PROPHET

a PeRsOnalized Prevention roadmap for the future HEalThcare

# D3.2. The PROPHET Framework for appraisal personalized preventive approaches

THL, INSA, UCSC

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**Deliverable Abstract**

Despite the growing focus on personalised prevention, there are currently no comprehensive frameworks to assess the impact of policies implementing personalised prevention interventions in clinical practice. Several frameworks have been proposed to assess genetic and genomic technologies, however, these frameworks do not include the assessment of policies based on these technologies. The PROPHET Framework proposed consists in a multidimensional appraisal framework for personalized prevention initiatives, with a sequential approach of Health Technology Assessment, Health Impact Assessment, and Monitoring. This integration bridges technical, clinical, and societal dimensions, ensuring that personalized prevention strategies are not only effective but also equitable and sustainable in real-world settings. We supported the development of the PROPHET framework through an in-depth analysis of a case study from a real-world scenario. The selected case study

involved the systematic DPYD genotyping of Colorectal Cancer patients treated with Fluoropyrimidines, conducted in three national contexts: Portugal, Italy, and Finland. The findings of this case study constitutes a valuable resource to support an effective monitoring framework for *DPYD* genotyping policy implementation. The case study demonstrated the value of using the HIA methodology, as it integrates diverse perspectives, ensuring equitable and sustainable implementation while supporting effective policy monitoring. Additionally, the PROPHET framework was validated on two further case studies conducted in Italy: a national approach to implementing *BRCA 1/2* testing for the personalized prevention of hereditary breast and ovarian cancer, and the implementation of a population-based approach for therapy personalization through the use of a Pharmacogenetic Passport. The results of the two validation case studies confirmed the insights gained from the *DPYD* case study, demonstrating the effectiveness of the framework in integrating different perspectives to uncover opportunities and barriers to implementing personalized prevention policies. The findings from the *BRCA 1/2* case study underscored the framework's ability to identify challenges, barriers, and the unequal implementation of an approach already partially adopted. Conversely, the Pharmacogenetic Passport case study showcased the framework's utility to prospectively assess policies for which the technology has established clinical utility but lacks implementation strategies or data in national contexts, thereby identifying potential interventions and synergies to facilitate sustainable implementation. All case studies revealed a systematic lack of data across all national contexts. Addressing this issue will require greater attention to data collection on the impact of these policies, supported by the development of clear and shared monitoring strategies designed a priori, as outlined in the PROPHET framework.

**Keywords**

Framework, Health Technology Assessment, Health Impact Assessment, Monitoring, Clinical utility, Equity, Personalised Prevention

# Table of Acronyms

| | |
|---|---|
| 5-FU | 5-Fluorouracil |
| ADR | Adverse Drug Reaction |

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|---|---|
| AGENAS | Agenzia Nazionale per i servizi sanitari Regionali (National Agency for Regional Healthcare Services) |
| AIFA | Agenzia Italiana del Farmaco (Italian Medicines Agency) |
| AIOM | Italian Society of Medical Oncology |
| AR | Attributable Risk |
| ASL | Azienda Sanitaria Locale (Local Health Authority) |
| BC | Breast Cancer |
| BPM | Bilateral Prophylactic Mastectomy |
| BRCA 1/2 | Breast Cancer Gene 1/2 |
| BSO | Bilateral Salpingo-Oophorectomy |
| CDSS | Clinical Decision Support Systems |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| CPS/EG | Clinical and Pathologic Stage and Estrogen Receptor Status |
| CRC | Colorectal cancer |
| CUR | Health problem and current use of technology |
| DALYS | Disability-Adjusted Life Years |
| DPD | Dihydropyrimidine dehydrogenase |
| DPSDNT | Department of Health Promotion and Prevention of Noncommunicabe Diseases |
| DPWG | Dutch Pharmacogenetics Working Group |
| EC | European Commission |
| ECO | Cost effectiveness |
| EFF | Clinical effectiveness |
| EHRs | Electronic health records |
| EMA | European Medicines Agency |

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|---|---|
| EMQN | European Molecular Genetics Quality Network |
| ETH | Ethical Issues |
| EU | European Union |
| EUnetHTA | European network for Health Technology Assessment |
| FCUL | Faculty of Sciences, University of Lisbon |
| FIGO | International Federation of Gynecology and Obstetric |
| FP | Fluoropyrimidines |
| FSE | Fascicolo Sanitario Elettronico (Italian Eletronic health records) |
| GI | Gastrointestinal |
| GLM | Generalized Linear Models |
| HBOC | Hereditary Breast and Ovarian Cancer |
| HCP | Healthcare Professional |
| HIA | Health Impact Assessment |
| HoR | Homologous Recombination |
| HTA | Health Technology Assessment |
| HTAR | Health Technology Assessment Regulation |
| ICER | Incremental Cost-Effectiveness Ratios |
| INE | National Institute of Statistics |
| INSA | National Institute of Health Doutor Ricardo Jorge |
| IPO | Portuguese Institute of Oncology |
| LEA | Livelli Essenziali di Assistenza (Essential Levels of Care) |
| LEG | Legal issues |
| MRI | Magnetic Resonance Imaging |
| NCCN | National Comprehensive Cancer Network |

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|---|---|
| NCDs | Noncommunicable diseases |
| NCI-CTCAE | Common Terminology Criteria for Adverse Events of the United States National Cancer Institute |
| NGS | Next-Generation Sequencing |
| NHS | National Health System |
| NICE | National Institute of Health and Clinical Excellence |
| NPP | National Prevention Plan |
| OC | Ovarian Cancer |
| ORG | Organizational aspects |
| PARP | Poly ADP Ribose Polymerase |
| PCPs | Primary Care Practitioners |
| PDTA | Percorsi Diagnostico Terapeutici Assistenziali (Care pathways) |
| PF | Preventive Fraction |
| PGx | Pharmacogenomics |
| PM | Personalised Medicine |
| PP | Personalised Prevention |
| PPI | Personalised Prevention intervention |
| PROPHET | Personalized Prevention roadmap for the future Healthcare |
| PV | Pathogenic Variant |
| QALY | Quality Adjusted Life Years |
| RCTs | Randomized Controlled Trials |
| RON | Portuguese National Cancer Registry |
| RR | Relative Risk |
| RRBSO | Risk-Reducing Bilateral Salpingo-Oophorectomy |

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|---|---|
| RRM | Risk-Reducing Mastectomy |
| RRSO | Risk-Reducing Salpingo-Oophorectomy |
| SAF | Safety |
| SC | Steering Committee |
| SD | Standard Dose |
| SEER | Surveillance, Epidemiology, and End Results |
| SIF | Italian Society of Pharmacology |
| SOC | Patient and social aspects |
| SPO | Portuguese Oncology Society |
| SPSS | Statistical Package for the Social Sciences |
| SRIA | Strategy Research and Innovation Agenda |
| SSN | Sistema Sanitario Nazionale (National Healthcare System) |
| TEC | Technical characteristics |
| ToR | Terms of Reference |
| UCSC | Università Cattolica del Sacro Cuore (Catholic University of Sacred Heart) |
| ULS | Local Health Unit |
| USPSTF | US Preventive Services Task Force |
| WHO | World Health Organization |

# INDEX

## Section IV: Conclusions and Recommendations for the PROPHET Framework

# Section I: The PROPHET Appraisal Framework for Personalised Prevention Approaches

## 1. Context

### 1.1 Personalised Medicine and Personalised Prevention

In 2015, the European Council defined Personalized Medicine (PM) as a medical practice that "utilises individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention" (1), hencedeparting healthcare approaches from the classical "one-size-fits-all" approach.

Focusing specifically on prevention approaches, the Personalised Prevention Roadmap for Future Healthcare (PROPHET) Consortium further agreed on a definition for Personalised Prevention (PP): *"Personalised prevention aims to prevent the onset, progression, and recurrence of disease through the adoption of targeted interventions that take into account an individual's biological information, environmental and behavioral characteristics, and socio-economic and cultural context. These interventions should be timely, effective, and equitable, ensuring the best possible balance in an individual's lifetime health trajectory*."

The relevance of personalised prevention approaches to healthcare is highlighted by data from the World Health Organization (WHO), which reports that non-communicable diseases (NCDs) account for 41 million people's deaths annually, with the majority (86%) of these fatalities being premature (2). As most of the risk factors contributing to these diseases are modifiable (3), there is a growing need to invest in prevention and health promotion. Furthermore, according to Wang et al., PP provides a valuable solution that offers better outcomes and greater cost-effectiveness than population-based approaches (4).

### 1.2 Context within the PROPHET project

The PROPHET project, funded by the European Union's Horizon Europe research and innovation program, aims to develop a Strategic Research and Innovation Agenda (SRIA) for PP in the European Union.

To support the implementation of innovative, sustainable and high-quality PP strategies, one of the main objectives of PROPHET is developing a multidimensional framework to appraise and adopt personalised prevention interventions (PPI). This framework was developed with an extensive reflection on existing approaches and methodologies, including Health Technology Assessment (HTA), and Health Impact Assessment (HIA) of policies. The development of the framework here

described was supported by a use case for tertiary prevention, namely the molecular testing of the DPYD gene prior to treatment of cancer patients with fluoropyrimidines. The framework was then validated in two additional case studies: BRCA gene testing and the Pharmacogenomics Passport (see Part 2).

## 1.3 Why the need for an appraisal framework for Personalised Prevention

Despite the growing interest in PP, there are currently no comprehensive frameworks to assess the impact of policies implementing PPI in clinical practice. Several frameworks have been proposed to assess genetic and genomic technologies, as highlighted by Pitini et al. (5). Their systematic review (5) and update (6) identified 30 frameworks designed for genetic testing evaluation. However, these frameworks are based mainly on the ACCE model from the Centre for Disease Control in the United States, and Health Technology Assessment (HTA). These two frameworks have very similar dimensions, and Pitini et al. propose using HTA, specifically the EUnetHTA HTA core model, as a consensus for the assessment of genomic technologies (6).

HTA is designed to evaluate health technologies and does not assess the health impact of implementing a policy using such technologies. The PROPHET project aims to address this gap by proposing a **multidimensional appraisal framework for PP approaches**, including the HTA dimensions. However, also others considered it relevant to assess the impact of policies that implement PP approaches based on genomic tests in clinical practice.

# 2. The PROPHET Framework: a proposal of a framework for personalised prevention

## 2.1 The Relevance of Health Technology Assessment

HTA is a well-established approach for evaluating health technologies, primarily focusing on medical devices and pharmaceuticals. HTA provides a comprehensive analysis that considers multiple dimensions, such as clinical effectiveness, safety, cost-effectiveness, organizational impact, organizational and patient aspects, and ethical, legal and social implications (**Table I-1**) (7).

| | | | |
|---|---|---|---|
| REA | CUR | Health problem and current use of technology | This domain outlines the target conditions, target populations, epidemiological context, as well as the availability of the technology in question. |
| | TEC | Technical characteristics | Description of the technology (when it was developed; for what purpose; who will use the technology; for what condition) |
| | SAF | Safety | An assessment of the safety of the technology to the patients |
| | EFF | Clinical effectiveness | This domain assesses the efficacy and effectiveness of the technology |
| National Appraisal | LEG | Legal issues | This domain detects rules and regulations which need to be taken into consideration |
| | ETH | Ethical issues | An assessment of the consequences of implementing or not a healthcare technology on social and moral norms |
| | ECO | Cost effectiveness | Gives information about costs, health-related outcomes and economic efficiency |
| | ORG | Organizational aspects | Assesses what resources are needed |
| | SOC | Patient and social aspects | This domain investigates patient and social groups experiences and perspectives |

**Table I-1:** Domains of Health Technology Assessment (adapted from EUnetHTA Core Model (7)).

Although HTA is not yet recommended for the evaluation of genetic tests in the newly launched Regulation (EU) 2021/2282 on health technology assessment (HTAR), its application in this context has been proposed in the literature by Pitini E et al. (6). The PROPHET Framework supports this idea, considering HTA as the first step for evaluating PP interventions.

