large amount of data, including biological data, in order to identify individuals and subgroups of populations that can benefit from a more targeted preventive approach. The PROPHET project consists of three distinct phases: after *mapping* current initiatives and programmes for personalised prevention, a concerted effort was made to develop a framework for *assessing* such initiatives. In a third *building* phase capacity building will be set up to disseminate the findings and help train policymakers, health authorities, health professionals, citizens and patients on personalised preventive options.

Pharmacogenomics (PGx) was identified by the PROPHET project as a pivotal domain for personalised prevention, assessing how genetic variations influence individual responses to medications. In this document, the terms pharmacogenomics and pharmacogenetics are used as synonyms.

In this Task 4.3 of the PROPHET project, we aim to lay the groundwork for adopting the PROPHET framework for assessment of pharmacogenomics in different health systems and strengthen the capacity for PGx testing implementation among policymakers and health authorities.

Therefore, an expert workshop was organised to discuss stakeholders’ experiences and challenges regarding integrating pharmacogenomics into health systems, guided by the PROPHET framework, so policymakers are better equipped to design evidence-based policies in close collaboration with relevant stakeholders. As part of this effort, two case studies – *DPYD* testing and the PGx pass – were selected to illustrate key contrasts in pharmacogenomic approaches and their role in personalised medicine. By examining these two applications, the workshop seeks to address what policymakers, healthcare professionals, patients (organisation), regulators, researchers, require for assessing and integrating pharmacogenomics into routine clinical practice.

1.1. Pharmacogenetic testing and its timepoints

PGx holds considerable promise for more precise and patient-centred therapeutic approaches, paving the way for enhancing drug safety and efficacy (2, 3).

Adverse drug reactions (ADRs) are estimated to account for approximately 5-15% of all hospital admissions in adults, with the figure rising to over 15% in patients with multiple chronic conditions (4-8). These reactions can negatively impact clinical outcomes and contribute to the strain on healthcare resources. Personalising drug prescriptions based on PGx may help reduce the incidence of ADR-related hospital admissions, potentially offering benefits in terms of patient safety and more efficient use of healthcare resources (9). To support the integration of pharmacogenomics into clinical practice, international working groups such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have developed standardised guidelines. These guidelines, regularly updated in the Pharmacogenomics Knowledge





Base (PharmGKB), provide recommendations on the optimal choice of medication once a pharmacogenetic variant is identified in a person. However, they do not specify when genetic testing should occur or in what populations (10).

For the expert workshop two, case studies, *DPYD* testing and the PGx Pass, were selected to study pharmacogenomic approaches as promising examples personalised medicine. These two cases are explored in more depth, representing different stages of implementation. *DPYD* testing is evidence-based, supported by established guidelines, and widely used in healthcare systems, whereas the PGx Pass is still in early stages, with clinical utility and cost-effectiveness under evaluation.

DPYD testing, a companion diagnostic performed as a single-gene test, is primarily used in oncology to identify deficiencies in the dihydropyrimidine dehydrogenase (DPD) enzyme, which can cause severe toxicity in patients treated with fluoropyrimidine-based chemotherapy. This test reduces the risk of ADRs and is supported by clinical guidelines and reimbursement pathways (9). In contrast, the PGx Pass is a pre-emptive, multi-gene test that covers 14 genes and applies to a range of therapeutic areas, including psychiatry and oncology. Although its full clinical utility and cost-effectiveness are still being established, it offers the potential to reduce ADRs and hospital admissions across multiple drug treatments (9).

The barriers and facilitators for implementing these approaches differ, with *DPYD* testing already integrated into clinical practice to considerable extent, while the PGx Pass faces challenges related to reimbursement and prioritising target groups versus wider populations. Comparing these cases provides insights into overcoming challenges in both targeted and broad-spectrum (companion diagnostic vs pre-emptive) pharmacogenomic testing.

Pharmacogenetic testing can be conducted at different time points using various techniques, and its implementation depends on multiple factors, including clinical utility and cost-effectiveness. Acceptance among healthcare professionals and patients are vital. Furthermore, the success of implementation may vary depending on the type of healthcare system in place, and national or regional factors, such as available ICT infrastructures. In the following sections, we will explore these factors in more detail and discuss key considerations for integrating/adopting PGx testing into clinical practice.

Pharmacogenomics is a valuable addition to prescribing medication and dosing which is currently based on clinical characteristics, including age, body weight, renal and hepatic function, and on concomitant medications. To prescribe personalised medication and dosing based on the patient's genetic profile, a pharmacogenetic test needs to be conducted. Individuals can get genetically tested for variants in pharmacogenes at different time points (Figure 1). Reactive testing is performed after an adverse drug reaction (ADR) has occurred or when drug efficacy is lacking (11). Usually, one and sometimes two or three pharmacogenes are examined with a reactive PGx test (12), however, also panel-based testing would be possible. When the PGx test is conducted right before medication is selected and dosage is determined, it is called companion diagnostics (11, 13). For instance, performing dihydropyrimidine dehydrogenase (*DPYD*) testing prior to cancer treatment with fluoropyrimidines (FP) is a clinical routine in the Netherlands and many other countries to reduce the risk of ADRs. Lastly, pre-emptive testing is performed without a clinical indication, and prior to any target drug prescription (9, 11). For instance, the pharmacogenomics (DNA) pass, reporting variants in more than 10 genes, is pre-emptive pharmacogenetic testing, by conducting testing before a clinical indication and before targeted drug prescription. Pre-emptive testing and companion diagnostics can be used in combination, for instance a *DPYD* test can be integrated into a PGx pass.



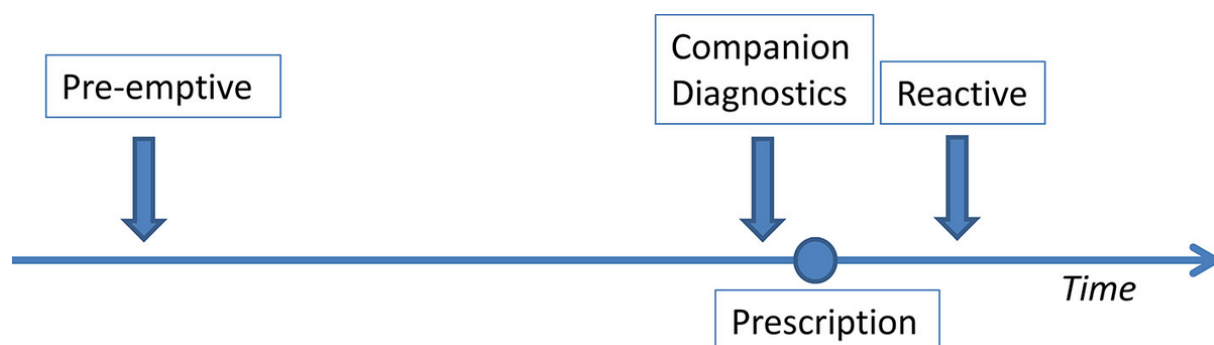


Figure 1: . Timepoints on which a pharmacogenetic test can be performed, related to medication prescription (Rigter et al., 2020).

1.2. Pharmacogenetic test techniques

Next to different timepoints on which individuals can be tested for genetic variants in their pharmacogenes, different pharmacogenetic test techniques can be used. When Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) data is already present, due to testing for a suspected genetic condition, these data can be reused to extract data on pharmacogenes. However, when WES or WGS data is not present, it might be too costly to perform broad exome or genome sequencing solely for pharmacogenetic purposes. Therefore, a more targeted pharmacogenetic test technique can be used, such as an array or a targeted panel with digital Multiplex Ligation-dependent Probe Amplification (MLPA) (14). With these techniques (WES, WGS, array, or targeted panel/digital MLPA) many pharmacogenetic variants can be mapped, which is mostly performed as pre-emptive strategy, such as for the case of a PGx pass. For companion diagnostics, such as the case of *DPYD* testing for oncology patients who will be treated with fluoropyrimidines, only one specific gene that can affect pharmacotherapy metabolism will generally be tested. Also, as a reactive strategy, only one or a few pharmacogenes will currently be tested, which can be done with a targeted digital MLPA panel or with array-based testing.

2. Methods

2.1. Study design, setting, and population

A European expert workshop on pharmacogenomics, organised under the PROPHET project, was held in Amsterdam on January 21st, 2025, with a hybrid format enabling participants to participate online as well as in person. Fourteen experts, with expertise spanning HTA, EU regulation, pharmacology, pharmacogenomics, ELSI, governance, human genetics, patient representation, and ICT, were invited to present their experiences on key domains for assessing and implementing pharmacogenomics in the following sessions:

- (1) **Evidence:** What information is required for the implementation of pharmacogenomics, and how can we effectively gather this information?
- (2) **Acceptance:** How can we engage patients and healthcare professionals? What roles can patient and professional organisations play in this process?
- (3) **Integration:** I- How does the national context influence the assessment and implementation of pharmacogenomics? II- What role do policies play in this process?





After each of the sessions, a brief discussion session was held, followed by a roundtable discussion in the concluding session, where the experts formulated key points to consider for integrating pharmacogenomics into healthcare systems.

Some participants attended the workshop virtually ($n=41$). In total 58 participants were present, either at the venue in Amsterdam, or online. Invitations to attend the workshop were distributed among PROPHET partners, their colleagues and officials interested in pharmacogenomics, and some members of the PROPHET Stakeholder Forum.

Speakers were selected based on their expertise regarding the assessment or implementation of pharmacogenomics. Prior to the meeting they received a handout introducing the PROPHET project and the aim of the workshop, their consent was asked for recording of the meeting for reporting (see Appendix I). Fourteen experts gave a presentation, of whom eight were online. At the start of the meeting also participants were notified about the recording. The expert workshop started with a brief introduction on the PROPHET project by Professor Stefania Boccia (PROPHET coordinator) and of the PROPHET framework by Associate Professor Astrid Vicente. Each round/session was facilitated by a PROPHET partner: Dr. Angelica Valz Gris; Carla van El, PhD; Tessel Rigter, PhD; and Professor Martina Cornel (Appendix III). In the following we will first give a short overview of this framework. Subsequently, this report will summarise the presentations and discussions at the expert workshop.

2.2. PROPHET Framework

The PROPHET framework was developed to address the need for a comprehensive and multidimensional approach to evaluating genomic and genetic technologies, along with the policies and programs required to implement them effectively. The PROPHET framework builds on the health technology assessment (HTA) model promoted by the new European regulation (15), which mandates a joint assessment of the efficacy and safety of the technology at the European level and an evaluation of context-specific dimensions, such as economic aspects, feasibility, and acceptability at the national level. However, HTA assessments are not specifically equipped to assess the broader policy dimensions necessary for the successful implementation of personalised prevention strategies.

A dedicated framework is essential for evaluating the health impacts of policies and programs that integrate genomic technologies. Unlike traditional health technology assessments, the PROPHET framework extends its focus to include diverse dimensions such as societal factors, healthcare systems, civil services, and public health infrastructure. These dimensions are crucial but often overlooked in conventional HTA methodologies.

To ensure that personalised prevention strategies such as that of pharmacogenomics are effective, equitable, and sustainable in real-world settings, the PROPHET framework relies on a multidimensional approach that bridges technical, clinical, and societal perspectives. This integration draws on three complementary steps; health technology assessment (HTA), health impact assessment (HIA) and monitoring (see Figure 1):

1. Health Technology Assessment (HTA):

HTA primarily focuses on the clinical utility of health technologies, such as genetic and genomic tools. While current regulations do not universally mandate the evaluation of genetic technologies through HTA, it is important to propose and incorporate relevant indicators of





clinical utility. These indicators can guide the assessment process, making it more applicable to the evaluation of personalised prevention strategies.

2. **Health Impact Assessment (HIA):**

HIA offers a broader and complementary perspective to HTA, focusing on the implementation and societal impact of policies. It emphasises equity, access, and the social determinants of health. Unlike HTA, HIA adopts a more participatory approach, actively involving stakeholders such as those most affected by or relevant to the success of a given policy or program. This structured and inclusive process ensures transparency and incorporates diverse perspectives, particularly around issues of equity. In the context of genetic and genomic tests, these policies can relate to determining the potential for reimbursement of such tests and establishing the pathways for these decisions within the health system.

3. **Monitoring:**

Continuous monitoring mechanisms are incorporated into the PROPHET framework to assess whether policies and programs are being implemented effectively and achieving their intended goals. These mechanisms help bridge technical, clinical, and societal dimensions, ensuring that strategies remain adaptable and responsive to real-world needs.

Monitoring plays a crucial role in demonstrating the long-term effects of policies as well as ensuring adequate adjustments to these policies. The proposed framework applies a logic model approach to monitoring by clearly defining key components: identifying necessary inputs, outlining key activities, specifying required data, categorising expected outputs, and systematically evaluating outcomes to measure impact. This structured monitoring process bridges the gap between technical evaluations of health technologies (e.g., through health technology assessment) and the broader policy-level impacts. By doing so, it facilitates a more informed decision-making process, enabling policymakers to make better and more effective choices.



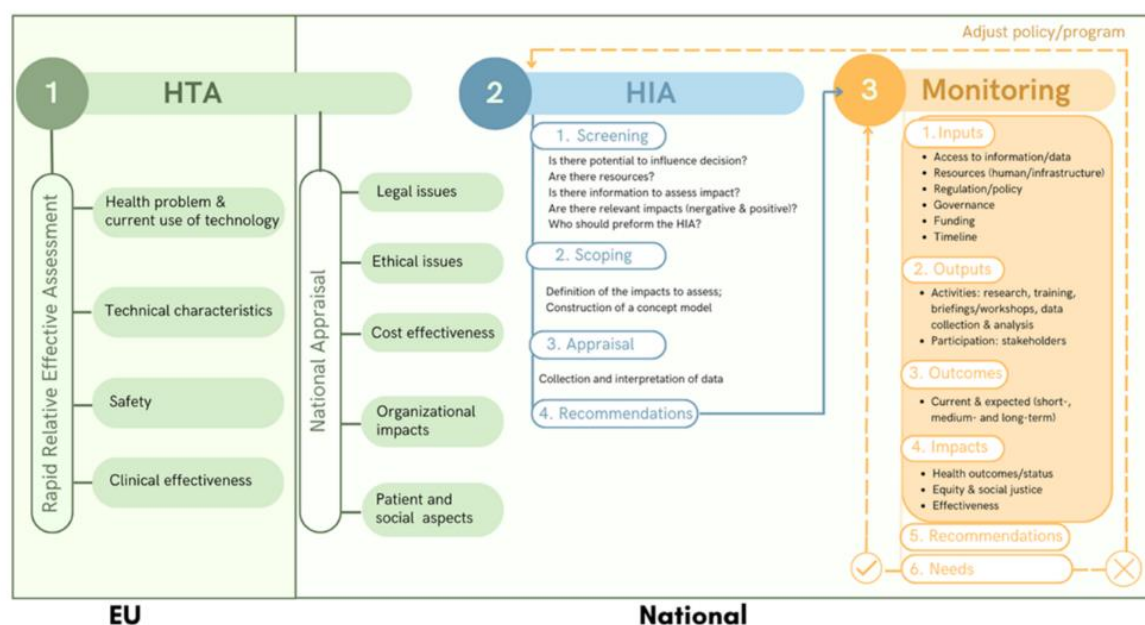


Figure 2: The PROPHET Framework for appraisal of personalised preventive approaches. Source: Deliverable 3.2.

2.2.1 Developing a HIA for Personalised Prevention

In the PROPHET project three case studies including pharmacogenomics have been conducted to develop and test the HIA framework tailored to personalised prevention policies based on genetic information. For each case study in the participating countries (Finland, Italy, and Portugal), the process of performing a HIA followed a structured approach. In the first *screening* phase, national technical teams were formed, with responsibilities that included designing project specifics according to country practices, collecting data, organising and inviting experts to join the steering committee. These steering committees included representatives from national cancer registries, patient groups, medicine agencies, regulators, clinicians, pharmacists, and laboratory experts, ensuring inclusivity and diverse perspectives. In this *scoping* phase the activities were planned. It was decided that impacts should be assessed on patient outcomes (e.g. morbidity and mortality), on the healthcare services (e.g. acceptability by health care professionals and strain on lab resources) and healthcare system (e.g. the economic impact of introducing testing). Subsequently, the core activity of the HIA consisted of *appraisal* in the *assessment* phase. For the case studies data was collected and analysed by using literature review, Markov models, and stakeholder consultations including surveys and expert interviews.

The HIA on the case studies, their analyses and subsequent [recommendations](#) were compiled in a report that was submitted to the EU. Not included in that Deliverable was the *monitoring* phase, that would need to be performed after implementation.

A summary of this process and the case studies can be found in the Appendix 2.





3. Results

The expert workshop followed a structured agenda (Appendix 3), with sessions dedicated to core domains of assessing and implementing pharmacogenomics: Evidence, Acceptance and Integration, followed by a Round Table discussion. Key points from the presentations and discussions are summarised below. The presentations are outlined in boxes.

3.1 Session 1: EVIDENCE

For implementing pharmacogenetic (PGx) testing in practice, evidence for clinical utility and cost-effectiveness are essential elements that need to be considered both in a HTA and HIA. Therefore, in the first session of the workshop, existing evidence for *DPYD* testing and for the PGx pass, based on a PGx panel test, were explored.

Strengthening Clinical Evidence for PGx testing

Jesse Swen (Leiden University Medical Center, the Netherlands) illustrated the current state of PGx implementation using the examples of the *DPYD*-5FU/Capecitabine drug-gene pair and for a 12-gene PGx panel test. He pointed out that all gene-drug pairs within the panel are already evidence based and are included in evidence-based guidelines (CPIC, DPWD, PharmKGB). Indeed, the implementation of companion diagnostic PGx panel testing in clinical practice has proven to be feasible, effective and reduce ADR risk. In general, the experts in the workshop expressed that PGx seems to be moving from a reactive to a pre-therapeutical panel approach.

Addressing Data Sharing and Integration challenges

John McDermott (University of Manchester, United Kingdom) showed in his presentation the development of a proof-of-concept interoperable and scalable solution for the implementation of pharmacogenetics in the National Health Service (NHS) in the United Kingdom (UK). He stated that the goal is to make pharmacogenetic data available for reuse throughout a patient's life, through reactive testing with planned reuse or fully pre-emptive testing. However, reusing data over time and across different healthcare settings, regions, and multiple clinical contexts is highly complex, specifically with regards to the management and sharing of data. As a solution, pharmacogenetic data can be stored in a cloud based clinical data repository using open standards, such of openEHR and FHIR, which clinicians can access. Currently, the open data platform is the only way to deliver a scalable and interoperable model for the delivery of PGx in the UK-NHS. However, for the future, there is an ambition to make prescribing guidance available in the patients' Electronic Health Record, making an external system for clinicians redundant and incorporating it better into the standard workflow of clinicians. Utilising an open standards approach reduces the need for point-to-point integration of genetic results with each different Electronic Health Record supplier, rather it allows separation of data from the different clinical applications that may need to display it to a range of healthcare professionals.

Demonstrating Cost-effectiveness and Economic Viability

Maureen Rutten (Erasmus Universiteit Rotterdam, the Netherlands) focused in her presentation on Health Technology Assessment (HTA) in which evidence for cost-effectiveness is included. She referred to the HEcoPerMed project (16) and stated that *DPYD* genotyping prior to fluoropyrimidine-based





chemotherapy with TOXNAV, a germline genetic test, is good value for money. Moreover, real-world data of effectiveness can be used in HTA in the absence of trial data and there is a need for better data on probabilities, costs and utility-decrements of ADRs. Currently, there is an ongoing debate about what combination of variants should be tested to maximise the cost-effectiveness of upfront *DPYD* testing.

Harmonising Regulatory and Policy Frameworks

The last presentation was by Marc Maliepaard (Medicines Evaluation Board (MEB) and European Medicines Agency (EMA), the Netherlands) and he elaborated on *DPYD* testing in Summary of Product Characteristics (SmPC), focusing on the EU regulation versus the national context. His presentation covered the history of pharmacogenetics, the evolution of guidance documents to promote its adoption, and the journey of integrating specific pharmacogenetic information (e.g. *DPYD* genotyping) into their label (SmPC).

HTA versus HIA

The discussion centred around the PROPHET Framework, highlighting the differences between Health Technology Assessment (HTA) and Health Impact Assessment (HIA), and exploring how to improve the implementation of PGx. The PROPHET Framework, designed for personalised prevention programmes, aims to be in line with the new European HTA regulation that in future may also be used for genetic/genomic tests, focusing on the international clinical assessment (Joint Clinical Assessment - JCA) as distinct from national context-specific evaluations. It was argued under the European HTA Regulation this clinical assessment contains solely relative effectiveness assessments and relative safety assessments, while the concept of HTA is broader and includes non-clinical dimensions such as acceptability, and economic impact, that, however, can also be seen as part of HIA. The part that is not covered by the JCA is usually taken up by national HTA bodies. It was noted that HTA might overlook equity aspects, which could be addressed by incorporating HIA, which is participatory and involves stakeholder consultations. It was mentioned that HIA could enhance service delivery in this way (e.g. looking at equitable access) and reflect the various impacts of personalised prevention approaches. How to integrate HIA and HTA is food for further discussion, as well as if a European body or network should be established to harmonise national initiatives for such broader HIA assessments.

Assessing Service Delivery

Irrespective of the framework used, the necessity of evaluating the broader implementation of a pharmacogenetic intervention, beyond just the PGx test itself was stressed, as the test's value depends on its integration into service delivery models.

Availability of Data

The data to assess these aspects are often scarce. While challenges exist in health economic modelling, experts suggested that real-world data could inform more accurate evaluations of PGx implementations.

EVIDENCE FOR PGX PANEL TESTING AS BASIS FOR IMPLEMENTATION

Box 1: Jesse Swen, Universiteit Leiden, the Netherlands

PGx is one of the contributing factors to variability in drug response. Many other factors (e.g. drug interactions) are already implemented in the process of drug prescribing to individualise drug





treatment. Traditionally, PGx tests are performed to explain toxicity retrospectively, however PGx testing has shifted from retrospective to pre-therapeutic for single gene-drug pairs. *DPYD*-5FU/Capecitabine is the first gene-drug pair implemented on a national scale in the Netherlands, which is the result of a multi-centre trial in the Netherlands. During the trials the test was accepted by the medical oncology community, since many centres reached out to the study group with the request to participate in the trials to have access to the test. Pre-therapeutic *DPYD* testing lowers risk for severe toxicities without compromising effectiveness. The uptake of *DPYD* testing in the EU has considerably grown after EMA recommendation in 2020. There are many other gene-drug pairs with a similarly high level of evidence as *DPYD*, however none of these are implemented to the same extent as *DPYD*.

There are evidence-based guidelines (e.g. from DPWG) for clinicians on how to translate the PGx test results into a meaningful clinical action. These guidelines are established based on systematic literature review to calculate dose adjustments to obtain similar exposure as normal metabolizer. Almost everyone worldwide has a variant in the genes covered in these guidelines. These aspects together build a strong case for pre-therapeutic panel testing, since there is evidence for single gene-drug pairs, there are DPWG, CPIC, CPNDS, and RNPx guidelines, and the potential impact is high because around 95% of the general population harbours at least one actionable variant and these drugs are frequently used. The clinical impact and utility of a pre-therapeutic panel was evaluated in the U-PGx study (17). This study combined a 12-gene PGx panel test with evidence-based DPWG recommendations. The outcome of the project focused on preventing ADRs for 39 drugs ranging from depression to anti-cancer. The results show that by implementing the panel test, the risk for ADRs is reduced by 30%. The publication in Lancet generated discussion in the news, in the Dutch parliament and in the scientific world. On the one hand, the study was criticized because of the unblinded design, but on the other hand there were also positive evaluations. The criticism surpasses the point that all the recommendations that were implemented in the study were already evidence-based. The overall cost-effectiveness analysis of the study is ongoing. There are already four country-specific analyses published which show positive beneficial results. The next step is to show overall cost-effectiveness and to identify groups that benefit most. In the future, pre-emptive testing can be performed by repurposing existing Whole Exome Sequencing (WES) data for PGx.