Pezzulo A. et al. (8), in their scoping review of assessment reports of genetic and genomic tests used for PP, identified that HTA was the most used framework, enhancing its potential for evaluating the

clinical utility of PP. In this work, the authors identified a list of indicators for assessing clinical utility that encompasses a wide range of dimensions including, for example, analytical validity, clinical validity, and clinical efficacy. The proposed dimensions are extremely useful when considering HTA of genetic tests in general, and particularly those developed with the purpose of PP and are thus recommended for the HTA component of the PROPHET framework.

## 2.2 Evaluating policies for Personalised Prevention: Health Impact Assessment

HTA primarily focuses on technology and, as identified by Pezzulo *et al*. (8), some dimensions, such as equity and acceptability are not sufficiently considered. Health Impact Assessment (HIA), on the other hand, is designed to address the implementation of policies, providing a complementary perspective for the PROPHET Framework, and considers broader impacts, for instance those related to equity. HIA, therefore, enables the assessment of how PP affects health determinants, populations, and societal well-being, moving beyond the clinical utility evaluated by the HTA.

HIA was defined in 1999 as "*a combination of procedures, methods and tools by which a policy, program or project may be judged as to its potential effects on the health of a population, and the distribution of those effects within the population*" (9). **Figure I-1** shows the five main principles of HIA, including contemplating health from a more comprehensive perspective that enhances the focus on social determinants of health. In line with this, HIA considers equity concerns and the identification of measures to reduce inequalities. Participation of various stakeholders is another key aspect of HIA, allowing the opportunity to consider the perspectives of those most affected by the policy, programme or project under scope. The process must be transparent, with evidence used according to accepted ethical principles. Lastly, a reflection on whether the policy or programme proposed is sustainable and is essential (10).

HIA is by definition prospective, so that it can maximize the positive effects of a policy before its implementation, thus supporting decision-making. In some cases, it can also be done retrospectively, in which case the HIA becomes closer to an outcome evaluation (10). For the purpose of the framework development, the *DPYD* genotyping HIA was a prospective exercise, performed before a related policy is implemented in any of the three countries, in spite of the existence if European guidelines.

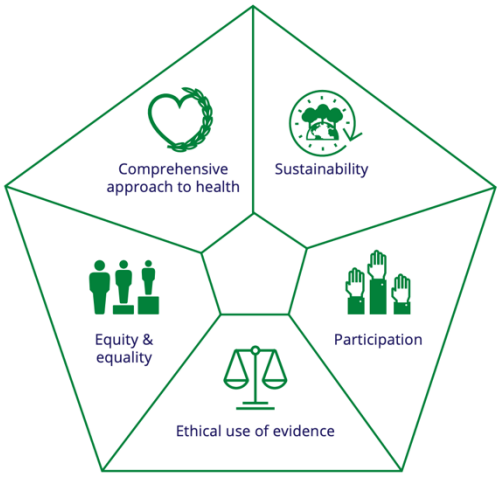


**Figure I-1:** Core principals of HIA (Pyper at al, 2021)

According to the WHO (11), the HIA process can be divided into four, five, or six phases depending on the framework adopted. For this framework, we structured the process into five sequential phases, illustrated in **Figure I-2**.

The first phase, screening, involves determining whether the HIA is necessary, assessing if it is timely, and evaluating whether it can add value to decision-making. During this stage, a technical team is assembled to lead the process. Once the need for an HIA has been established, the process moves into the scoping. Here, the focus shifts to planning the assessment by identifying and prioritizing key issues and developing a conceptual framework to guide the analysis. This phase also includes the formation of a steering committee with relevant stakeholders to oversee and contribute to the process, ensuring inclusivity and diverse perspectives (12).

Following the scoping phase, the HIA proceeds to the assessment phase, its core activity. In this phase, data is collected and analysed using a combination of quantitative and qualitative methods to evaluate potential health impacts. The analysis is documented in a detailed report that describes all phases of the HIA and presents findings, addresses challenges, and provides recommendations tailored to mitigate negative impacts and enhance positive ones (12). This report is developed to communicate findings transparently and effectively to decision-makers and stakeholders.

Finally, a monitoring and evaluation phase is proposed. This phase consists of defining what aspects need to be monitored, including key indicators.

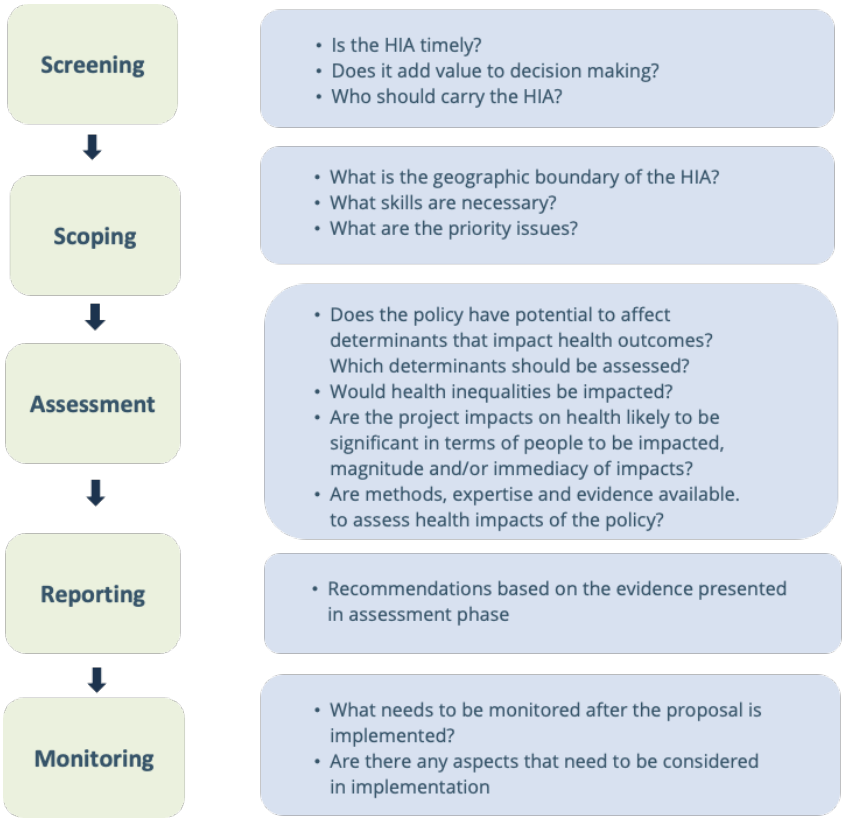


**Figure I-2:** Health Impact Assessment process. Adapted from WHO (11).

HIA has not previously been used for assessing policies based on genetic or genomic testing, particularly for PP at any prevention level. **The application of HIA in the context of Personalised Medicine is novel, and the PROPHET Framework considers it key to complement the clinical and technical assessment performed by HTA**. HIA expands the evaluation scope to include the broader impacts of policies on population health and societal well-being, particularly emphasizing equity. Furthermore, it is a participative evaluation, providing an opportunity to gather stakeholders' perspectives on a policy that is not possible in HTA and is extremely valuable for its successful implementation.

By incorporating HIA, the PROPHET Framework ensures a more holistic appraisal of PP strategies, addressing not only their clinical utility but also their implications for the equitable distribution of benefits. This dual approach bridges the gap between technical evaluations and policy-level impacts, enabling a more informed decision-making process.

## 2.3 Monitoring of policy implementation

Monitoring of policy implementation is proposed as a component of the framework, highlighting its fundamental role in ensuring long-term effectiveness. Throughout the monitoring stage, indicators

play a central role and should be carefully selected before the policy is implemented and monitoring is established. These indicators must be developed in collaboration with stakeholders to reflect shared goals and priorities and align with established or desired objectives.

The proposed monitoring in the PROPHET framework is grounded in the logic model framework (13) (**Figure I-3**), providing a structured approach to monitor the implementation and impact of PP strategies.

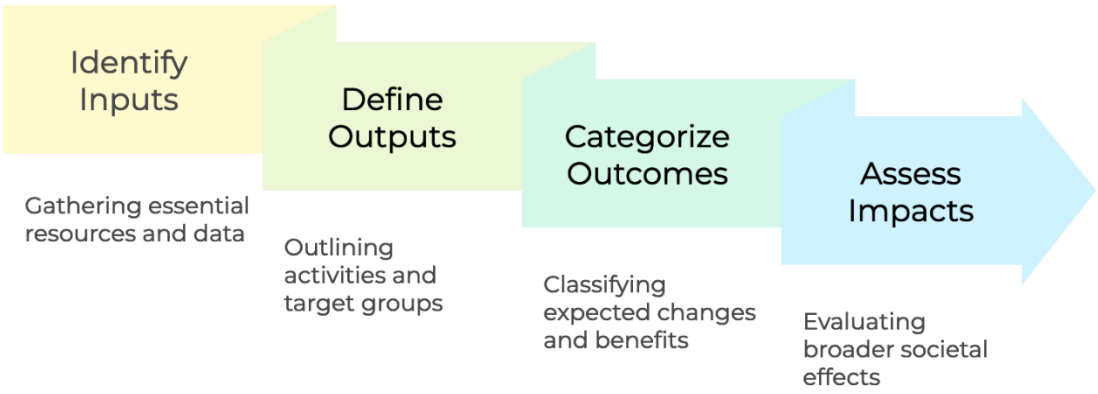


**Figure I-3:** Structure of the logic model framework for monitoring purposes.

Inputs encompass all the essential elements needed for monitoring. These can include, for example, data access and resources (for example human, material or financial resources).

Outputs refer to the immediate results of the policy/program being implemented, such as the resultant activities and their direct products. In PP, examples of outputs can be the number of individuals who did a personalised risk assessment, and the training of healthcare professionals in specific PP areas, such as pharmacogenomics. By tracking outputs, it is possible to verify whether the policy is being implemented as planned and whether the direct results are sufficient to progress toward the desired outcomes.

The outcomes represent the changes or benefits expected as a result of the implemented policy, which can be short-term, medium-term and long-term. For example, training in pharmacogenomics (an output) might lead to increased awareness, a short or medium-term outcome. Lastly, Impacts are the broader anticipated effects on society. These are related to wider aspects, such as the quality of life, or healthcare system efficiency.

When monitoring the policy, if the indicators reveal unfavorable outcomes, the policy should be reviewed and adjusted to address the identified issues at any time in the process. Continuously monitoring results ensures that time and resources are used sustainably.