DEVELOPING AN INTEROPERABLE AND SCALABLE PLATFORM FOR THE IMPLEMENTATION OF PGX IN THE NHS

Box 2: *John McDermott, University of Manchester, United Kingdom*

In the current healthcare landscape, there is a range of genetic tests available, each ordered by different healthcare professionals and performed by various laboratories across the UK. The tests offered include both single-gene tests and multi-gene panels. One of the most established examples is *DPYD* testing, which is mandated for all patients undergoing fluoropyrimidine treatment and has a high uptake in the UK. Genetic testing must be embedded within a model of service delivery, which can be reactively, companion diagnostic with planned reuse since a gene panel is used from which the results can be informative for the future, or fully pre-emptive testing or rapid point of care testing. Currently, reactive single-gene testing is transitioning to more comprehensive models like panel-based testing with data reuse. The goal is to make genetic data available for reuse throughout a patient's life, whether through reactive testing with reuse or fully pre-emptive testing. However, reusing data over time and across different healthcare settings, regions, and multiple clinical contexts is challenging. With single-gene testing, the information is used at a single point in time, but with panel-based testing, multiple genes are involved, which introduces greater complexity in managing and sharing data. Another challenge is that, as more genes and clinical contexts are added, the model must account for





how data is transferred across multiple healthcare settings and geographies. On a population level, implementing such tests on a broader scale is complex and requires careful planning to ensure accessibility and integration into routine care.

It is essential to consider that genetic testing, particularly in a panel-based model, will become part of clinicians' daily workflows to ensure minimal disruption to clinical practices. The key is to develop service delivery models that balance the complexity of managing genetic data with the need for efficient and scalable implementation. There is significant interest in PGx within the NHS since the potential for substantial cost savings.

NHS England has launched the *Network of Excellence for Pharmacogenomics and Medicines Optimization*, focusing on developing strategies for genetic testing, data integration, and the practical delivery of PGx within clinical practice. The work is embedded within the *PROGRESS* study. While the NHS has a robust laboratory system for genetic testing, the main challenge lies in how to make genetic data accessible across the healthcare system. The key issue is not the testing itself, but how to present genetic data in a clinically relevant and timely format that is useful for healthcare professionals. Traditional genetic test reports often present raw data that are not easily interpretable by healthcare professionals. Therefore, these reports may be meaningless to the majority of clinicians unless the data is processed and presented in an actionable format, for example including CPIC recommendations. However, the real challenge lies in how to make this data accessible across different parts of the healthcare system, since the NHS is highly fragmented in terms of electronic healthcare records (EHR).

Different regions and healthcare settings may use different systems leading to difficulties in sharing and integrating data. To overcome this challenge, a solution has been developed to separate the genetic data from the applications used by clinicians. This data is stored in an open data repository in the cloud, adhering to open data standards. Clinicians can access the data from this repository through a system that interacts with their EHRs. Therefore, a system called Gen-O is developed which is a clinical tool integrated into the NHS clinical genetics program. Healthcare professionals can search for a patient's records via the patient's NHS number and can access their pharmacogenetic information within the system. The long-term goal is to integrate pharmacogenetic data directly into patients' EHRs, which removes the need for clinicians to access external systems to view genetic information. But for now, the benefits of the Gen-O approach are that consistent guidance and standardised implementation across the entire NHS healthcare system can be ensured and a patient's pharmacogenomic information can be continuously updated as new tests are conducted throughout their lifetime. The open data platform with openEHR data standards approach is the only way to deliver scalable and interoperable model for the delivery of PGx. It might become possible for patients to interact with their PGx data via the NHS app.

Two overarching principles are: 1) PGx is not just for rare diseases or cancer: PGx should not be treated as a specialty reserved for rare diseases or cancer. The way pharmacogenomic data is used in these contexts is fundamentally different from how it will be used in routine clinical practice. Clinicians who work with patients on a day-to-day basis need to be able to use pharmacogenomic data without treating it as a specialised field, and 2) PGx as a clinical variable: rather than viewing PGx as a unique or exceptional tool, it should be treated as just another clinical variable that can inform decision-making. The focus should be on developing practical models that integrate PGx into routine clinical decision-making without causing disruption.

HTA FOR PHARMACOGENETICS, WHAT SHOULD BE ON THE AGENDA?

Box 3: Maureen Rutten, Erasmus Universiteit Rotterdam, the Netherlands





There is a need for Health Technology Assessment (HTA) to optimize health gains for the investments made in healthcare, since the (Dutch) healthcare budget is constrained. Theoretically, if PGx testing is added to the benefit package, another intervention must forgo. Or the healthcare budget can be increased, but then premiums or taxes have to be increased or budgets in other publicly funded sectors have to be reduced. The HTA core model consists of relative effectiveness and relative safety. Extensive HTAs also include a cost-effectiveness analysis and budget impact analysis to inform affordability. The HTA core model also requires assessments of ELSI aspects (ethical, legal, social issues, as well as organisational aspects and environmental sustainability). Equity elements are a part of HTA as well, e.g. there is potentially an unequal distribution of toxicity burden among cancer patients because of their ethnic background, as the CPIC variants are predominantly found in Caucasian populations.

The heart of the HTA study is a cost-effectiveness analysis, resulting in an incremental cost-effectiveness ratio (ICER). A cost-benefit analysis can also be performed, resulting in an incremental net monetary benefit (INMB). In the Netherlands HTA is performed from a societal perspective, including multiple cost categories such as intervention costs, other healthcare costs (un)related to disease of interest, patients' out-of-pocket expenses, future related and unrelated healthcare costs during life-years gained, costs in other sectors, and costs of future non-medical consumption (not formally required in the Netherlands). A cost-effectiveness analysis requires modelling for four reasons: 1) to combine different data from different sources of evidence, 2) to extrapolate results of clinical trials to longer time horizons, 3) to expand the number of comparators beyond that used in a clinical trial, and 4) to simulate real-world conditions.

The [HECoPerMed](#) consortium (2019-2022) is about Health ECONomics for PERsonalized MEDicine (PM). The project was funded by the European Horizon 2020 program via the European Commission. In HECoPerMed, methodological guidance for improving and harmonizing economic evaluations of PM (test-treatment combinations) was developed. This was done in response to concerns about the current HTA methods not being adequate for PM. The conclusion was that PM should be subjected to the same HTA-methodology for consistency and comparison reasons. There is no reason for a specific new methodology to be developed.

The methodological guidance was applied in the HECoPerMed project to *DPYD* testing with the TOXNAV test (3 CPIC variants and 15 additional variants) in women with metastatic breast cancer. The aim was to evaluate the cost-effectiveness of upfront *DPYD* testing for patients with metastatic breast cancer prescribed capecitabine/5FU from the UK healthcare perspective. Tested patients were compared to untested patients to assess the impact of TOXNAV on hospital costs. Moreover, a model-based cost-effectiveness analysis was performed with a decision tree and Markov model, demonstrating cost dominance (net cost savings for the healthcare system and significant QALY gains). In addition, a budget impact analysis was performed to assess affordability, showing yearly net cost savings.

DPYD TESTING IN SMPC: EU REGULATION VERSUS NATIONAL CONTEXT

Box 4: Marc Maliepaard, Medicines Evaluation Board (MEB) and European Medicines Agency (EMA), the Netherlands

A study from 2015 by Ehmann et al., showed that 176 (34%) of all EMA authorised products (1995-2014) contained PGx information in their label (SmPC). PGx information was primarily found in section 4.4 (warnings), 4.5 (interactions), and 5.2 (pharmacokinetics). These sections are only for information purposes, with no actions reported. In a few cases, PGx information is mentioned in section 4.1 (therapeutic indications), 4.2 (posology), or 4.3 (contra-indications), and in that case the dose should be adjusted for example.





Regarding guidance, the first guideline (2012) was on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. The overarching aim was to make pharmacogenetic information available to prescribers at time of registration, since for old, already registered medicines, it proves to be difficult to obtain adequate pharmacogenetic data. The second guideline (2016) was on key aspects for the use of PGx in the pharmacovigilance of medicinal products. In case potential clinically relevant polymorphisms have been identified but not studied, this is considered missing information or a potential risk for subpopulations.

EMA provides guidance on an EU level and also registration conditions are the same for all EU countries. However, the different countries in the EU have different conditions and possibilities with respect to pharmacogenetics in their healthcare system. In the Netherlands for example, pharmacogenetic testing is relatively easy and financially feasible. In some other EU countries options for pharmacogenetic testing are less extensive, or financially not feasible. Moreover, individual countries have different healthcare and reimbursement systems and sometimes different preferred pharmacogenetic test systems.

DPYD testing is important for treatment with 5-FU, capecitabine and tegafur. In the SmPC of these three medications, *DPYD* is included in section 4.3 (contraindications; for complete deficiency) and 4.4 (warnings; reduced dose should be considered; genotyping and phenotyping are mentioned). A reasonable amount of information is provided, which has led to an increased number of *DPYD* testing in the EU, but the information is not as extensive or detailed as the Netherlands wishes. However, up to 2016 only a contraindication was included in the SmPC of 5-FU/capecitabine/ tegafur for patients with 'known' total DPD deficiency, and a non-specific warning that patients with partial DPD deficiency should be treated with caution. No advice was given at that time. In the meantime, academic research was ongoing in the Netherlands towards a lowered dose in case of partial DPD deficiency to avoid serious toxicity. In 2016, the EMA was therefore requested by the academic group to include the following in the SmPC; genotype patients with respect to *DPYD* prior to treatment with 5-FU or capecitabine and give carriers of heterozygote *DPYD* polymorphisms a specific reduced dose. At that time, *DPYD* genotyping was already widely applied in the Netherlands, but was not yet included in the SmPC. The EMA PGx Working Party (PGWP) was consulted to give advice on inclusion of a genotyping advice/warning in the SmPC. The PGWP considered the research to be robust enough to include information in the SmPC, and prevention of potentially lethal adverse events was also a driver for the inclusion. However, the company behind capecitabine was not convinced of the necessity to include genotype information, since the adjusted dose is based on too few data and not all relevant polymorphisms are assessed. Also, other member states had comments, such as preferring a phenotypic assay and expressing worries about high reimbursement costs. Therefore, the specified dose reduction was not included in section 4.2 (posology), and both the option of genotyping and phenotyping are mentioned in section 4.4 (warning). Further information should be obtained by the prescriber from (local) treatment guidelines.

This process proves again that after registration it is difficult to provide sufficiently robust academic research data to substantiate a PG-based dose advice. Moreover, innovator Companies do not always collaborate in the post-registration phase and sometimes are risk averse. Information in the SmPC is their advice. Scientific research often has a local (national) aspect. There is no a-priori overarching aim to investigate in collaboration due to local interests. In the Netherlands, prescribers are convinced that *DPYD* genotyping is the best and based on national guidelines it works well in clinical practice, while in other countries prescribers consider phenotyping being the optimal method. Still, with all its limitations, providing this information in the SmPC has helped genotyping being applied more extensively for 5-FU and capecitabine in the EU.





3.2. Session 2: ACCEPTANCE

The second session focussed on acceptance for PGx testing, in particular for *DPYD* testing and panel testing for a PGx pass. To create support among healthcare professionals, education is a key facilitating factor. Moreover, patient and citizen engagement can be used to create empowerment and acceptance among patients and citizens.

Educational Approaches and Public Awareness

Ron van Schaik (Erasmus University Medical Center Rotterdam, the Netherlands) presented how healthcare professionals in primary and secondary care can be educated about PGx, for example on education days, via e-learning or journals. In addition to educating primary and secondary healthcare professionals, the general public and stakeholders have to be informed, for instance via websites, a PGx helpdesk or online applications.

Access to PGx information: Experience from a biobank

In Estonia, the Biobank initiative My Genome Portal offers access to PGx reports to Estonian Biobank's participants. Liis Leitsalu (University of Tartu, Estonia) explained in her presentation that Estonian Biobank participants can give consent to get insight in their personalised PGx recommendations informed by CPIC guidelines. Such a portal can contribute to user engagement and education, and it was highly valued by participants.