## 2.4 The PROPHET framework

The PROPHET Framework (**Figure I-4**) for the assessment of PP proposes a sequential approach of HTA, HIA, and Monitoring, offering a multidimensional and comprehensive methodology to support decision-making on the implementation of PP policies. This integration bridges technical, clinical, and societal dimensions, ensuring that PP strategies are not only effective but also equitable and sustainable in real-world settings.

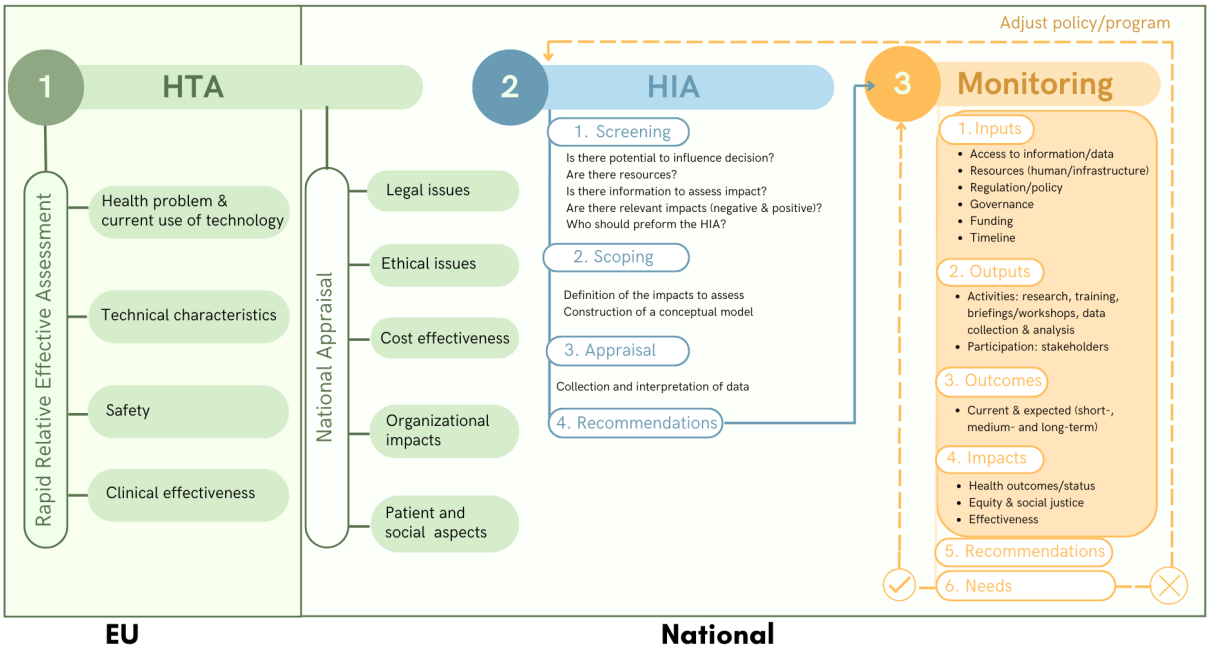


**Figure I-4:** The proposed PROPHET framework

One of the PROPHET Framework's most distinctive features is its inclusion of HIA, a methodology that complements the technical focus of HTA by addressing broader societal and equity considerations. HIA inherently fosters collaboration among diverse stakeholders, creating a platform for inclusive decision-making. As Costa A. *et al*. emphasize, "*collaborative efforts are needed to elevate visibility and engage stakeholders, facilitating the integration of personalized prevention (PP) interventions into healthcare systems for widespread adoption*" (14).

This participatory process ensures that diverse perspectives are incorporated into the evaluation and implementation of PP strategies. By fostering interdisciplinary engagement, the PROPHET Framework facilitates the adoption of PP interventions and ensures they are tailored to the unique needs and contexts of different populations. Moreover, the framework's emphasis on monitoring provides a mechanism for continuous improvement, enabling the iterative refinement of policies to maximize their long-term impact.

We supported the development of the PROPHET framework through the analysis of a case study,

namely the systematic DPYD genotyping of Colorectal Cancer patients treated with Fluoropyrimidines, conducted in three national contexts: Portugal, Italy, and Finland. Additionally, the PROPHET framework was validated on two further case studies conducted in Italy: a national approach to implementing BRCA 1/2 testing for the personalized prevention of hereditary breast and ovarian cancer, and the implementation of a population-based approach for therapy personalization through the use of a Pharmacogenetic Passport.

# 3. A policy for *DPYD* gene testing prior to treatment of cancer patients with Fluoropyrimidines – a case study

## 3.1 Rationale for the PROPHET Framework

The development of the PROPHET Framework was supported by an in-depth analysis of a case study from a real-world scenario. The case study selection focused on a PP interventions involving genetic testing that is widely used, with previously developed HTA (15), but for which a policy is not available in any of the three countries that volunteered to participate. One of the main goals of the PROPHET framework was to test the adequacy of the HIA methodological approach to support PP policies based on genetic information. We further sought to understand how this tool, applied in such an innovative context, could be used to better inform decision makers, as a crucial element of the PROPHET Framework.

The PP case study selected was a policy for the systematic *DPYD* genotyping in colorectal cancer patients eligible to be treated with fluoropyrimidines (FP). Fluoropyrimidines (FP) are extensively used for treating various solid tumors such as digestive, breast, and head and neck cancers (16, 17). However, severe toxicity occurs in 10% to 30% of patients following FP administration (18-20). This severe toxicity can lead to hospitalization, dose reduction, treatment delay, or interruption, and can be fatal in up to 1% of patients (21). Dihydropyrimidine dehydrogenase (DPD) is the principal enzyme responsible for FP metabolism, and its deficiency is estimated to account for 20% to 60% of toxicity cases (22, 23). This enzyme is encoded by the *DPYD* gene, for which multiple variants determining enzyme activity have been identified, thus influencing FP toxicity.

*DPYD* genotyping prior to treatment with FP has been established for some time, and HTA has been carried out previously (15). Furthermore, in 2020 the European Medicines Agency (EMA) issued a recommendation for DPD deficiency testing before initiating FP-based oncological treatments (24). This allows mitigation of severe toxicity by enabling drug dose adjustments or suggesting alternative treatments (24). Despite this recommendation, genotyping for *DPYD* prospectively is not mandatory in most countries and, consequently, the quality of care for cancer patients may not be consistent.

To evaluate the impact of a policy that makes *DPYD* genotyping mandatory, a HIA was performed in three European countries: Portugal, Italy and Finland. The case study focused on colorectal cancer (CRC), as it is one of the major causes of morbidity and mortality worldwide (25). It is important to note that the HTA component of the PROPHET Framework for this use case relies on European guidelines for *DPYD* genotyping, and therefore was based on existing literature (15). On the other hand, the HIA of a policy for *DPYD* genotyping is based on national contexts. The HIA component of the framework is innovative, as it has not been performed for genetic-based PP approaches. Monitoring was not carried out in this context, however, it is proposed to be an integral and

fundamental component of the PROPHET framework, and therefore recommendations are proposed.

Below, we summarize the main outcomes of this HIA, as a basis for discussion of the PROPHET framework. The full report of the HIA for a policy for *DPYD* genotyping prior to FP treatment in CRC patients is provided in Section II of the present deliverable.

## 3.2 Validating the feasibility of Health Impact Assessment for a policy on *DPYD* testing

A common protocol was designed for the HIA on *DPYD* genotyping, with three main perspectives considered:

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

In each country, national technical teams managed the respective process, with responsibilities that included designing project specifics according to country practices, collecting data, organizing and inviting experts to join the Steering Committee.

To determine and select the impacts and guide the assessment process, a conceptual model (**Figure I-5**) was developed that hypothesized the connections between the proposal and potential health outcomes, illustrating the potential ways in which a *DPYD* genotyping policy can impact health.

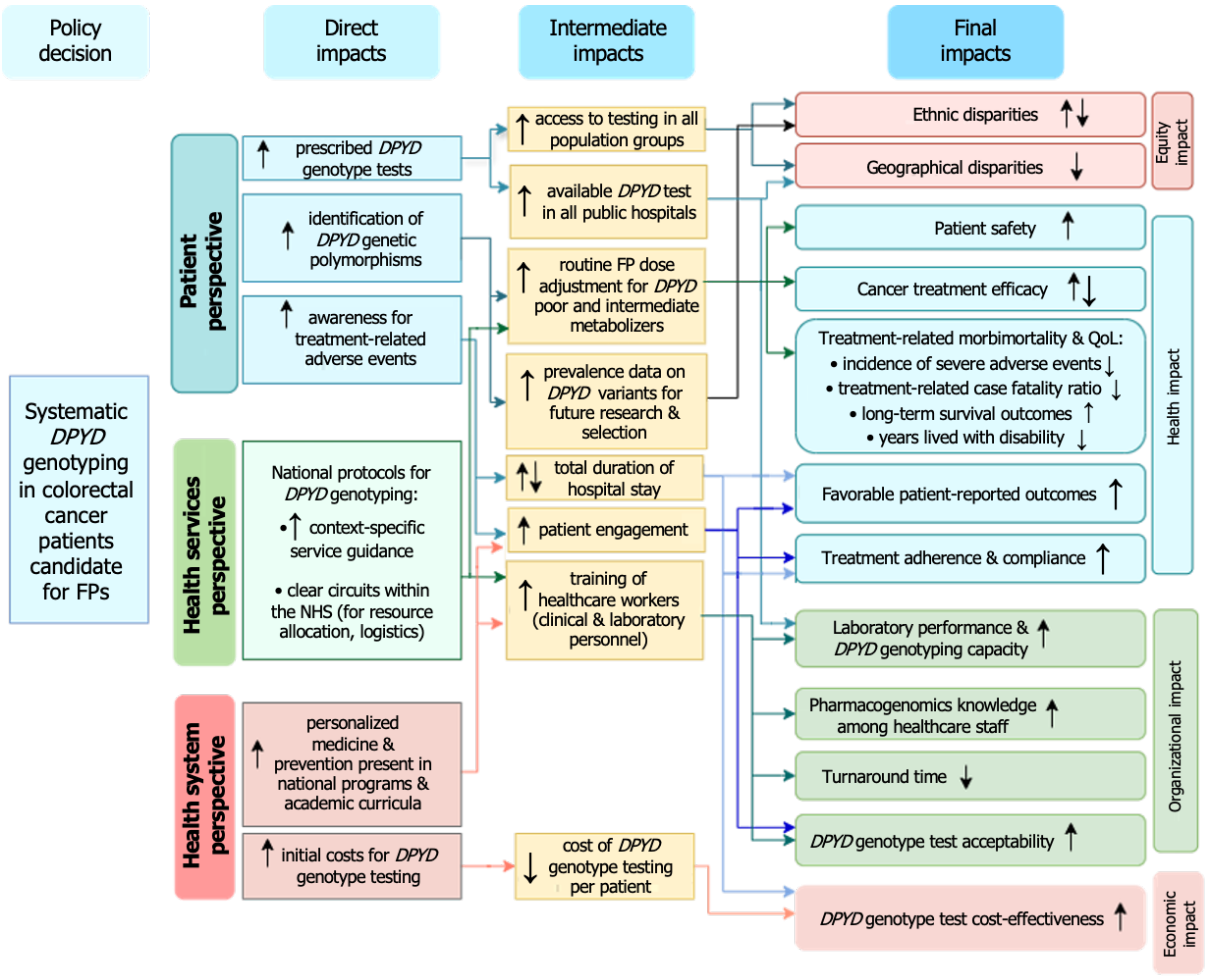


**Figure I-5:** Conceptual model for prospective pre-treatment *DPYD* genotyping in CRC patients. FP: Fluoropyrimidines; QoL: Quality of Life.

To assess the selected impacts, both quantitative and qualitative methods were adopted. A Markov Model was applied to predict the impact on the number of severe toxicity events and mortality. For the Markov Model, a decision tree was designed based on a cost-effectiveness study conducted by Brooks et al. (26). The probabilities assumed for severe toxicity events and mortality in both Brooks et al. study and our Markov Model were based on studies (27-29) mentioned in the *DPYD* HTA (15), when assessing the clinical effectiveness dimension. Additionally, surveys, stakeholders' consultations and interviews were conducted to gather insights from various participants. The detailed methodology for each country, ultimately defined based on the available data sources and after each national steering committee validation, as well as detailed results and main discussions are described in detail in **Section II** of this document.

## 3.3 Impact of a DPYD testing policy from the patient, organizational and healthcare system perspectives

*i) Patient perspective:*

The results of the Markov Model, predicting the total expected severe toxicity events and the number of toxicity-related deaths for three prescription scenarios (systematic genotyping, current estimated rate of genotyping, and no genotyping) showed that systematic *DPYD* genotyping would moderately but consistently reduce the incidence of severe toxicities compared to the estimated ongoing practice, for the three countries (details in the Section II). It should be noted that present day frequency of genotyping is already relatively high, with slight variations in the three countries, so the results are relevant even for relatively small improvement of genotyping rates. The results further emphasize the clinical significance of systematic *DPYD* testing to improve overall patient outcomes, reducing not only the incidence of severe toxicities but also preventable treatment-related deaths in CRC patients.

*i) Organizational perspective (for additional details see Section II):*

While the benefits of *DPYD* genotyping are widely acknowledged, the implementation of testing remains inconsistent between and among countries. In Portugal, regional prescription disparities were identified. Organizational factors such as oncology departments' size (larger vs. smaller) and the existence of testing protocols are associated with significantly higher adherence to *DPYD* genotyping. Other factors contributing to the likelihood of test prescription included shorter turnaround times and affiliation with the National Health Service. Conversely, the low prevalence of *DPYD*-deficiency variants and delays in receiving test results were the primary reasons physicians did not prescribe *DPYD* genotyping. Regarding the acceptability, both physicians and lab staff supported routine *DPYD* genotyping for at-risk cancer patients and believed it would enhance patient safety.

In Italy, a substantial implementation of *DPYD* genotyping was found, indicating its clinical uptake and clinical value. However, some challenges were identified. All consulted units reported turnaround times exceeding one week, potentially delaying treatment decisions, which may reduce the test acceptability. Additionally, oncological units reported the absence of a specific reimbursement code for the *DPYD* genotyping test as a potential financial barrier to its wider implementation. Positively, the majority of consulted oncological units include both variant identification and dosage recommendations in reports, supporting clinical decisions.

In Finland, *DPYD* genotyping is highly accepted among physicians, who recognize its clinical value and demonstrate confidence in its application, with a prescription coverage of around 95%. *DPYD* genotyping is offered nationwide as part of a pharmacogenetic panel. A high percentage of physicians' view *DPYD* genotyping as a valuable tool for adjusting chemotherapy doses to prevent

adverse effects. However, while genetic testing is widely integrated into practice, operational challenges, such as test turnaround times and regional processing timelines differences, may impact treatment delays. Delays in genetic testing often stem from logistical issues, such as sample collection and transportation. Moreover, laboratory systems do not always integrate seamlessly with hospital patient record systems, which could lead to inefficiencies in data access and result interpretation.

*ii) Economic perspective (for additional details see Report in Section II):*

A literature review assessed the cost-effectiveness of systematic *DPYD* genotyping before FP treatment in CRC patients. Across 12 studies, genotyping consistently demonstrated cost savings and improved outcomes, primarily by reducing severe toxicity and related healthcare costs. The studies showed favourable incremental cost-effectiveness ratio (ICER) and other economic measures, indicating that genotyping is a cost-effective strategy that enhances patient safety and optimizes healthcare resources. Overall, systematic *DPYD* genotyping was cost-effective, enhancing patient safety and optimizing healthcare resource allocation.

## 3.4 Discussion and main recommendations for policy implementation and monitoring

Globally, the cross-country analysis demonstrated positive impacts from the three perspectives. The Markov Model projected moderate but consistent reductions in severe toxicity events and mortality with systematic *DPYD* genotyping. From an organizational perspective, healthcare professionals expressed strong support for a policy mandating *DPYD* genotyping. Furthermore, the literature consistently highlights that *DPYD* genotyping prior to treatment is a cost-effective approach, reinforcing its feasibility for integration into healthcare systems.

Across all three countries, the findings highlighted the potential benefits of implementing a policy for *DPYD* genotyping. Equity aspects related to access were also raised, with existing inequities due to geographic and organizational aspects. Furthermore, this exercise underscored the importance of conducting HIA to identify and address inequities that could be mitigated with a policy. A policy for mandatory *DPYD* testing would ensure equitable access and standardized care for all patients, regardless of where they are treated, a fundamental principle that should support any healthcare system. In Italy, standardization of the reimbursement process could improve test uptake. Ensuring consistent and equitable access and addressing logistical or systemic barriers, such as reimbursement or turnaround times, will be crucial to maximizing its implementation and benefits in practice. All findings were presented to and discussed with country-specific steering committees ensuring a holistic and multidisciplinary approach with a focus on equity.

This HIA exercise led to a list of recommendations for a policy on *DPYD* genotyping, shown in Table I-2. These include creating an information system that integrates data from different data sources,

allowing continuous monitoring of the process, training the healthcare professionals who treat cancer patients on pharmacogenomics and its applications, raising awareness among patients for severe toxicity events and their reports, and creating internal guidelines and workflows to optimize the entire process.

| | |
|---|---|
| Information systems | To monitor the impact of the policy, having an information system that integrates data from different data sources is essential. |
| Training | Training on pharmacogenomics for oncologists, lab personnel, and other professionals enrolled in CRC treatment. |
| Awareness | Raising awareness among patients about drug adverse reactions and the importance of reporting them (for example, through PROMs). |
| Guidelines | Establishing internal guidelines for systematic *DPYD* testing. |
| Workflow | Creating a workflow to optimize the time between the test prescription and the test results, allowing for dose adjustments. |

**Table I-2:** List of recommendations for a *DPYD* policy

The findings from the HIA provide a solid foundation for the development and implementation of a monitoring system to support a *DPYD* genotyping policy. Below are key considerations integrating both the case study findings and practical aspects for real-world application:

1. ***Integration of the conceptual model for monitoring***: developed to support the HIA, the conceptual model, a diagram of proposed causal linkages among a set of concepts believed to be related with the *DPYD* genotyping, outlines the anticipated outcomes and impacts of the policy (**Figure I-5**). This prospective approach provides a basis for:

- Establishing a logic model to guide monitoring activities;
- Defining expected short-, medium-, and long-term impacts;
- Selecting outcome-focused indicators that measure both positive and unintended policy effects, with an equity focus;

By leveraging this conceptual model, the monitoring process can maintain a structured and evidence-based approach.

2. ***Identification of indicators, sources, and methods***: the list of indicators, sources, and methods generated during the HIA highlights critical factors that must be monitored to ensure the policy's impact on clinical practice, patient safety, and health outcomes. These include:

- Number of CRC patients undergoing FP treatment;
- Incidence of severe grade toxicity events;

- Mortalities associated with severe toxicity;
- Number of *DPYD* tests performed;
- Quality of life outcomes for CRC patients;
- Acceptability of *DPYD* testing by patients;
- Number of training activities on *DPYD* testing utility;

While this list serves as an initial guide, it is important to refine and adapt the indicators during implementation, considering all policy elements. Continuous dialogue with stakeholders, including healthcare professionals, patient representatives, and policymakers, will ensure the indicators remain relevant and aligned with both clinical and patient needs.

3. ***Addressing identified challenges:*** The HIA case study highlighted key methodological challenges, particularly the scarcity of reliable national and local data sources. To address these limitations, the following actions are suggested:

- Identification and ensuring access to the necessary data to assess, monitor, and evaluate policy outcomes. This action will also allow recommendations for the development of a robust information systems to streamline data collection, reporting, and analysis;
- Triangulation of data and methods, combining national and international data, both quantitative and qualitative, to fill existing data scarcity and to provide a comprehensive overview of policy implementation outcomes;

4. ***Strengthening stakeholder engagement****:* The case study emphasized the importance of stakeholder engagement to ensure equitable and sustainable implementation. Stakeholder collaboration should include:

- Identifying and prioritizing key monitoring activities;
- Co-designing with stakeholders tailored actions to maximize benefits and mitigate unintended effects;
- Encouraging active participation from healthcare providers, policymakers, and patient representatives to increase awareness and acceptability;

5. ***Considering actions for policy implementation***: The HIA study outlined concrete actions to ensure that the *DPYD* genotyping policy achieves its intended goals. These actions can be incorporated into the monitoring framework to assess their adequacy and effectiveness. Examples include:

- Ongoing training programs to improve healthcare professionals' understanding and use of *DPYD* testing;
- Strengthening laboratory infrastructure to enhance operational efficiency and ensure that healthcare providers receive actionable insights in a timely manner;
- Awareness campaigns to promote patient acceptability and informed decision-making;

- Continuous evaluation of the policy's clinical efficiency and equity of access;

6. ***Adaptability of the Monitoring***: In the context of real-world implementation, a flexible framework capable of evolving with emerging evidence and stakeholder feedback is recommended. Key elements of adaptability include:

- Periodic review and refinement of indicators;
- Integration of new data sources as they become available;
- Responsive mechanisms to address challenges and gaps identified during monitoring.

In summary, the findings from the HIA case study constitute a valuable resource to support an effective monitoring framework for *DPYD* genotyping policy implementation. By combining prospective insights, stakeholder collaboration, and continuous feedback, the framework can ensure equitable, sustainable, and impactful outcomes in clinical practice and patient care. This dynamic approach will enable ongoing assessment, continuous improvement, and informed decision-making to promote patient safety and clinical efficiency.

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# Section II: The *DPYD* Case Studies *DPYD* Genotype Testing and Prevention of Fluoropyrimidine Toxicity in Colorectal Cancer Patients in Finland, Italy and Portugal

## 1. Context

### 1.1. Policy Background

CR is a major cause of morbidity and mortality worldwide, with approximately 2 million new cases and 1 million related deaths reported in 2020 (1). In the EU, CRC accounts for 13% of diagnosed cancers in men and 12% in women. FPs, 5-FU and its oral prodrugs capecitabine and tegafur, are extensively used in treating various solid tumors such as digestive, breast, and head and neck cancers (2,3). FPs remain one of the most widely used and effective drug groups in CRC treatment, and the primary component of chemotherapy regimens used (2). Worldwilde, every year, over two million patients receive FP treatment (4). However, severe toxicity (grade 3 or higher according to the Common Terminology Criteria for Adverse Events of the US National Cancer Institute [NCI-CTCAE]) occurs in 10% to 30% of patients following FP administration (5-7). This toxicity can manifest as hematological effects (e.g., neutropenia, anemia, thrombocytopenia), gastrointestinal reactions (e.g., mucositis, diarrhea, nausea, vomiting), or dermatological issues (e.g., hand-foot syndrome), potentially leading to hospitalization, dose reduction, treatment delay, or interruption, and can be fatal in up to 1% of patients (4).