Patient engagement

A method to engage patients and learn from patient experiences can be by involving patients as a patient representative in assessments, which was elaborated on by Helena Kääriäinen (Finnish Institute for Health and Welfare, Finland). Mervi Kaartoaho (Colores, Finnish Colorectal Cancer Association) shared her experience as a patient representative, following serious adverse effects due to cancer treatment. She has given valuable insights from contributing to a HIA process in Finland on patient impact of implementing *DPYD* testing bringing it from a theoretical level nearer to real life.

Importance of Patient Experiences and Strategies for Acceptance

It was concluded that patient experiences are needed for implementing personalised preventive approaches, especially for developing sufficient and comprehensible information for all the parties involved.

During the discussion session following the presentations, participants explored potential strategies to enhance patient and professional engagement in PGx testing programs. They also examined the role that patients and professional organisations can play in increasing the acceptance of PGx testing.

Educational Resources

A central theme was the development of accessible, interactive educational resources aimed at patients and healthcare providers. For example, clear explanations about the types of genetic tests, their significance in treatment decisions, and the real-world benefits, such as improved outcomes and reduced adverse drug reactions, were highlighted as critical to building understanding. Public outreach campaigns were suggested to raise awareness about the benefits of PGx testing, such as its potential to avoid harmful side effects from medications.

Engaging Healthcare Professionals

Engaging healthcare professionals first was emphasised, as patient understanding and acceptance hinges on the readiness of HCPs to integrate PGx testing into practice. This could be achieved through targeted training programmes designed for clinicians, pharmacists, and other healthcare professionals.





It was also proposed that discussions about PGx testing be incorporated into regular health assessments or during diagnoses, normalising it as part of preventative care.

Guidelines and Protocols

Additionally, establishing clear guidelines and protocols for PGx testing is essential to ensure HCPs are equipped to integrate these tests into routine care effectively. Professional organisations can help standardise the clinical interpretation of PGx results and develop consistent guidelines. For example, aligning Biobank results with PGx recommendations and [European Medicines Agency \(EMA\) guidelines](#) could help reduce confusion and conflicts in the application of test results, thus increasing the acceptance and integration of PGx testing.

Role of Patient Organisations

Patient organisations were seen as key in helping patients navigate the healthcare system, understand test results, and reduce stigma or fear related to genetic testing through peer-support networks.

TRAINING PGX IN PRIMARY AND SECONDARY CARE

Box 5: Ron van Schaik, Erasmus Universiteit Rotterdam, the Netherlands

At Erasmus MC, PGx testing is performed since 2005. The turn-around time in general is 2-5 working days, and for *DPYD* testing specifically 48 hours. PGx tests are performed for the Netherlands as a whole and included 32,000 PGx test requests in 2024. A PGx pass was introduced in 2013 in Erasmus MC. The DPWG provides evidence-based dosing guidelines per genotype for over 60 drugs. The level of evidence is rated from 1 to 4 (RCT) and the clinical effect from A to F (death).

Regarding education of healthcare professionals, the strategy in the Netherlands is to train pharmacists first, since they have an important role in guiding therapy and giving advice to other HCPs in the Netherlands. Pharmacists are educated via education days, e-learning, and journals. Every pharmacist in the Netherlands has access to the PGx information and can therefore adjust the dose for the patient based on their PGx pass/PGx results. It is a national initiative, therefore, independent on the location of the Dutch pharmacy, you receive the same dosing advice. It is important that pharmacists are aware that they can find the PGx information in their computer system.

Secondary care specialists can be convinced of the value of PGx testing by evidence, for example the study by Hendricks et al., 2018 (18) showed that dose reduction results in decreased toxicity. Based on this study the EMA changed the SmPC and it was also included in the medical oncology guideline, raising uptake among secondary care specialists.

For primary care, it has been researched how many PGx tests performed at Erasmus MC are requested by General Practitioners (GPs). It turned out that 27% of tests were requested by GPs for 14% of patients, mostly for the drug clopidogrel. In general, GPs are enthusiastic about the potential of PGx and request a PGx test in reaction to side-effects or non-response. A few requests are made prior to therapy. This is according to the guideline for GPs ([‘NHG richtlijn’](#), 2018, updated November 2024). In 66% of the cases, a GP requests a panel test, which is useful for future medication dosing as well. PGx tests for patients are covered by insurance but patients still have to pay a part out-of-pocket (deductible), so for patients it is also better financially to choose for a broader panel once they get tested.

A survey among GPs showed several experienced barriers by GPs on PGx testing, including unclearness about when to test, costs for patients, lack of experience, unclearness about which test to request, unclearness about how to request tests, unclearness about how to interpret results, and doubt of clinical value (19). According to these results, there is value in educating GPs. Regarding the sources consulted by GPs with regard to PGx, pharmacists were mentioned mostly as the main source





(34%), followed by publications of the Dutch College of General Practitioners (NHG) (21%) and the website www.farmacogenetica.nl (17%). There are interactive courses developed for GPs. In addition, it is important to educate medical students, for example via Schola Medica: all new GPs in the Netherlands receive a full day training (lecture and workshop) in PGx as part of their education. Moreover, at Erasmus MC PGx is included in several master programs.

Also the general public and all stakeholders have to be informed, this is done via the website www.farmacogenetica.nl, Erasmus MC has a PGx helpdesk which answers all questions regarding PGx from the public and HCPs, congresses and symposia are organized, FTO meetings (GPs-pharmacists), and presentations about PGx are given at the Ministry of Health and insurance companies.

A [Farmacogenetica Profiel App](#) is developed, in which patients can access their pharmacogenetic DNA information directly on their phone after being tested in Erasmus MC. This initiative promotes patient empowerment and shared decision making.

Since there keeps on coming new information, it is important to keep on educating. Guidelines of CPIC and DPWG are regularly updated based on new knowledge. In order to be consistent within the Netherlands, a network of clinical PGx in the Netherlands is set up to yearly discuss the new guidelines and to discuss how every centre uses PGx. In that way, in the Netherlands PGx is performed in a uniform way as much as possible.

Pharmacists have guidance for 60 drugs and 18 genes (according to DPWG). Clinicians should not be overfed with information; therefore, it might be better to select certain genes for example for drugs used in first-line care.

There is attention from the government about the value of PGx in first-line care. Therefore, the P4Care consortium sent in a grant proposal.

FIRST IMPRESSIONS FROM ESTONIAN BIOBANK'S MY GENOME PORTAL

Box 6: Liis Leitsalu, University of Tartu, Estonia

The Biobank initiative My Genome Portal offers pharmacogenetic reports to Estonian Biobank's participants. The Biobank aims to collect health and genetic information, promote the development of genetic research, and improve public health. As stated in the Biobank legislation, the Biobank is allowed to recontact participants and participants have the right to be informed about research results. Around 20% of the Estonian population is a Biobank participant.

Over the years, phenotype data and omics data are generated via many research projects. All Biobank participants have genotype information available and return of results projects have been taken place. The most recent return of result project is My Genome Portal (2023). This portal is a user-friendly and secure platform for reports (offering personalised genetic results), education (improving genomic literacy), and research (providing a platform for research). The portal is a tool to conduct research projects rather than a research project in itself. The reports were registered as in-house devices, ensuring compliance while allowing the offering of pharmacogenetic results. For the development of the portal, feedback from early users was collected, and policymakers and HCPs were engaged via webinars. Moreover, videos were developed and integrated into the portal to educate participants on genetic results and their implications, and a helpdesk was established to provide quick support to portal users, addressing inquiries via email and phone.

In the initial phase, the portal included tailored insights across five domains, research findings, and educational resources on genetics. Before accessing personalised genetic information, participants must give consent, specify the type of information they want to view, agree or disagree to allow their information to be updated over time, and agree or disagree to be send alerts when information is updated, or new projects are added to the portal. Consents are saved and stored securely and are accessible to participants for review or updates.





Within the portal, participants are encouraged to update their health and lifestyle data to enhance risk prediction accuracy, participants can view the sources of their current data, and updated information is securely important into the biobank database with participant consent. The provided medications and recommendations follow the Clinical PGx Implementation Consortium (CPIC) guidelines.

Most users of the portal reported no regrets and expressed willingness to participate again. The majority was calm and content after receiving their results. However, a small subset of participants felt upset, primarily due to the lack of information they had hoped to receive. Most users found the balance between information and visual representation appropriate. Interactive tools and simple language were appreciated. Participants suggested including more personalised and detailed information on risk reducing recommendations. Some participants expressed confusion about how the portal connects to the broader healthcare system, e.g. how the information would reach physicians.

To improve the portal, the next steps are public communication to reach more participants and develop strategies to keep users engaged over time.

AN ACCOUNT OF PATIENT REPRESENTATION AND PATIENT VIEWS IN FINLAND

Box 7: Mervi Kaartoaho, Colores, Finnish Colorectal Cancer Association & Helena Kääriäinen, Finnish Institute for Health and Welfare, Finland

The aim of the *DPYD* case study in Finland was to evaluate the value of HIA (in addition to HTA) for appraisal of personalised preventive approaches in the healthcare. In order to do so, the THL-team invited several stakeholders, including one patient representative (Mervi), to form an Advisory Board. There was also indirect representation of patients via the presence of the Finnish Cancer Society representative. Mervi's started cancer treatments in 2017 at a time when *DPYD*-testing was not yet in the guidelines of oncology clinics, and it was performed only occasionally. Mervi was therefore not *DPYD* tested. On the second day after starting capecitabine, she experienced serious side effects which continued even after reducing the dose, leading to numerous breaks in the medications. According to the doctor, there was strong probability that Mervi would have died due to ADRs.

Mervi felt that it was very important to have (at least one) patient representative in the Advisory Board, since the voice of patients must be heard. She felt that her voice would have been heard if she had had any opposing opinions about the HIA process. She felt that the language/terminology was sometimes difficult but that did not seriously disturb her following the discussions. For the future, she suggests adding a family member (spouse, sibling) to this kind of HIA process.

In addition to Mervi's experiences, 6 CRC patients were interviewed about their experiences. All had fluorouracil or capecitabine or both, all had had side effects, most were unsure if they had had the *DPYD* test (they were treated at a time when testing was already widely used). If the test had been offered, 5/6 would have taken it. But if the testing had required postponing the medications for 1-2 weeks: 5/6 would have liked the medication to start immediately and then to be adjusted if needed. If the test had revealed high risk of serious side effects: 3 would have wanted normal treatment anyway and adjusting the dose if needed, the others would be uncertain or "let the doctor decide".

To conclude, having a patient representative involved in the HIA process brings the process from a theoretical level nearer to real life. Patient representation helps to understand that things like the seriousness of the adverse effects or the relevance of a delay of one or two weeks in starting cancer treatment are difficult for patients to understand. For appraisal of personalised preventive approaches, and even more for implementing them, a lot of patient experience is needed, especially for developing sufficient and comprehensible information for all the parties involved.





3.3. Session 3: (National) INTEGRATION

Next to evidence and acceptance for PGx testing, the actual integration of PGx testing in clinicians' workflows and in (inter)national regulations and policies are crucial. The last session encompasses therefore two panels addressing integration. The first panel focused on how the national context matters in assessing and implementing PGx. The theme for the second panel was (how) do policies matter in assessing and implementing PGx.

PANEL 1: HOW DOES THE NATIONAL CONTEXT MATTER IN ASSESSING AND IMPLEMENTING PGX?

National Context in PGx Implementation: Government support in Spain

Adrian Llerena (Universidad de Extremadura, Spain) discussed why PGx implementation in Spain is going well. In Spain every legal resident has the right to be genotyped for 65 drugs upon prescription. The clinical implementation in Extremadura (region in Spain) serves as a model, supported by national regulations, political decisions, government funding, and health policies and health providers facilitating the national implementation. Since the Spanish government decided that people have the right to get tested, the tests are also reimbursed, further advancing this model. While Spain has successfully implemented PGx testing, a key barrier identified was the ICT infrastructure, which complicates integration into healthcare systems across the country.

Integrating PGx in Routine Care: Real-Time Clinical Decision Support

Videha Sharma (University of Manchester, United Kingdom) pointed out that PGx is most effective when integrated into routine care through with real-time clinical decision support. A key challenge is embedding PGx results into existing systems to aid prescribing decisions. For this to work, results should be available within the prescriber's ICT systems, ideally as automated alerts or integrated information. This represents the core of clinical decision support: a digital tool delivering timely, evidence-based insights to enhance decision-making. Proposed solutions to overcome these barriers, include separating data from the application, tailoring results to healthcare professionals' needs, and storing data using open standards to facilitate integration.

Finland's Biobank Experience in Returning PGx Information

Markus Perola (University of Helsinki, Finland) presented Finland's experience with biobanks returning PGx information. He outlined the benefits of pre-emptive testing, mentioning that the implementation of PGx in Finland has been supported by cost-effective pre-emptive testing using Next-Generation Sequencing (NGS), alongside a strong patient consent model for receiving genetic data. However, national implementation faces barriers such as the integration of PGx data into electronic health records and ensuring consistent access to genetic results across the healthcare system.

Barriers and Facilitators in National PGx Implementation

The first panel showed several examples of facilitators and barriers to national implementation in general. One common lesson was that implementation goes beyond the test itself and involves broader service delivery, including barriers such as ICT integration, political agenda setting, and regulatory uncertainties. Facilitators included stakeholder engagement such as the involvement of pharmacists in the Netherlands and the presence of national and European guidelines. Public education and raising awareness about PGx testing are emphasised to ensure that existing





recommendations, such as those in the SmPCs (Summary of Product Characteristics) for healthcare professionals, are effectively translated and implemented. Furthermore, key topics included identifying the stakeholders responsible for various tasks and determining the next steps for effective integration.

(WHY) IS PGX IMPLEMENTATION IN SPAIN GOING WELL? WHAT ARE FACILITATORS?

Box 8. Adrian Llerena, Universidad de Extremadura, Spain

A roadmap about the steps of implementing PGx testing in Spain showed key initiatives regarding regulation by the European Medicines Agency (EMA) and the Spanish regulatory agency, politics/parliament, and health policies/health providers. Nationally, for the whole healthcare system, for 65 drugs and 12 genes it is obligatory to conduct PGx testing before prescription. 34% of drugs have genetic biomarkers in their summaries of product characteristics (SmPC). In Spain, 55 drugs have genetic biomarkers with information on drug choice, justifications, interactions, toxicity, efficacy, and ethnicity.

The strategy for implementation has been data-driven and aligned with regulatory recommendations. It is important to follow SmPC guidelines to implement PGx and to address these regulatory directives.

In 2023, the Spanish Ministry of Health created a committee with the 17 regional healthcare providers to establish national pharmacogenetic recommendations. The decision mandated the analysis of 12 genes prior to prescribing 65 drugs. This guideline applies to all legal residents in Spain, ensuring equal access to pharmacogenetic care. All 17 public healthcare providers agreed to these recommendations.

Later on a publicly accessible application was developed to assist doctors, pharmacists, and patients in identifying gene-drug interactions and recommended analyses based on ethnicity and clinical factors. Moreover, a database similar to the FDA Biomarkers Table was created in collaboration with the Spanish Drug Regulatory Agency offering detailed pharmacogenetic recommendations.

In parallel, clinical implementation studies took place. Ten years ago, in the Spanish region Extremadura, the universal implementation pioneers initiatives project was conducted. The project provides pharmacogenetic services for 1 million inhabitants, focusing on 65 drugs and analysing 12 genes based on the SmPCs of the drug regulatory agency. Clinical decision support is present as well as a PDF report that goes directly to the electronic medical record. Patients have also access to the results via their medical record.

There are four steps in the evaluation process; 1) clinical evaluation during which ADRs or efficacy failures are identified, 2) genotyping/ phenotyping, 3) pharmacovigilance evaluation, and 4) providing actionable reports to healthcare providers. Initial results include 7,000 patients, with findings indicating that 28% of patients had previous ADRs and in 40% of these patients changes in drug choices or associations or interactions were found.

A research initiative, called IMPACT, is a network which covers nearly 30 million inhabitants, aiming to translate PGx into routine clinical practice through research and real-world data validation. A comprehensive health technology assessment is planned to evaluate the clinical and economic impact of pharmacogenetic implementation. This is critical for demonstrating the value of PGx in improving patient outcomes and reducing ADRs.





FROM DATA TO ACTION – THE ROLE OF ICT AND CLINICAL DECISION SUPPORT IN REALISING THE POTENTIAL OF PGX

Box 9. *Videha Sharma, University of Manchester, United Kingdom*

In general, genomics will become increasingly routine in healthcare. The potential benefits for panel-based pre-emptive PGx are significant. These potential benefits are only realized if PGx is integrated in everyday care, such as real-time clinical decision support for prescribing decisions. A diagnostic service starts from selecting the patient, all the way through prescribing. The steps are: patient selection (who to test and when); test ordering (the operational process required to complete the test order and who is responsible); samples (how samples are taken and laboratory processes, including logistics and testing); receiving results (the process for sharing results and linking them with local systems and workflows); actioning results (who receives the results and is responsible for ensuring these are actioned); and prescribing (how prescriptions are altered and patients informed of decision-making). Actioning results and prescribing need to get more attention, since these aspects are not yet successfully translated.

(Example from the US: In the US a PGx panel was funded last year, however as of the first of January this funding is stopped due to the following reason: ‘the use of pharmacogenetic multigene panels (five or more genes) for the evaluation of drug-metabolizer status is unproven and not medically necessary for any indication due to insufficient evidence of efficacy’).

The challenge is not that the use of PGx multigene panels for the evaluation of drug metabolizer status is unproven, but the ability to impact prescribing is challenging. Supporting prescribing decisions is dependent on digital infrastructure and integration with existing systems, which is really hard. Therefore, research and infrastructure development should go in parallel to transition into a service that benefits patients.

A PGx result report only does not realize the benefits you hope to achieve. We need to move from data (raw genetic data) to actionable insights (PGx report) and next translate the insights into action (clinical decision support). Bridging the gap between insights to action is challenging because each genomic lab set up is independent (technology, bioinformatics, workflows); each health IT ecosystem is unique (EHRs, HIEs, data standards); and the majority of healthcare is now supported by IT solutions (legacy of ICT systems which might not be as modern). Genomic data has not been widely used in routine healthcare yet, which is actually an opportunity to think of a way of designing the genomic data infrastructure to support that use across care settings. Prescribing is the most common medical therapeutic intervention, and prescribing happens across all care settings (mostly primary care). PGx results must be available in existing clinical ICT systems, at the point of prescribing in the form of interruptive alerts to impact prescribing.

In order to do so, data should be separated from the application; instead of reports, results should be used and adjusted to the HCP; data should be stored in a structured format using open standards (openEHR/FHIR); we need to work with existing health IT suppliers but do not silo data in their applications (EPIC, Cerner, Chipsoft, etc.).

EXPERIENCES FROM FINLAND AND ITS BIOBANK IN RETURNING PGX INFORMATION

Box 10. *Markus Perola, University of Helsinki, Finland*

Finland's approach to integrating PGx into healthcare highlights several important findings. The study revealed that a significant portion of the Finnish population carries pharmacogenetically relevant genotypes, underlining the potential for personalised healthcare. At Helsinki University Hospital, real-





world data indicated that the most commonly prescribed drugs included ondansetron, warfarin, and antidepressants, with ibuprofen being prescribed to 25% of patients over a two-year follow-up. Moreover, over 20% of patients had actionable gene-drug pairs, and 60% of pharmacogenetically relevant prescriptions were linked to these interactions, emphasising the need for PGx in routine medical practice. The implementation of preemptive PGx testing, using a comprehensive Next-Generation Sequencing (NGS) panel, has been shown to be cost-effective, saving €17 per patient by reducing complications and improving drug efficacy. Since 2022, the hospital has made the NGS panel available to 10,000 patients annually, reducing the cost of testing to approximately €50, making it accessible for clinical use. Although patients can access their PGx data through personal health records, challenges remain in integrating this data into the hospital's electronic health record (EHR) system. Feedback from pilot studies returning actionable genetic results, such as for statin metabolism and breast cancer risk, showed that patients generally understood the results, though technical issues related to accessing data were the primary concern. Furthermore, under Finland's Biobank Law, clinically relevant genetic findings must be returned to participants, with a high level of interest in receiving such data. The ethical obligation to return actionable PGx information to biobank participants is emphasised, particularly as 95% of Finnish participants consent to receiving clinically relevant genetic results.

PANEL 2: (HOW) DO POLICIES MATTER IN ASSESSING AND IMPLEMENTING PGX?

Panel 2 focused on the role of policies in assessing and implementing PGx across Europe.

Role of Policies in Assessing and Implementing PGx

Carmen Laplaza Santos (European Commission, Belgium) highlighted EU funded initiatives, such as U-PGx and PROPHET, which aim to integrate PGx into clinical practice and improve drug prescribing efficiency. Americo Cicchetti (Università Cattolica del Sacro Cuore, Italy) discussed the challenges Italy faces due to its decentralised healthcare system and the need for regulatory reforms to synchronise drug approvals and genomic testing. Tessel Rigter (Amsterdam UMC & RIVM, Netherlands) stressed the importance of a shared national vision and clear frameworks for successful PGx implementation.

The Need for Coordinated Policies and Infrastructure Investment

The discussion stressed the need for coordinated policies at EU, national and regional levels with a focus on harmonised frameworks, and further investment in infrastructure (ICT) to effectively integrate PGx into healthcare systems. The importance of policies addressing the roles of pharmacists and physicians in PGx integration was highlighted.

Challenges in Policy Consensus and Transfer of Best Practices

A key challenge identified was the lack of consensus on the evidence required for policy decisions, indicating a need for alignment or discussion, as exemplified by the EMA workshop in September (20). Additionally, the transfer of best practices across nations, such as those initiated by HEcoPerMed, was seen as crucial to avoid starting from scratch and duplicating efforts.

Engaging Policymakers: Economic Impact of PGx

The panel discussed strategies to engage policymakers, focusing on the economic impact of PGx testing. Policymakers need to understand how PGx can contribute to cost savings and broader





economic priorities, such as competitiveness and productivity. It was suggested that finance ministers should be involved in the conversation, as economic growth can sometimes take precedence over health priorities in policymaking.

Prioritising Drug Overuse and ADRs for Policymakers

The importance of addressing drug overuse and adverse drug reactions (ADRs) was also discussed, with, for instance in Spain, healthcare managers emphasising the escalating number of ADRs over the past decade. The Spanish parliament was encouraged to focus on how PGx can help reduce these issues while saving costs.

EU POLICIES ON PGX, RESEARCH VERSUS CARE BUDGETS

Box 11. *Carmen Laplaza Santos, Head of Unit Health Innovations and Ecosystems at European Commission, Belgium*

The European Commission has been pushing for research and innovation in personalised medicine (PM) and PGx, funding projects such as U-PGx and initiatives in collaboration with the pharmaceutical industry. While many projects have been supported, the key challenge remains ensuring real-world impact, as funders seek to move beyond research towards tangible healthcare benefits.

National policies on PM and PGx are advancing, often driven by motivated individuals, visionaries, or policymakers who recognise the need for change. Romania has enshrined PM into law, ensuring universal access, and also Spain has made significant strides in PGx implementation. PM remains a strong priority on the policy agenda, with three consecutive EU presidencies dedicating events to its development. Key initiatives such as the One Million Genomes project and PGx working groups are expanding sequencing capacities across Europe.

To further drive progress, the PROPHET project was funded as part of Horizon Europe, aiming to address the full innovation cycle and accelerate the implementation of PM. The Commission recognises that despite existing evidence, PGx adoption can be slow, with healthcare systems often “turning in circles.” PROPHET was established to help bridge this gap by providing actionable recommendations that support the integration of PGx into clinical practice.

A major focus is reducing inefficiencies and waste in healthcare, particularly in drug prescribing. Many patients receive medications that are either ineffective or cause severe side effects, leading to avoidable hospitalisations and additional costs. PGx offers a solution by enabling more precise prescribing, ensuring that patients receive the right medication at the right dose from the start. The Commission stresses that these inefficiencies are not only a clinical issue but also a financial one, making it essential to engage policymakers and finance ministers. By optimising drug prescribing, resources can be allocated more effectively, contributing to more sustainable and resilient healthcare systems.