Dihydropyrimidine dehydrogenase (DPD) is the principal enzyme responsible for 5-FU metabolism (8,9). Reduced DPD activity slows down 5-FU metabolism, leading to the accumulation of active metabolites and an increased risk of toxicity after FP administration (4,8). Although multiple factors can influence FP-associated toxicity (such as age, renal function and mode and duration of drug administration), DPD deficiency is estimated to account for 20% to 60% of toxicity cases (9-11). The *DPYD* gene, located on chromosome 1p22, encodes the DPD enzyme. Variants in *DPYD* can result in structural alterations of the DPD enzyme, leading to reduced or absent enzymatic activity (3,8). Such variants show significant ethnic diversity (12,13). For instance, common pathogenic *DPYD* variants like c.1905+1G>A (*DPYD** 2A), c.2846A>T, c.1236G>A/HapB3, and c.1679T>G (*DPYD**13) are well-studied in Caucasian populations, where their combined prevalence can be as high as 12% (12,13). However, these variants are less prevalent or even absent in other ethnic groups.

As variants that influence DPD enzyme activity and, consequently, fluoropyrimidine toxicity vary widely across different ethnic groups, this can lead to unequal risks of adverse drug reactions and treatment outcomes if genotyping strategies are not appropriately tailored. In Caucasians, variants such as c.1905+1G>A and c.2846A>T are strongly associated with severe toxicity, prompting dose

adjustments based on genotype to prevent adverse effects (12). However, these variants are rare in Asian and African populations, where other, less studied or novel variants may have significant clinical implications. Studies indicate that certain *DPYD* variants, such as c.577A>G (rs115232898), are more frequent in African-American populations, resulting in a marked reduction in DPD activity and necessitating substantial dose reductions to mitigate toxicity risks (13,14). Additionally, the *DPYD* variants c.85T>C and c.496A>G, relatively common in South Asian populations, also correlate with increased FP-related toxicity (12,13). This significant ethnic genetic diversity in *DPYD* variants underscores a crucial challenge in achieving equity in cancer treatment outcomes. Ethnically tailored genotyping and dose adjustments are essential to optimize fluoropyrimidine chemotherapy safety and efficacy across diverse populations, ensuring that all patients receive the most appropriate and effective treatment based on their genetic profile.

## 1.2. Context within the PROPHET project

Patients with DPD deficiency are at risk of severe and potentially fatal toxicity when treated with standard doses of FPs (3). In light of the accumulating evidence on this topic, in 2020, both the European Medicines Agency (EMA) and the Portuguese drug regulatory agency Infarmed, I.P., issued recommendations for DPD deficiency testing before initiating FP-based oncological treatments (15,16). The objective of DPD deficiency testing is to mitigate severe toxicity risks by enabling dose adjustments of these drugs or suggesting alternative treatments based on the level of deficiency detected, in line with recommendations from various international scientific societies, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics working group (DPWG) among others (3,15).

In recent years, several European countries have implemented clinical guidelines and norms regarding *DPYD* genotype testing. For instance, the DPWG in the Netherlands has established guidelines recommending *DPYD* genotyping before initiating fluoropyrimidine therapy, with specific dosing adjustments based on the presence of certain *DPYD* variants (4). Similarly, Italy has developed national recommendations through collaboration between the Italian Association of Medical Oncology (AIOM) and the Italian Society of Pharmacology (SIF), which also endorse pre-treatment *DPYD* genotyping (17).

In Portugal, despite recommendations from the national drug regulatory agency (INFARMED, IP) supporting pre-treatment *DPYD* genotype testing, there are currently no established clinical guidelines or norms addressing this issue. As a result, the prescription of pre-treatment *DPYD* genotype testing remains inconsistent and voluntary, highlighting a gap that could be addressed through health policy initiatives.

In Finland, *DPYD* genotyping has been integrated into clinical practice at regional and institutional levels, making it a standard procedure for assessing safety prior to fluoropyrimidine treatment (42). Following the 2020 EMA recommendations (15), *DPYD* testing is routinely available as part of pharmacogenetic panels across various laboratories (42,44). While Finland lacks a comprehensive

national strategy or policy for pharmacogenetic testing, this approach reflects a growing commitment to personalized medicine and aligns with international initiatives.

In Italy, a substantial implementation of *DPYD* genotyping was found, indicating its clinical uptake and clinical value. However, some challenges were identified. Results highlight the need for continued efforts to standardize practices, address regional disparities, and ensure equitable access to this important pharmacogenetic test across the country.

## 1.3. Why the need for an appraisal framework for Personalised Prevention

An important goal of the PROPHET project work plan is the development of an appraisal framework for PPI. For this purpose, as mentioned in Section I, we sought to establish a methodology for health impact assessment for standards, policies, or projects of personalized prevention. The present section evaluates the potential benefits and risks, with a focus on equity, of the systematic pre-treatment *DPYD* testing for CRC patients. The purpose is to provide a well-informed, evidence-based perspective on the systematic adoption of a personalized prevention strategy in oncological treatment and the potential implications of this adoption.

# 2. Methodology overview

## 2.1. Health Impact Assessment

A HIA evaluates planning and policy proposals, providing recommendations to improve health outcomes, through a structured, six-step process (**Figure II-1**). The primary objective of HIA is to ensure that health considerations and health inequities are effectively integrated in the decision-making process. This is achieved through an objective and scientific approach, and active stakeholder engagement (18).

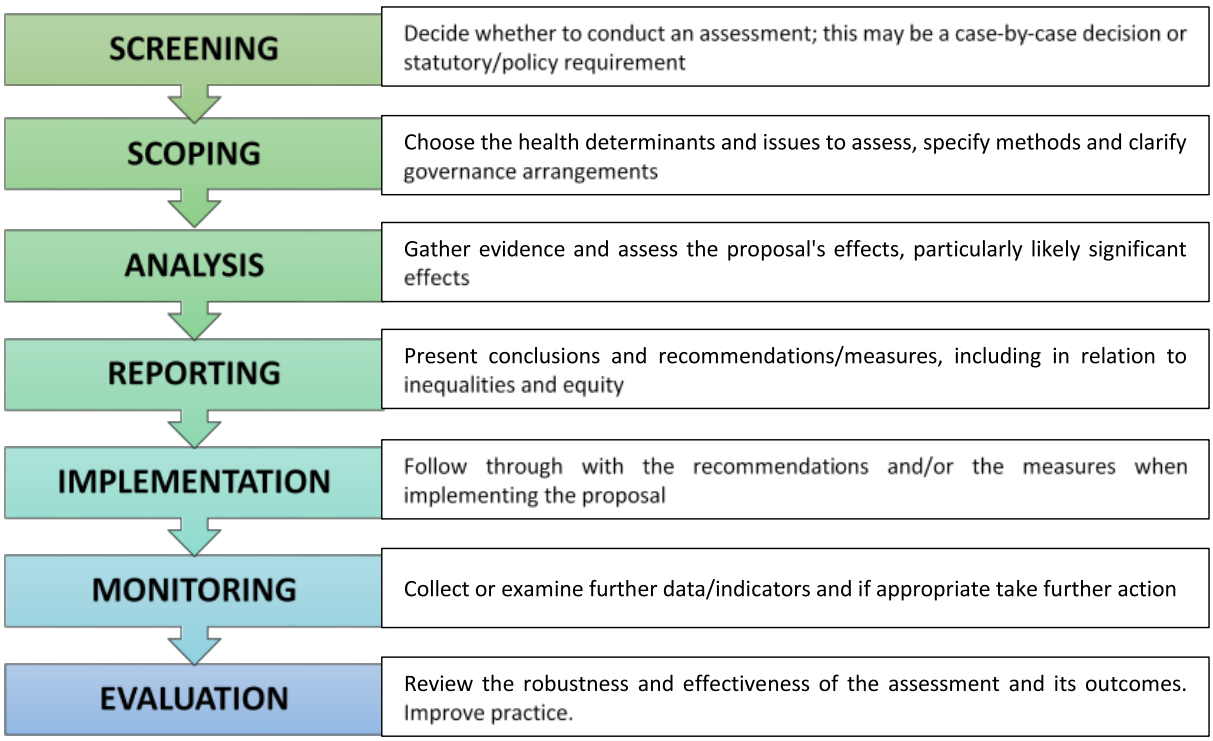



**Figure II-1.** Health Impact Assessment: the process. Adapted from: Pyper, R., Cave, B., Purdy, J. and McAvoy, H. (2021). *Health Impact Assessment Guidance: A Manual. Standalone Health Impact Assessment and health in environmental assessment.*

## 2.2. Screening

The initial phase of a HIA is the screening, which establishes the value and feasibility of an HIA for a given context. A technical team, responsible to conduct the screening and subsequent phases is established. During screening, essential questions are addressed to determine the appropriateness of the study and to conduct preliminary research on the health determinants potentially affected by the proposed policy.

In this specific HIA, the screening phase deviated from standard practices as it was conducted as part of a pilot study within the PROPHET project. Unlike typical circumstances where the need for HIA is evaluated during the screening phase, in this case the decision to carry out the assessment was made in advance. Nevertheless, aligning with evidence and recommendations from the

European Medicines Agency for DPD deficiency testing prior to initiating FP-based oncological treatments, this assessment is both timely and capable of significantly contributing to policy decision-making.

In each country participating in this HIA case study, national technical teams managed the respective process, with responsibilities that included designing project specifics, collecting data, organizing and inviting experts to join the steering committee, analyzing data, and presenting the final results.

The primary partner responsible for the study design and preparation of this report was the technical team at the National Institute of Health Doutor Ricardo Jorge (INSA), which led the study in Portugal, drawing on its experience on previous assessments. Additional national teams involved in conducting the HIA included the Department of Life Sciences and Public Health at Università Cattolica del Sacro Cuore in Rome, Italy, and the Finnish Institute for Health and Welfare in Helsinki, Finland.

To ensure consistent alignment and collaboration throughout the HIA process, progress across the three countries was regularly assessed through online meetings.

## 2.3. Scoping

While the proposed policy might influence various health determinants, constraints in time and resources invariably motivate a priority-setting process and focused approach. The scoping step in an HIA aims to pinpoint the main areas for analysis. develop goals for the HIA and prioritize research questions and methods to guide the assessment.

During scoping the national teams established geographic and temporal boundaries for the analysis, built agreement on the Terms of Reference (ToR) and the decision-making protocol content.

The geographic boundaries of the current HIA are those of the three countries (Portugal, Finland and Italy), albeit separately. This HIA looked at immediate and long-term impacts of the DPYD test policy implementation, considering temporal boundaries that spanned from immediate to five years into the future.