The next phase of PGx implementation will require a full innovation cycle, ensuring its integration into healthcare systems. The Commission sees this as an opportunity to optimise resources, reduce inefficiencies, and improve health outcomes, while maintaining a sustainable and competitive healthcare sector in Europe.

For the next five years, the Commission’s focus will be on:

- Preventing non-communicable diseases (NCDs) and increasing sequencing capacity in Europe
- Raising awareness among patients and citizens to drive acceptance and adoption
- Strengthening Europe’s competitiveness in the biotech and life sciences sectors
- Ensuring resilience and sustainability, with a focus on “greening” healthcare by reducing waste from ineffective prescriptions





- Addressing ethical concerns, particularly the issue of prescribing unnecessary drugs while patients face shortages of essential medications

HEALTH PLANNING IN THE FIELD OF PGX

Box 12. *Americo Cicchetti, Università Cattolica del Sacro Cuore (UCSC), Italy*

The integration of PGx into European healthcare systems requires a coordinated approach across policy, regulation, and clinical practice. The structural and policy challenges in implementing PGx are evident in Italy's decentralised healthcare system, where 21 autonomous regional health bodies operate independently, leading to disparities in resource distribution and service provision. While the national core benefit package, known as "Livelli Essenziali di Assistenza" (LEA), aims to standardise services, regional execution remains inconsistent, affecting equitable access to pharmacogenomic advancements.

Italy has developed a structured model for evaluating and prioritising healthcare innovations. The Italian National Drug Agency (AIFA) assesses drugs, medical devices are reviewed through a national health technology assessment (HTA) framework, and genetic testing undergoes evaluation by the National Committee using HTA reports. However, these evaluations occur in isolation, creating a fragmented system that disrupts the synchronisation of pharmacogenomic drug approvals with genomic testing. This results in delays, inconsistencies, and disparities in patient access. While AIFA determines the reimbursement of molecular targeted drugs, genomic testing is regulated separately. Some regions fund these tests through national or regional budgets, whereas others depend on research funding, exacerbating inequalities in availability.

Efforts are underway to reform regulatory mechanisms by allowing AIFA to evaluate both targeted drugs and their companion diagnostic tests simultaneously. This shift is expected to streamline decision-making, accelerate availability, and reduce regional disparities. However, such changes require adaptations to HTA models to ensure that drugs and tests are assessed as integrated interventions. Additionally, economic evaluation frameworks must evolve to account for their combined costs and benefits.

Collaboration and knowledge exchange across Europe are essential for the successful integration of PGx into healthcare systems. A harmonised approach that standardises regulatory frameworks and ensures economic sustainability will be crucial. By sharing best practices, European healthcare systems can improve equitable access to PGx, ultimately enhancing patient outcomes and advancing personalised medicine.

WHAT INFORMS CURRENT GOVERNMENT POLICIES ON PGX IN THE NETHERLANDS?

Box 13. *Tessel Rigter, AmsterdamUMC & RIVM, the Netherlands*

The Netherlands has made an effort to get the topic of PGx on the national agenda. In 2021, the Dutch Ministry of Health commissioned a [field consultation](#) on integrating DNA technology, including PGx, to guide policy decisions. This led to further parliamentary studies in 2022, including an assessment of a PGx passport and a call for the development of a national DNA programme.

Stakeholders identified uniform PGx implementation as a key opportunity, particularly in psychiatry and oncology. However, critical requirements include a shared vision, uniform guidelines, reimbursement policies, increased professional training, and structured data infrastructure. While early implementations in hospitals show promise, the absence of systematic data registration creates





inefficiencies. The lack of a national framework for recording and sharing pharmacogenomic data makes processes time-consuming and inconsistent, complicating clinical decision-making.

The Minister of Health concluded that large-scale implementation is premature due to insufficient evidence on cost-effectiveness and clinical benefits. Key barriers include governance challenges, unclear leadership roles, cost-effectiveness uncertainty, and limited professional knowledge. The Minister suggested PGx may require re-evaluation in the future, leaving further initiatives to the field. Despite challenges, promising developments are emerging. Studies, including those published in *The Lancet*, highlight PGx potential to reduce side effects and improve patient outcomes (17). Ongoing pilot studies show positive participant experiences, empowering patients and enhancing medication compliance. If scaled effectively, these pilots could provide insights into the broader integration of PGx within Dutch healthcare.

To address limitations, national funding initiatives support research in personalised medicine and PGx, focusing on validated pharmacogenetic passports and cost-effectiveness analysis. Moving forward, key steps include defining clear responsibilities at the national level, developing a financial framework for integration, expanding professional training, and promoting further pilot studies. While a comprehensive implementation strategy is yet to be defined, ongoing efforts in data infrastructure and pilot projects indicate gradual progress.

Collaboration and knowledge exchange across Europe remain crucial to overcoming PGx adoption challenges. A harmonised regulatory framework and sustainable economic model are essential to ensuring equitable access and optimising patient outcomes through personalised medicine.





3.4. Roundtable discussion. What do stakeholders need for sustainable integration of PGx in healthcare systems

This roundtable examined key challenges, stakeholder roles, and policy actions needed for the sustainable integration of PGx at national and EU levels. Five themes were discussed, sometimes supported by the use of Menti-Metre.

3.4.1. Key Challenges in implementing pharmacogenetics at the national level

Seventeen participants responded to a question via Menti-Metre to identify challenges in implementing PGx at a national level. A word cloud generated from the responses highlighted *reimbursement, policy and ICT integration* as the most frequently mentioned challenges, followed by *education, funding and equity of access*. Below is a synthesis of insights drawn from the discussions when participants were asked to explain their choices.



Figure 3: Word Cloud generated from interactive discussions on the Menti-Metre platform.

Key challenges in implementing PGx at the national level include **insufficient reimbursement frameworks**, which hinder adoption despite the potential for financial incentives. However, reimbursement alone does not guarantee uptake, as seen in Italy, where fully reimbursed DPD testing remains underutilised due to organisational, educational and policy gaps presenting a significant barrier.

The lack of **clear, consistent policies** around PGx testing impedes its widespread integration into healthcare systems. Additionally, **education gaps** among physicians, pharmacists, patients and policymakers and a lack of awareness about PGx further limit its implementation. Many healthcare professionals lack the training to interpret PGx data or understand its clinical applications, creating a gap in capacity. The **absence of interoperable ICT systems and inconsistent data standards** obstruct seamless integration of PGx information. Securing sustainable **funding** also remains a challenge, as robust **health economic evidence** is needed to justify investment. Finally, **equity of access** is a concern,





with high costs and lack of reimbursement creating disparities, limiting access to those who can afford it.

3.4.2. Priorities for Advancing the Implementation of Pharmacogenetics

Experts were asked via Menti-Metre to identify their top three priorities for accelerating the implementation of PGx in healthcare. The responses highlighted five key areas that require targeted action (Figure 4).

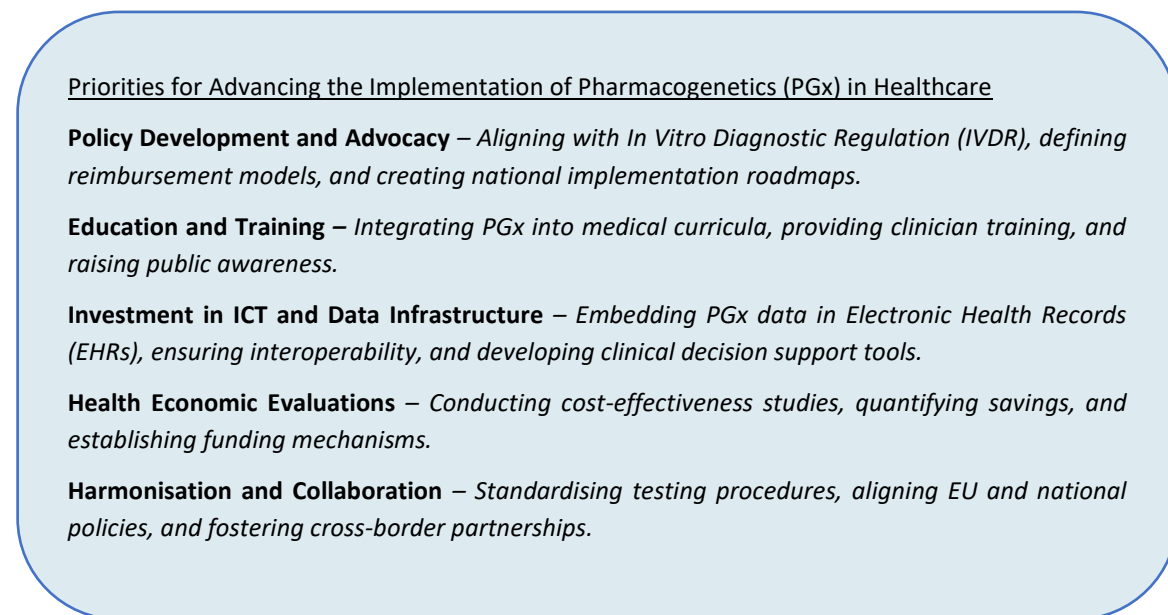


Figure 4: Five key priorities for advancing the implementation of pharmacogenetics (PGx) in healthcare.

1. Policy Development and Advocacy

Establishing clear regulatory guidelines is crucial for PGx implementation, particularly in alignment with the In Vitro Diagnostic Regulation (IVDR), which sets requirements for test validation, quality assurance, and clinical application. There is a need for well-defined reimbursement models that specify which PGx tests are covered, under what conditions, and for which patient populations, ensuring financial sustainability. Additionally, national PGx implementation roadmaps should be developed, detailing how testing is incorporated into routine care, which institutions oversee the process, and how compliance is monitored. Without a structured policy framework, PGx risks remaining a niche practice rather than becoming standard care.

2. Education and Training

A lack of awareness and training among healthcare professionals remains a major barrier to PGx implementation. To address this, PGx education should be integrated into medical, pharmacy, clinical pharmacology and nursing curricula to ensure that future healthcare providers are equipped to interpret and apply genomic data in prescribing decisions. Continuing professional education programmes, including case-based learning and certification courses, should be developed for clinicians already in practice. In parallel, public awareness campaigns are essential to educate patients on the benefits of PGx, the availability of testing, and the implications of genetic results on medication safety and effectiveness. Without widespread education, the clinical utility of PGx may not be fully realised, limiting its impact.





3. Investment in IT and Data Infrastructure

The successful implementation of PGx relies on the integration of genetic data into healthcare systems. Electronic Health Records (EHRs) must be adapted to securely store and retrieve PGx information, ensuring that genotype-specific drug recommendations are automatically available to prescribers. Developing interoperable digital platforms that enable secure data exchange across healthcare settings is essential, particularly in line with GDPR and other data protection regulations. In addition, automated clinical decision support tools should be incorporated into prescribing systems, providing real-time, guideline-based recommendations for PGx-informed medication choices. Without a robust IT infrastructure, PGx risks being underutilised due to practical barriers in accessing and applying genomic data at the point of care. Furthermore, there is a substantial risk of unnecessary re-testing if data are not shared throughout the entire healthcare chain.

4. Health Economic Evaluations

Demonstrating the cost-effectiveness of PGx is essential for securing funding and widespread adoption. Large-scale studies should be conducted to quantify the impact of PGx on reducing adverse drug reactions, hospital admissions, and treatment failures. Economic models comparing PGx-guided prescribing to standard practices will help illustrate the long-term cost savings for healthcare systems. Establishing national funding mechanisms, including coverage through public and private insurance schemes, will be key to ensuring that PGx testing is financially viable. Without clear economic evidence, policymakers and insurers may be reluctant to prioritise PGx, limiting its accessibility for patients.

5. Harmonisation and Collaboration

A fragmented approach to PGx implementation across Europe presents challenges in standardisation and scalability. To address this, testing procedures, laboratory processes, and reporting frameworks should be harmonised to ensure consistency and reliability. Collaboration between national and EU-level stakeholders is needed to align regulatory requirements, share best practices, and streamline market access for PGx tests. Establishing joint procurement initiatives could reduce costs and improve availability by coordinating purchasing agreements between health ministries, hospitals, and industry stakeholders. Without cross-border collaboration, PGx risks remaining unevenly implemented, leading to disparities in patient access and healthcare quality.

By addressing these priorities, policymakers, healthcare providers, and researchers can accelerate the systematic and sustainable integration of PGx into healthcare. A coordinated effort will be essential to ensure that PGx transitions from an emerging innovation to a standard component of personalised medicine across Europe.

3.4.3. Enhancing Uniform Data Collection of Key Indicators to Promote Equitable Pharmacogenomics Policies Across Europe

To address how to improve and promote the collection of high-quality data, the collection of uniform key indicators across Europe for equitable PGx policies is recommended. Key indicators are critical factors to monitor policy impact on clinical practice, patient safety, and outcomes, such as: number/percentage of colorectal cancer (CRC) patients undergoing fluoropyrimidine (FP) treatment, severe toxicity rates, number of *DPYD* tests performed, and number of training activities on *DPYD* utility. The following approaches can enhance data collection and standardisation:

1. Leverage Existing Electronic Data Systems

Identify and utilise routine data collection systems (e.g., cancer registries) to avoid duplication. Collaborate with health IT providers (e.g., Epic) to electronically extract and standardise data using





formats like Observational Medical Outcomes Partnership (OMOP). As most countries already collect data electronically, hence, the focus should be on identifying data collectors and ensuring structured, digital utilisation, building on existing systems for efficiency and consistency.

2. Promote Data Aggregation and Integration:

Encourage cross-country data aggregation to enable large-scale analysis and comparison of data. Integrate real-world data with research efforts like conducting pilots to enhance accessibility and utility.

3. Enhance Collaboration Between Ministries:

Improve coordination between ministries (e.g., HTA and HIA) and align data collection efforts at the European level to ensure uniformity and elevate political prioritisation.

4. Monitor Progress:

Regularly surveys in e.g. labs to track changes over time in PGx practices and adherence to EMA guidelines across different countries.

5. Develop Country-Specific Strategies:

Address structural differences in data collection by creating tailored strategies for each country, ensuring protocols for standardisation and quality control, especially for recent data (less than three years old).

3.4.4. National level: Who needs to do what? / Stakeholder Activation for Pharmacogenetic Testing Implementation

The successful implementation of pharmacogenetic testing relies on the active engagement of key stakeholders, including healthcare professionals, patients (representatives), policymakers, and citizens. Experts identified which stakeholders should be involved and how they can contribute to its assessment and adoption. Increasing attention is being given to the role of citizens, patients, and individuals as champions, fostering awareness, acceptance, and informed decision-making.

To develop the PROPHET framework national steering committees have been set up to perform HIAs on the various PP case studies, which helped to identify and connect key stakeholders. Lessons from National Contexts include:

- **Portugal:** Strong awareness and enthusiasm among healthcare professionals and patients stem from participatory initiatives. **Steering committees as initiated for developing the PROPHET framework** have proven effective in assessing developments and incorporating stakeholder insights, a model that could be applied elsewhere.
- **Italy:** Engagement has been challenging due to clinician overrepresentation, limiting input from patient groups. **Multidisciplinary teams** are needed to ensure balanced decision-making and inclusive policy development.

At the workshop **two examples were discussed on national biobanks exemplifying ways to gauge participants' experiences**

- **Estonia & Finland:** Experiences from the biobanks illustrate how **citizen participation** enhances pharmacogenetic initiatives. Patient experiences offer critical insights into real-world applications, supporting more patient-centred policies. Patients can contribute by





sharing their experiences with pharmacogenetic testing and its impact on their care, thus offering valuable insights into how individuals use and perceive pharmacogenetic information.

3.4.5. Policy Support for Pharmacogenetics in Healthcare at National and EU Levels

The implementation of PGx varies across Europe due to differences in national regulations and political decisions.

At the EU level, the European Medicines Agency (EMA) plays a key role in supporting PGx integration. Regulatory mentions, such as those for *DPYD*, can drive adoption without imposing strict measures or rigid mandates. Including pharmacogenetic guidelines in drug labels, as seen with DPWG and CPIC, would further support implementation. However, there is uncertainty about which organisation should lead international efforts.

However, regulatory heterogeneity across Europe presents challenges as national policies differ significantly. In the UK, PGx tests are classified as genetic tests and subject to strict regulations (e.g. can only be done by the academic hospitals). In the Netherlands, they are treated as chemical tests with fewer restrictions, affecting who can conduct them. In Spain, political decisions play a major role in shaping implementation.

The EU In Vitro Diagnostic Regulation (IVDR) (21) adds another layer of complexity, providing structure and setting stricter requirements for PGx testing, which may impact access and uptake across countries. A coordinated EU and national strategy are essential to balance regulation with practical implementation in healthcare.

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References

1. Pastorino R, Pezzullo AM, Osti T, Adany R, Borry P, Barnhoorn F, et al. The PROPHET project paves the way for personalized prevention in the future healthcare. *Eur J Cancer Prev.* 2024;33(5):387-9.
2. Haga SB, Burke W. Using pharmacogenetics to improve drug safety and efficacy. *JAMA* 2004(1538-3598 (Electronic)).
3. Wu A, Raack EJ, Ross CJD, Carleton BC. Implementation and Evaluation Strategies for Pharmacogenetic Testing in Hospital Settings: A Scoping Review. *LID* - 10.1097/FTD.0000000000001243 [doi]. *Therapeutic drug monitoring.* 2024(1536-3694 (Electronic)).
4. Proposal for a regulation amending, as regards pharmacovigilance of medicinal products for human use, (2008).





5. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *Bmj*. 2004;329(7456):15-9.
6. Osanlou R, Walker L, Hughes DA, Burnside G, Pirmohamed M. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. *BMJ Open*. 2022;12(7):e055551.
7. Parameswaran Nair N, Chalmers L, Bereznicki BJ, Curtain CM, Bereznicki LR. Repeat Adverse Drug Reaction-Related Hospital Admissions in Elderly Australians: A Retrospective Study at the Royal Hobart Hospital. *Drugs Aging*. 2017;34(10):777-83.
8. Hartholt KA, van der Velde N, Looman CWN, Panneman MJM, van Beeck EF, Patka P, et al. Adverse Drug Reactions Related Hospital Admissions in Persons Aged 60 Years and over, The Netherlands, 1981–2007: Less Rapid Increase, Different Drugs. *PLOS ONE*. 2010;5(11):e13977.
9. Roden DM, McLeod HL, Relling MV, Williams MS, Mensah GA, Peterson JF, et al. Pharmacogenomics. *Lancet* (London, England). 2019;394(10197):521-.
10. Thorn CF, Klein TE, Altman RB. PharmGKB: the Pharmacogenomics Knowledge Base. *Methods Mol Biol*. 2013;1015:311-20.
11. Rigter T, Jansen ME, de Groot JM, Janssen SWJ, Rodenburg W, Cornel MC. Implementation of Pharmacogenetics in Primary Care: A Multi-Stakeholder Perspective. *Front Genet*. 2020;11:10.
12. Haidar CE, Crews KR, Hoffman JM, Relling MV, Caudle KE. Advancing Pharmacogenomics from Single-Gene to Preemptive Testing. *Annual review of genomics and human genetics*. 2022;23:449-73.
13. Jørgensen JT. Predictive biomarkers and clinical evidence. *Basic & Clinical Pharmacology & Toxicology*. 2021;128(5):642-8.
14. Holland M. digitalMLPA [Available from: <https://www.mrcholland.com/technology/digitalmlpa>.
15. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance), (2021).
16. Health Economic Models for Personalised Medicine: HEcoPerMed; n.d. [Available from: <https://hecoopermed.eu/>.
17. Swen JJ, van der Wouden CH, Manson LEN, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *The Lancet*. 2023;401(10374):347-56.





Appendix 1: Participant Handout



a PeRsOnalized Prevention roadmap
for the future HEalThcare



Amsterdam UMC



Instituto
de Salud
Carlos III



UNIVERSITÀ
CATTOLICA
del Sacro Cuore



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Participant Handout: PROPHET Expert workshop pharmacogenomics

INTEGRATING PHARMACOGENOMICS INTO HEALTHCARE SYSTEMS

Comparing DPYD Testing & PGx Pass

Logistics

Date: Tuesday, 21st January 2025, 10:00–17:00 CET

Location: Amsterdam University Medical Centre (location VUMC),

Changed location: polikliniek (outpatients building) [De Boelelaan 1117, 1081 HV Amsterdam](#), see also Campus [Map](#). Take the elevator after the reception on your right hand side, sixth floor: **Room PK 6X 206**, or join online:

Microsoft Teams [Join the meeting](#) Meeting-id: 323 979 262 199 Password code: aW6D3iz2

We ask your consent to record the session to prepare a Report for the EU as Deliverable for the PROPHET project. We will summarise presentations and the discussions as part of this report.

Thank you for your time and participation in this workshop drawing upon your expertise and insights on integrating pharmacogenomics (PGx) into healthcare systems.

Purpose

This workshop is part of the PROPHET project: [a Personalised Prevention ROadmap for the future HEalThcare](#). The PROPHET project is an European wide collaboration to create a roadmap based on a strategic research and innovation agenda, with input from a broad range of stakeholders, to help implement personalised prevention. Pharmacogenomics is one of its case studies.

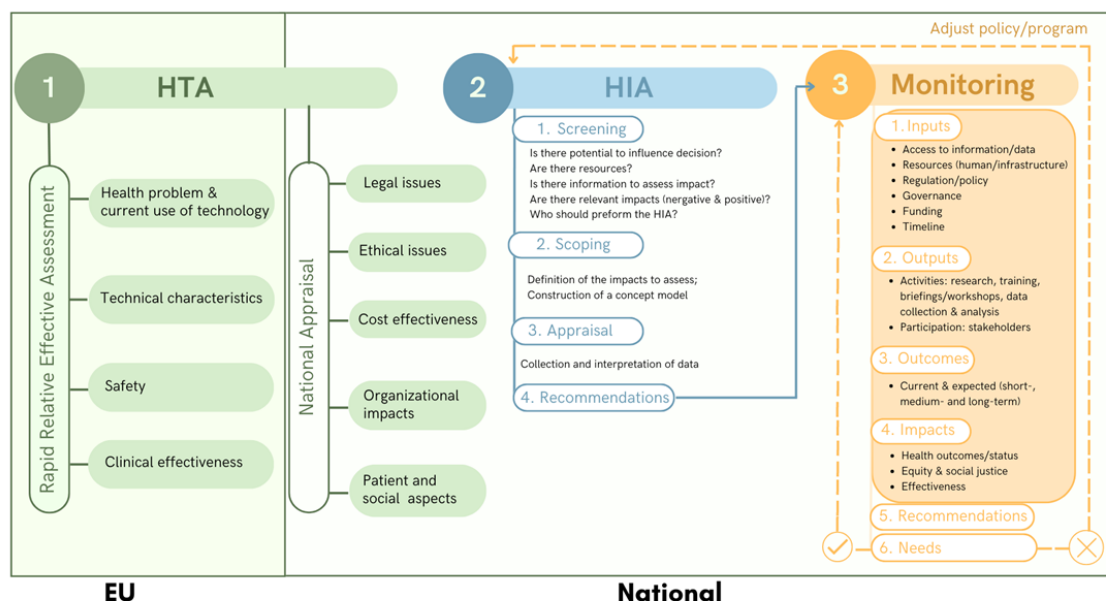
The PROPHET project is developing an assessment framework for implementing pharmacogenomics combining three pillars: health technology assessment (HTA), health impact assessment (HIA) and monitoring (see Figure 1):

HTA regarding the *international/EU* context (e.g. scientific evidence and regulation), as well as regarding the *national* context and indicators (cost-effectiveness, organisational aspects, education and





acceptability for health care professionals and patients as part of Ethical Legal and Social Issues). **HIA** is proposed as an additional layer addressing broader societal impact and (health) equity, by including various disciplines and target groups (e.g. patients) into assessments of impacts on patients, health services and their organisation (e.g. lab performance) and health systems. HIA may be used prospectively to support decision making or retrospectively as an outcome evaluator. **Monitoring** is important to ensure that the policy is actually working (e.g. establishing indicators, such as proportion of *DPYD* tests performed, coverage of education for healthcare professionals).