Other key aspects were included in the ToR as non-negotiables, such as the focus of this HIA on CRC patients. This decision was made based on several factors: first, clinical relevance, as CRC is one of the most common cancers globally and its treatment often includes FPs; second, specific evidence and guidelines, as robust data links DPYD mutations to adverse reactions to FPs in CRC patients, making it a well-supported focus for an HIA; and, third, feasibility and resource allocation issues, as focusing on CRC patients would enable a more manageable and cost-effective assessment, potentially leading to clearer and actionable insights for policy-making. In addition, during the scoping process there was an overall agreement on both the timing (prospective) and level (intermediate) of the HIA to be conducted, which were considered important factors to help to determine the range and depth of the exercise. In order to select the impacts and guide the assessment process, a conceptual diagram was developed (**Figure II- 2**) that hypothesized the

connections between the proposal and potential health outcomes, illustrating the potential ways in which a *DPYD* genotype testing policy can impact health. The pathways guided the steering committee to reflect on the major risk factors and possible health outcomes, including intermediate effects, in order to provide a greater perception of the main determinants of health involved in pre-treatment *DPYD* genotyping of CRC patients.

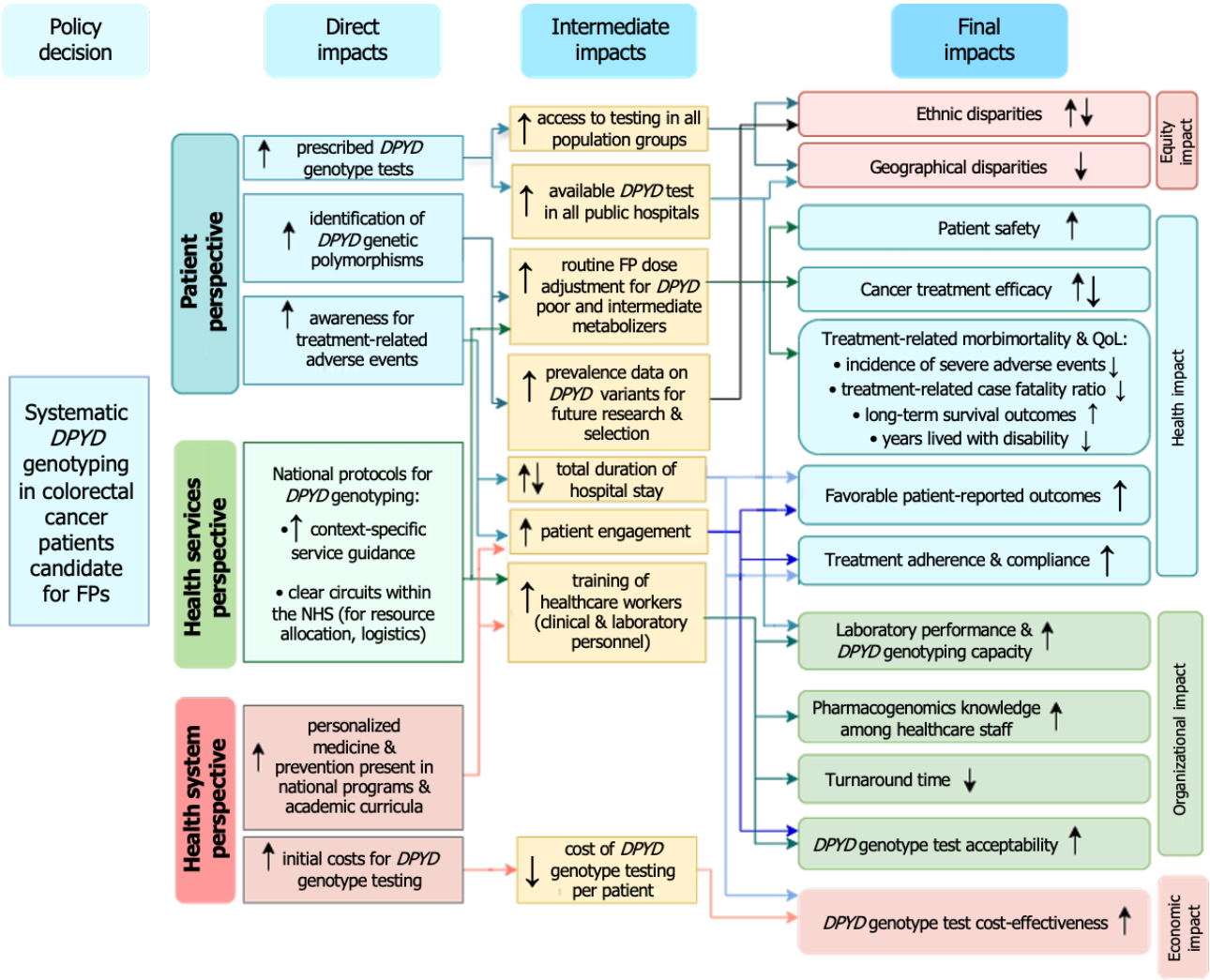



**Figure II-2.** Conceptual model for pre-treatment *DPYD* genotyping in colorectal cancer patients. *FP: fluoropyrimidines; QoL: quality of life.*

Based on the conceptual model, the working group proposed the following potential impacts for assessment, prioritizing them as follow:

- Impact 1: The impact of *DPYD* genotype testing on morbidity and mortality of CRC patients, with a focus on equity [impact on individual/population health];
- Impact 2: The impact of *DPYD* genotype testing on the organizational level [impact on health services]; and
- Impact 3: The economic impact of *DPYD* genotype testing [impact on health system].

**Table II-1** outlines the indicators, data sources and types of analysis considered at this stage for assessing the identified potential impacts.

| Indicators | Description | Period | Effect distribution | Data source | Analysis |
|---|---|---|---|---|---|
| *Morbidity & Mortality (impact on individual/population health)* | | | | | |
| CRC incidence | No. new cases of CRC / average population in same period | 2023 (or proxy) | Sex, age group, district | Portuguese data source (RON)<br>Italy data source<br>Finland data source | Quantitative (via Markov Model) |
| Proportion of CRC patients candidate for FP based-tx | No. CRC cases candidate for FP based-chemotherapy / total CRC cases | | - | Literature | |
| Proportion of CRC patients candidate for FP based-tx who underwent DPYD genotyping | No. CRC cases candidate for FP based-tx who underwent DPYD genotyping/ No. CRC cases candidate for FP treatment | | Region, district, size & type of healthcare unit | Survey – average prescription rate (mean) | |
| Incidence of CRC post FP-treatment toxicity | No. of CRC cases of toxicity post FP-treatment / No. CRC cases candidate for FP treatment | | Toxicity grade (0-2; 3-4) | Literature[1] | |
| CRC mortality | No. CRC deaths / average population in that period | | - | Literature[1] | |
| CRC FP-specific mortality | No. CRC deaths due to toxicity post FP-treatment/ total CRC in that period | | - | Literature[1] | |
| *Organizational (impact on healthcare services)* | | | | | |
| Capacity | Laboratory capacity (resources, turnout time, etc.) & technical capacity (results interpretation, etc.) | 2023 (or proxy) | Region, size of healthcare unit | Literature + national data (stakeholders + lab survey) | Qualitative & quantitative analysis |
| Acceptability by:<br>1) Prescribers<br>2) Laboratory staff<br>3) Patients | How patients, physicians and laboratory personnel perceive and react to the test. | | Region, district, size and type of healthcare unit | Literature + National data (stakeholders + prescribers' survey + lab survey) | |
| *Economic (impact on health system)* | | | | | |
| Economic outcomes | Results from economic analyses (e.g. cost-minimization, cost-benefit, | 2023 (or proxy) | - | Literature review (systematic | Narrative quantitative analysis |

| | | | | | |
|---|---|---|---|---|---|
| | cost-utility, cost-effectiveness) describing financial and utility impacts of an intervention or program. | | | reviews, HTA, and economic analyses) | |

[1]Calculated using collected national data and parameter values derived from the literature. *CRC - colorectal cancer; FP - Fluoropyrimidines; HTA - health technology assessment; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life years; RON - National Cancer Registry.*

**Table II-1**. List of indicators, period of reference, data source, and type of analysis planned, by major group of indicators

In the following sections, the study of the three impacts is described in more detail.

### 2.3.1. Study of the impact of *DPYD* genotype testing on morbidity and mortality of CRC patients, in an equity perspective

FPs are frequently used therapeutic solutions in chemotherapy regimens for treating CRC. However, a significant disadvantage of these drugs is the occurrence of severe toxicity, which can affect up to 30% of patients. Reduced activity of the DPD enzyme is one of the main causes of toxicity after FP administration, as it leads to slower drug degradation, resulting in greater exposure to cytotoxic metabolites. Patients with reduced DPD activity are more likely to be exposed to supra-therapeutic drug concentrations after administration of the recommended doses, and consequently, are at risk of developing severe adverse events or even death related to FP administration. There is growing evidence that genotyping *DPYD* prior to starting FP therapy results in a lower incidence of toxicity events and contributes to patient safety and quality of life.

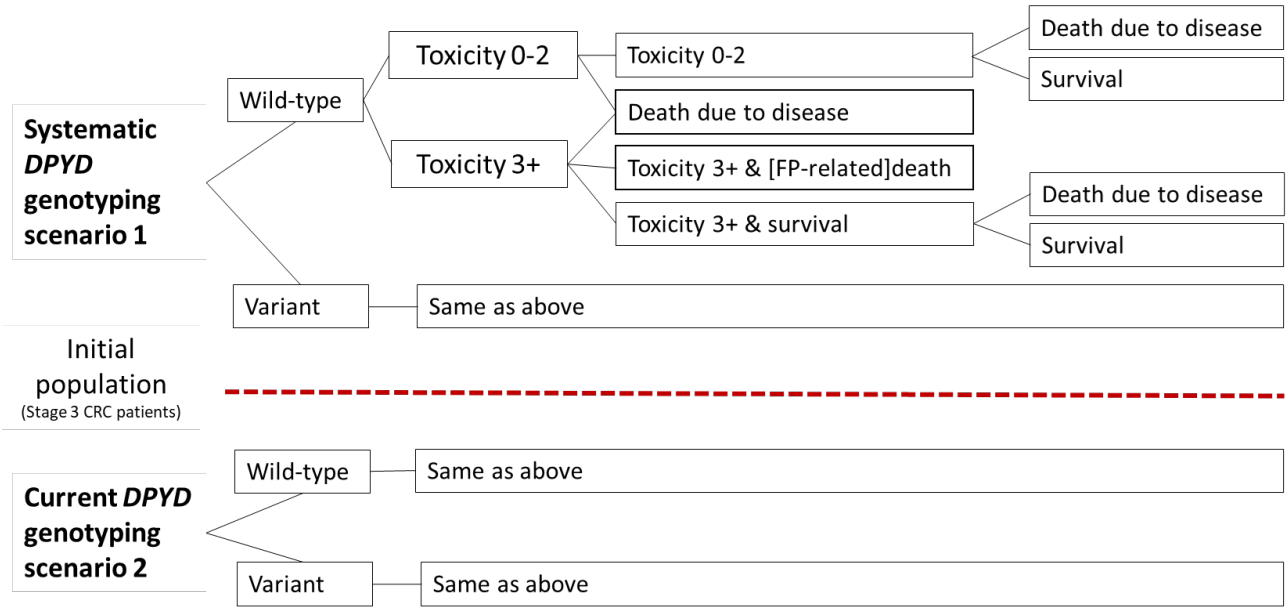
The overall objective of this study is to evaluate the impact of implementing systematic *DPYD* genotyping before administering FPs on post-treatment morbidity and mortality in CRC patients.