Source: Deliverable 3.2 *The PROPHET Framework for appraisal of personalised preventive approaches*

The workshop brings together stakeholders such as pharmacists, researchers and policymakers. The aim of the workshop is to discuss stakeholders' experiences and challenges regarding integrating pharmacogenomics into health systems, guided by the PROPHET framework, so policymakers are better equipped to design evidence-based policies in close collaboration with relevant stakeholders. The workshop aims to contribute to guidance for policymaking and stakeholder engagement specifically based on comparing two case studies: *DPYD* testing and a PGx pass.

These two applications represent two different stages of implementation: *DPYD* testing is based on evidence, supported by guidelines and widely implemented in healthcare systems. While clinical utility and cost-effectiveness are being established for a PGx pass, implementation of such a pass is still in early stages. PGx testing for *DPYD* is companion diagnostics and is performed as a single-gene test. In contrast, PGx testing to generate a PGx pass is performed pre-emptively for multiple genes at once. Barriers and facilitators for implementing might differ for *DPYD* testing and the PGx pass respectively and therefore experiences on overcoming challenges can be compared.

In this workshop we will ask a broad range of speakers to share their experiences and include some of the following aspects:

-What are the **roles/needs of (a specific) stakeholder(s)** you want to emphasize given the (inter)national context: e.g. who collects information for assessment, who has authority to influence agendas and priorities for implementation, who oversees the monitoring, (policy) priorities for who should do what?





-(How) are **structural or cultural aspects** (in your country or healthcare system – e.g. publicly funded) relevant to assessment or implementation of PGx (e.g. connections with research/biobank, proactive innovation policies, laws regarding patient information, ICT infrastructure, resources, et cetera)

Objectives of the workshop

- Strengthen capacity for PGx testing implementation among policymakers and health authorities
Lay the groundwork for adopting the PROPHET framework for assessment of pharmacogenomics (with a focus on *DPYD* testing and PGx pass) in different health systems

Appendix 2: Background Deliverable 3.2.

Background Deliverable 3.2. - Developing a HIA for personalised prevention

In the PROPHET project case studies have been conducted to develop and test the HIA framework tailored to personalised prevention policies based on genetic information. *DPYD* Testing was used to develop the framework, while the PGx pass, and *BRCA*-related breast cancer were used to validate the framework. The case study on breast cancer will not be discussed in this appendix 2. These case studies aim to explore how HIA can be adapted to address the specific challenges and opportunities presented by genomic technologies, providing actionable insights into their implementation and long-term impacts.

For each case study in the participating countries (Finland, Italy, and Portugal), the process of performing a HIA followed a structured approach. In the first *screening* phase, national technical teams were formed, with responsibilities that included designing project specifics according to country practices, collecting data, organising and inviting experts to join the steering committee. These steering committees included representatives from national cancer registries, patient groups, medicine agencies, regulators, clinicians, pharmacists, and laboratory experts, ensuring inclusivity and diverse perspectives. In this *scoping* phase the activities were planned, and a conceptual framework was made to guide the analyses.

A common protocol was designed for the case studies, with three main perspectives considered:

1. The patient perspective: including the impact of *DPYD* genotyping or PGx pass on morbidity and mortality of patients, with a focus on equity.
2. The organisational perspective: The acceptability of healthcare professionals and laboratory staff regarding *DPYD* genotyping and the PGx pass.
3. The healthcare system perspective: the economic impact of *DPYD* genotyping and the PGx pass.

Subsequently, the core activity of the HIA consisted of *appraisal* in the assessment phase. For the case studies data was collected and analysed by using literature review, Markov models, and stakeholder consultations including surveys and interviews of experts and patients. The HIA on the case studies, their analyses and subsequent *recommendations* were compiled in a report that was submitted to the EU.

Not included in this Deliverable was the *monitoring phase*, that would need to be performed after





implementation. In the following sections we will summarise the case studies performed for Deliverable 3.2 of the PROPHET project.

HIA Case Study: DPD Testing and DPYD Genetic Variants

Deficiencies in the DPD enzyme, caused by variants in the *DPYD* gene, can lead to severe adverse reactions to cancer treatments like fluoropyrimidines. Although the European Medicines Agency (EMA) recommends *DPYD* testing before using these drugs, no country has implemented a national policy, though sometimes national guidelines are available such as in Finland. This lack of policy made *DPYD* testing a valuable case study for a Health Impact Assessment (HIA) within Deliverable D 3.2. The study focused on Finland, Italy, and Portugal. Not all relevant data was available, and for some aspects additional research, such as consultations or surveys, needed to be performed.

Key findings:

- **Patient Impact:** In Portugal, baseline mean prescription rates were found to be 78.3% and similar results were estimated in Italy (70% prescription rate) and Finland (95% prescription rate). Systematic *DPYD* testing reduced severe toxicity and mortality. In Finland *DPYD* genotyping is offered nationwide as part of a pharmacogenetic panel. In this case study equity was considered by mapping regional differences and different hospital sizes and public vs. private sector institutions to address disparities in healthcare access and outcomes. In countries with a high uptake of *DPYD* testing, such as Finland, regional disparities may be less problematic.
- **Organisational Impact:** In Portugal, prescription rates were influenced by factors such as type (private vs. public) and size of institution, test turnaround time, existing *DPYD* testing protocols in place. Acceptability among oncology physicians and laboratory technicians was high and some identified challenges included workflow inefficiencies and capacity constraints impacting turnaround time. In Finland, *DPYD* genotyping is seen by many physicians as a valuable tool for modifying chemotherapy dosages to prevent ADRs, recognising its clinical value and demonstrating confidence in its application.
- **Economic Impact:** Through extensive literature reviews, the systematic *DPYD* testing was found to be cost-effective, enhancing patient safety and optimising healthcare resource use.

The recommendations from the study highlight the need for the development of national guidelines to address regional disparities in *DPYD* testing and ensure equitable access to care. It is essential to improve access to data to enhance the quality of genetic testing and decision-making in healthcare settings. Additionally, training healthcare professionals, particularly oncologists and laboratory staff, is crucial to ensure that they are well-informed and motivated to implement genetic testing effectively. Optimising healthcare workflows, including reducing inefficiencies and workload burdens, will also help improve the overall success of *DPYD* testing implementation. Furthermore, establishing robust monitoring will be key to assessing the impact of these measures and ensuring continuous improvement in patient care and healthcare delivery.

HIA Case Study: PGx pass

The pharmacogenetic passport or pass offers personalised treatment based on genetic variants, improving drug safety and efficacy. This second case study within PROPHET Deliverable 3.2. on the PGx passport is intended to validate and refine the PROPHET framework. This included conducting a Health





Impact Assessment (HIA) to evaluate its implementation in Italy. This case study assessed the impact on health regarding effectiveness as established in the PREPARE study, and conducted literature studies on patient acceptance, organisational feasibility and barriers, and cost-effectiveness. Since real-world implementation data is scarce, consultations with stakeholders have been essential in shaping the approach and informing the recommendations. Policy surrounding implementation of PGx panel testing is critical to ensure widespread adoption and accessibility. Based on the Italian case study, recommendations for implementing the pharmacogenetic passport were drafted emphasising targeting high-risk populations such as the geriatric populations and oncology patients. It calls for integrating genetic data into the healthcare infrastructure, with secure digital health technologies, standardised testing protocols, and centralised data management. A phased approach, starting in primary care, hospitals, and residential settings, is advised for broad adoption. Education and training for healthcare professionals, alongside public campaigns, will be key in promoting understanding and trust. Policy development should include national guidelines, reimbursement frameworks, and pilot programs to demonstrate feasibility. Ethical and equity concerns, such as data privacy and access for vulnerable populations, must be addressed to ensure fair and effective implementation.

Appendix 3: Program Outline

Program outline

PROPHET Expert workshop pharmacogenomics: Integrating Pharmacogenomics into healthcare systems

Comparing *DPYD* Testing and PGx Pass

10:00	Welcome and introduction
10:00-10:05	Introduction to PROPHET Project <i>Stefania Boccia, Università Cattolica del Sacro Cuore (UCSC), Italy</i>
10:05-10:30	Introduction to PROPHET Framework <i>Astrid Vicente, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal</i>
10:30	Session 1: EVIDENCE (<i>DPYD</i> Testing and PGx pass)
10:30-10:45	Evidence for PGx panel testing as basis for implementation <i>Jesse Swen, Universiteit Leiden, the Netherlands</i>
10:45-11:00	Implementing Pharmacogenomic Guided Prescribing in the NHS – Creating a Scalable and Interoperable Solution <i>John McDermott, University of Manchester, United Kingdom</i>
11:00-11:15	HTA for Pharmacogenetics, what should be on the agenda? <i>Maureen Rutten, Erasmus Universiteit Rotterdam, the Netherlands</i>
11:15-11:30	<i>DPYD</i> testing in SmPC: EU regulation versus national context <i>Marc Maliepaard, Medicines Evaluation Board (MEB) and European Medicines Agency (EMA), the Netherlands</i>





11:30-12:00 Discussion: From HTA to HIA, international versus national context, what (more) information do we need for implementation, and how do we organize obtaining that information?
Angelica Valz Gris, Università Cattolica del Sacro Cuore (UCSC), Italy

12:00 Lunch break

12:45 Session 2: ACCEPTANCE (DPYD Testing and PGx pass)

12:45-13:00 Training PGx in primary and secondary care
Ron van Schaik, Erasmus Universiteit Rotterdam, the Netherlands

13:00-13:15 First impressions from Estonian Biobank's MyGenome Portal
Liis Leitsalu, University of Tartu, Estonia

13:15-13:25 An account of patient representation and patient views in Finland
Mervi Kaartoaho, Colores, Finnish Colorectal Cancer Association
Helena Kääriäinen, Finnish Institute for Health and Welfare, Finland

13:25-13:45 Discussion: How to engage patients and professionals? What role can patient and professional organisations play?
Carla van El, AmsterdamUMC, the Netherlands

13:45 Coffee break

14:00 Session 3: (National) INTEGRATION (DPYD testing and PGx pass)

Panel 1: How does the national context matter in assessing and implementing PGx?

14:00-14:10 (Why) is PGx implementation in Spain going well? What are facilitators?
Adrian Llerena, Universidad de Extremadura, Spain

14:10-14:20 From data to action – the role of ICT and clinical decision support in realising the potential of PGx
Videha Sharma, University of Manchester, United Kingdom

14:20-14:30 Experiences from Finland and its biobank in returning PGx information
Markus Perola, University of Helsinki, Finland

14:30-14:45 Discussion: Given barriers and facilitators, which stakeholders need to be engaged; what information is lacking, and who is responsible for the next steps of gathering information for assessment and implementation?
Tessel Rigter, AmsterdamUMC & RIVM, the Netherlands





Panel 2: (How) do policies matter in assessing and implementing PGx?

14:45-14:55	EU policies on PGx, research versus care budgets <i>Carmen Laplaza Santos, Head of Unit Health Innovations and Ecosystems at European Commission, Belgium</i>
14:55-15:05	Health planning in the field of pharmacogenomics <i>Americo Cicchetti, Università Cattolica del Sacro Cuore (UCSC), Italy</i>
15:05-15:15	What informs current government policies on PGx in the Netherlands? <i>Tessel Rigter, AmsterdamUMC & RIVM, the Netherlands</i>
15:15-15:30	Discussion: Information needs and priorities for policymakers <i>Martina Cornel, AmsterdamUMC, the Netherlands</i>
15:30	Coffee break
15:45	Roundtable discussion
15:45-16:45	What do stakeholders need for sustainable integration of PGx in healthcare systems Focus: • Value of the PROPHET framework in addressing aspects of Evidence, Acceptability and Integration, Evaluation/monitoring for sustainable adoption of pharmacogenomics in health systems • Stakeholder engagement strategies and patient-centric considerations • Use of MentiMeter for prioritising points to consider <i>Martina Cornel, AmsterdamUMC, the Netherlands</i>
16:45	Workshop wrap-up
16:45-17:00	Closing remarks <i>Carla van El, AmsterdamUMC, the Netherlands</i>