The specific objectives of the study are:

- To estimate the effect of systematic *DPYD* genotyping on the incidence of severe toxicity (grade ≥ 3) post-treatment with FPs in CRC patients.
- To estimate the effect of the systematic *DPYD* genotyping on the mortality of CRC patients treated with FPs.

A Markov model was developed through direct collaboration between the INSA team and -the Faculty of Sciences of the University of Lisbon (FCUL), sought as an external collaborator, with contributions from the literature and validation by clinical experts. Each cycle of the Markov model spans six months. During the first cycle patients receive treatment, and outcome measures include severe (grade 3-4) treatment-related toxicity, treatment-related mortality, and non-treatment-related mortality. In the subsequent 9 cycles, the outcome measured is death by any cause. The decision tree for the Markov model is shown in **Figure II-3**.

**Figure II-3.** Markov model decision tree for pre-treatment *DPYD* genotype testing of colorectal




cancer patients.

In the systematic *DPYD* genotyping (scenario 1), all patients undergo *DPYD* genotyping, and those identified with a pathogenic *DPYD* gene variant receive a reduced dose of FP chemotherapy or alternative drug. Conversely, in the current *DPYD* genotyping (scenario 2), *DPYD* genotyping is performed only sporadically. Consequently, in the latter, a proportion of patients with *DPYD* gene variants associated with DPD deficiency remain unrecognized (due to the absence of testing) and consequently receive standard FP doses instead of the recommended reduced doses or alternative regimens.

The assumptions for the Markov model, including state transition probabilities and other data, were derived from international literature (included in Annex 1). However, potential differences were evaluated through sensitivity analyses considering different scenarios. The range of estimates tested in the sensitivity analyses (minimum and maximum values representing each parameter's upper and lower bounds) was based on relevant literature (**Annex I**).

### 2.3.2. Study of the impact of *DPYD* genotype testing on the organizational level

When healthcare providers and patients perceive a health technology as beneficial and easy to integrate into routine practice, the likelihood of its successful implementation increases significantly.

In healthcare interventions, "acceptability" is defined as the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses. This multi-faceted construct includes perceptions of the intervention's effectiveness, comfort, convenience, ethical alignment, and cultural appropriateness (19).

On the other hand, "capacity" in terms of healthcare interventions refers to the ability of the healthcare system, including its infrastructure, workforce, and resources, to effectively implement and sustain the intervention (20).

Systematic *DPYD* genotype testing before treatment with FPs is a strategy that can impact various groups of individuals, including healthcare professionals and patients. The acceptability of the pre-treatment *DPYD* genotype testing is a crucial matter, as it influences both the uptake and the adherence to the policy. Assessing the acceptability of this test among all stakeholders also helps to identify potential barriers and specific concerns, as the perceived relevance of the results. Addressing these barriers through targeted communication and education strategies can then foster a supportive environment for the implementation of the test.

Moreover, the successful implementation of the *DPYD* genotype testing policy heavily relies on the capacity of laboratories. Adequate laboratory infrastructure is crucial to ensure the timely and accurate processing of genotyping tests. This includes having well-trained personnel, appropriate equipment, and robust quality control measures. Without sufficient laboratory capacity, there could be significant delays in testing and reporting, which could hinder clinical decision-making and ultimately affect patient outcomes. Therefore, investigating and promoting laboratory capabilities is essential to support the widespread adoption and effectiveness of *DPYD* genotyping in clinical practice.

The aim of this study was to survey the acceptability and the laboratory capacity for implementing systematic *DPYD* genotyping before administration of FPs in CRC patients.

### 2.3.3. Study of the economic impact of *DPYD* genotype testing

Extensive research has established that some genetic variants in *DPYD* cause a deficiency in DPD enzyme activity, thereby markedly increasing the risk of severe toxicity during the administration of FPs. In such cases, treatment must be interrupted, and the patient may require hospitalization, which not only affects the quality of life and increases the suffering of individuals but also significantly escalates healthcare costs.

Currently, healthcare systems face significant pressures due to constrained human and material resources, emphasizing the need for efficient resource allocation. Therefore, it becomes

increasingly important to explore the cost-effectiveness of personalized treatment strategies including those based on the potential of pharmacogenetic testing.

The overall objective of this study was to evaluate the cost-effectiveness of implementing systematic *DPYD* genotyping before FP treatment in colorectal cancer patients.

### 2.3.4. HIA equity considerations

Health inequities are defined as systematic disparities in health status or in the major social determinants of health between groups with different social advantage /disadvantage (e.g., health, power, prestige) (21). Policy effects in any of these domains may either benefit or harm specific populations who are experiencing or vulnerable to health inequities. An equity focused HIA typically considers impacts on different groups in terms of location, socioeconomic status, existing disability, age, ethnicity, gender, and sexuality during their scoping. Indeed, equity is a crucial perspective in this HIA, particularly regarding the primary impact considered (impact on morbidity and mortality of CRC patients). However, it is important to note that the equity considerations and analysis in subsequent steps of the HIA were limited, due to the lack of national-level data, particularly concerning ethnicity and ancestry. Despite this, an effort was made to compensate by conducting a critical analysis based on existing literature.

# 3. Assessment: Country Case Studies

From this point onwards, Section II focuses on the specific context of each participating country. While the initial phases of the project were conducted in parallel, the data collection approach, as well as the data gathered, vary according to the unique contexts and organizational structures of each country. Thus, the assessment phase is addressed separately for Portugal, Italy, and Finland to reflect the distinct methodologies and realities encountered in each case.

## 3.1. Portugal

### 3.1.1. Process

In the HIA case study in Portugal, the INSA technical team managed the project, organized stakeholder engagement, developed the analytic plan, conducted literature reviews, and prepared the report. The team also collaborated with international partners from the PROPHET Project, with progress on the HIA in all the three countries being regularly assessed through online meetings.

| **Technical Team** | | |
|---|---|---|
| INSA | Astrid Vicente (coordination) | Head of Department of Health Promotion and Prevention of NCDs |
| INSA | Alexandra Costa | Health Policy Researcher |
| INSA | Cristina Costa | Public Health Consultant |
| INSA | Filipa Garvão | Health Promotion MSc. Student |
| INSA | Maria de Fátima Lopes | Bioscience Researcher |
| INSA | Maria Luís Cardoso | Genetics Specialty Pharmacist |
| ***Steering Committee*** | | |
| SPO | Cátia Faustino | Medical Oncology Consultant |
| ULS Santa Maria | João Paulo Cruz | Head of Pharmacy Department |
| IPO-Porto | Manuel Teixeira | Head of Department of Laboratory Genetics |
| INFARMED | Márcia Silva | Pharmacovigilance Assessor |
| RON | Maria José Bento | Head of National Cancer Registry |
| FCUL | Raquel Fonseca | Assistant Professor, Economist |
| ULSTMAD | Rosário Pinto Leite | Head of Department of Clinical Genetics |
| Europacolon | Vítor Neves | President of Patient Association |

FCUL – Faculty of Sciences, University of Lisbon; INSA – National Health Institute Dr. Ricardo Jorge; IPO – Portuguese Institute of Oncology; NCDs – Noncommunicabe Diseases; RON – Portuguese National Cancer Registry; SPO – Portuguese Oncology Society; ULS – Local Health Unit; ULSTMAD – Local Health Unit of Trás-os-Montes and Alto Douro

**Table II-2**. Composition of the technical team and the steering committee for the health impact assessment on *DPYD* genotyping

The INSA technical team established an advisory panel known as the Steering Committee (SC), composed of 8 stakeholders This advisory group consisted of individuals who contributed voluntarily to the project and whose mission was to validate the study protocol and outcomes, and provide guidance, scientific and technical support throughout the HIA process. In this study, the SC included clinical and laboratory experts from healthcare institutions specialised in medical oncology, clinical genetics and cancer genetics, along with expert pharmacists, academics and pharmacovigilance, epidemiology and public health specialists. Representatives from CRC patients' associations were also included in order to ensure a transparent and participatory process. Experts were invited via email, chosen based on their relevant areas of expertise. Table 2 provides a detailed list of the experts, their affiliations and brief description of their roles. For this study, aggregated data on annual CRC incidence (colon, rectosigmoid junction, and/or rectum [codes C18 to C20 in the International Classification of Disease ICD10CM/PCS Version 2019/2020]) was obtained from the Portuguese National Oncology Registry (RON). As the latest data available at the time of this study reported to 2021, the year 2019 was used as a proxy for 2023 in order to avoid the disruptions and potential impacts on incidence rates caused by the COVID-19 pandemic. This decision was validated by the SC, which included clinical and epidemiology cancer experts.

Since not all treatment modalities for CRC include FPs, it was important to ascertain the number of CRC patients who were indeed candidates for FPs. Due to the lack of national data for this matter, it was decided to focus the Markov analysis specifically on stage III CRC patients. This choice was guided by the fact that most European cancer guidelines recommend FPs as first-line therapy for this stage, a decision which was validated by experts within the SC.

To predict the impact that systematic *DPYD* genotyping would have, it is necessary to estimate the current rate of prescription in Portugal. For this purpose, a national survey targeting medical oncology doctors was conducted to investigate the perceptions and habits of prescribers regarding pre-treatment *DPYD* genotyping in CRC patients. The survey was developed with contributions from the literature and integrated inputs from experts at different development stages, as well as pre-testing before electronic distribution. It was also validated by the SC. Oncology physicians were invited to participate in the anonymous online survey via the Portuguese Oncology Society newsletter and direct email invitation to hospitals. Contributions were collected in the months of May and June 2024. The survey results were presented in tables and visualized using boxplots to display the distribution of prescription rates for *DPYD* genotype testing across different groups. Median and interquartile ranges (IQR) were calculated to summarize the central tendency and

variability within each group. Non-parametric tests, such as the Mann-Whitney U test and Kruskal-Wallis test, were used due to the non-normal distribution of data in several groups.

In order to shed some light on how the policy could affect some population subgroups differently, focusing in an equity perspective, a Markov chain model extended analysis was used to simulate the impact considering effect distribution according to hospital dimension (small, medium or large) and workplace healthcare sector (exclusively NHS vs. exclusively private sector). A hypothetical population of 1000 stage III CRC patients was used as input data for testing these scenarios and assumptions for the *DPYD* prescription rates were based on data collected from the survey. All other assumptions for the Markov model, including state transition probabilities, were kept unchanged.

To obtain an overview of the existing evidence regarding laboratory capacity and acceptability of *DPYD* genotype testing before treatment with FPs among healthcare workers and patients, a narrative literature review was conducted (Table II-1). Relevant terms were searched in national and international databases and repositories (Pubmed, Scopus, Web of Science, and RCAAP) for scientific papers published from January 2020 onwards.

To complement the literature review with data from the national context, information on the prescription practices and acceptability of *DPYD* genotype testing in Portugal was collected through two separate online surveys.

The first survey was directed at colorectal oncology physicians in Portugal and aimed to gather data on the *DPYD* genotyping prescription rate as well as perceptions of the test's acceptability, based on the seven-component constructs of the Theoretical Framework of Acceptability (TFA). A second online survey was administered to laboratory personnel from Portuguese genetic laboratories to gather data on capacity indicators and the acceptability of the *DPYD* genotyping test. Additionally, a consultation with stakeholders was conducted to discuss these indicators, enhancing the data on the acceptability and capacity for the intervention. This approach aimed to better estimate the organizational impact of the intervention in Portugal.

For assessing the economic impact of systematic *DPYD* genotyping, a literature review was conducted on PubMed, Web of Science, and Scopus, employing search terms such as “DPYD”, “genotype”, and “cost-effectiveness” (the complete query is detailed in Annex II). Duplicate entries were removed, and the screening process was conducted in three stages: initially by title, followed by abstract, and finally through full-text analysis. The inclusion criteria were: (a) studies assessing the cost-effectiveness, cost-utility, or economic impact of *DPYD* testing prior to FPs treatment specific to, or including, CRC. The exclusion criteria were: (a) studies on the cost-effectiveness, cost-utility, or economic impact of *DPYD* testing prior to FPs treatment that do not mention CRC; (b) studies on *DPYD* testing before FPs treatment in CRC that do not evaluate cost-effectiveness, cost-utility, or economic impact; (c) review articles, (d) opinion articles, (e) studies done exclusively on pediatric populations, and (f) studies written in a language other than Portuguese or English.

### 3.1.2. Findings

#### *3.1.2.1. DPYD Genotyping Prescription Survey Results*

The results of the survey to oncology physicians shows that the mean prescription rate of *DPYD* genotyping in Portugal for the year 2023 was 78.63% (SD 35.27). There were no statistically significant differences in the pre-treatment *DPYD* genotype prescription rate based on physicians' sex, age group, or years of professional experience in medical oncology (see **Table II-3**).

| | | n (%) | Mean (SD) | Median (IQR) | p-value |
|---|---|---|---|---|---|
| **Sex** | **Male** | 20 (23.8) | 77.95 (33.91) | 93.05 (19.25) | 0.283 |
| | **Female** | 64 (76.2) | 78.84 (36.21) | 100.00 (38.00) | |
| **Age group (years)** | **<35** | 24 (28.6) | 80.17 (36.88) | 100.00 (9.50) | 0.209 |
| | **35-49** | 46 (54.8) | 74.34 (37.28) | 100.00 (38.00) | |
| | **50 and over** | 14 (16.7) | 90.11 (24.65) | 100.00 (0.00) | |
| **Professional experience as an Oncology physician (years)** | **Oncology resident** | 14 (16.7) | 83.89 (34.49) | 100.00 (0.00) | 0.708 |
| | **Less than 5** | 22 (26.2) | 73.23 (40.89) | 100.00 (56.75) | |
| | **5 to 10** | 19 (22.6) | 74.90 (39.31) | 100.00 (38.00) | |
| | **11 to 20** | 17 (20.2) | 78.53 (31.57) | 100.00 (38.00) | |
| | **More than 20** | 12 (14.3) | 88.46 (26.41) | 100.00 (3.25) | |
| **Region of workplace** | **North** | 42 (50.0) | 94.04 (22.16) | 100.00 (0.00) | **<0.001*** |
| | **Centre** | 10 (11.9) | 86.15 (28.58) | 100.00 (9.75) | |
| | **Lisbon and Tagus Valley** | 25 (29.8) | 45.80 (39.20) | 37.00 (74.50) | |
| | **Alentejo** | 1 (1.2) | 62.00 (0.00) | 62.00 (0.00) | |
| | **Algarve** | 3 (3.6) | 100.00 (0.00) | 100.00 (0.00) | |
| | **Azores** | 2 (2.4) | 93.50 (9.19) | 93.50 (6.50) | |
| | **Madeira** | 1 (1.2) | 100.00 (0.00) | 100.00 (0.00) | |

**Table II-3**. Descriptive statistics of the survey on prescription practice of oncology physician

*regions with less than three data points were excluded.

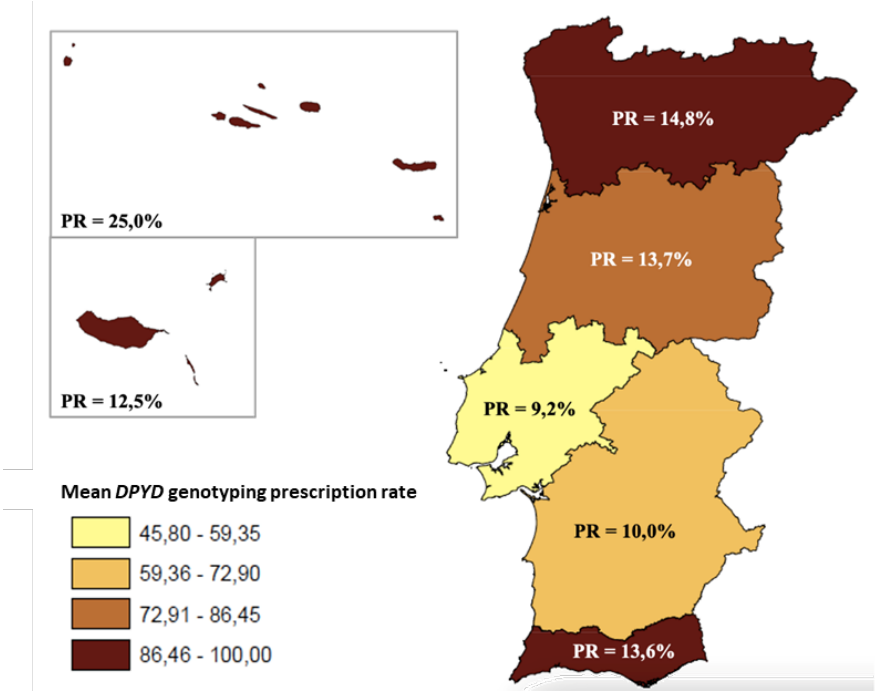



**Figure II-4**. Mean *DPYD* genotyping prescription rate among medical oncology physicians in Portugal, by region. PR: estimated participation rate.

**Figure II-4** shows the mean prescription rates by region of practice of physicians. A statistically significant difference was observed between regions, with the North region having the highest prescription rate (mean = 94.04% [SD 22.16]; p < 0.001) among the four regions tested (North, Centro, Lisbon and Tagus Valley and Algarve) [**Table II-3**].

The department's dimension (for which the number of specialist oncologists was used as a proxy), having *DYPD* genotype protocols in place, and the turnaround test time all seem to be associated with pre-treatment *DPYD* genotype test prescription rate (**Table II-4**).

| | | n (%) | Mean (SD) | Median (IQR) | p-value |
|---|---|---|---|---|---|
| **Pre-existing department *DPYD* genotype test protocol** | **Yes** | 68 (81.0) | 88.15 (26.76) | 100.0 (0.00) | **<0.001** |
| | **No** | 16 (19.0) | 38.16 (40.09) | 12.5 (52.50) | |
| **Type of workplace** | **Exclusively works in NHS** | 71 (87.7) | 79.86 (35.17) | 100.0 (38.00) | **0.045** |
| | **Works in both NHS and private sector. or in PPP** | 3 (3.7) | 62.33 (54.37) | 87.00 (50.00) | |

| | | | | | |
|---|---|---|---|---|---|
| | **Working in private sector only** | 7 (8.6) | 64.00 (36.95) | 87.00 (49.75) | |
| **Department dimension** | **Small** | 15 (17.9) | 61.40 (34.86) | 62.00 (56.50) | **0.011** |
| | **Medium** | 23 (27.4) | 83.61 (31.88) | 100.00 (13.00) | |
| | **Large** | 46 (54.8) | 81.76 (36.40) | 100.00 (0.00) | |
| **Turnaround *DPYD* genotype test time (working days)** | **< 5** | 4 (4.8) | 100.00 (0.000) | 100.00 (0.00) | **0.005** |
| | **5 a 10** | 48 (57.1) | 92.35 (19.49) | 100.00 (0.00) | |
| | **> 10** | 26 (31.0) | 64.31 (39.52) | 81.00 (81.36) | |
| | **Do not know/ cannot recall** | 6 (7.1) | 16.667 (40.83) | 0.0 (0.00) | |

**Table II-4.** Descriptive statistics of the survey of laboratory departments NHS - National Health Service; PPP - public-private partnership hospitals

Larger departments and those with existing *DPYD* genotype testing protocols exhibited significantly higher prescription rates (mean = 81.76% [SD 36.40], p = 0.011; and mean = 88.15% [SD 26.76], p < 0.001, respectively). Shorter turnaround times were also associated with higher prescription rates (p = 0.005) [**Table II-4**].

Physicians working in hospitals from the Portuguese National Health Service (NHS) had statistically significantly higher *DPYD* genotype test prescription rates (mean = 79.86% [SD 35.17]; p = 0.045) compared to those working in private sector [**Table II-4**].

### 3.1.2.2. Markov Model - main morbidity and mortality outcomes

According to RON, there were 8163 cases of CRC diagnosed in Portugal in the year 2019, used as proxy for 2023 in this study. The distribution of cases according to stage is shown in **Table II-5**. **Table II-6** shows the sex and age group distribution of these cases.

| CRC Stage | N (%) |
|---|---|
| **I** | 1675 (20.5) |
| **II** | 1973 (24.2) |
| **III** | 2210 (27.1) |

| | |
|---|---|
| **IV** | 1521 (18.6) |
| **Unknown** | 784 (9.6) |
| **Total** | 8163 (100) |

Source: RON

**Table II-5**. Number of CRC cases in 2019 in Portugal, by stage

| **CRC Stage III** | **N (%)** |
|---|---|
| **Sex** | |
| **Female** | 927 (41.9) |
| **Male** | 1283 (58,1) |
| **Age group (years)** | |
| **≤ 24** | 3 (0.1) |
| **25 to 64** | 795 (36.0) |
| **65 to 74** | 624 (28.2) |
| **≥ 75** | 788 (35.7) |
| **Total** | 2210 (100) |

**Table II-6**. Number of stage III CRC cases in 2019 in Portugal, by sex and age group Source: RON

In the main analysis, the Markov model assumptions included an initial population of 2210 CRC stage III patients and an average current *DPYD* genotype test prescription rate of 78.63% for Portugal. **Table II-7** displays the outcomes in total expected serious (grade 3+) toxicity events, number of toxicity-related deaths, and number of deaths at 5 years follow-up for the scenario 1 (systematic *DPYD* genotyping) and scenario 2 (current *DPYD* genotyping).

| **Outcome** | **Scenario 1 Systematic *DPYD* genotyping; n (%)** | **Scenario 2 Current *DPYD* genotyping; n (%)** | **Relative risk (RR)** | **Preventive fraction** |
|---|---|---|---|---|
| Severe (grade 3-4) toxicity | 534.47 (24.18%) | 546.35 (24.72%) | 0.978 | 2.2% |
| Toxicity-related mortality | 2.37 (0.11%) | 3.11 (0.14%) | 0.764 | 23.6% |
| 5-year mortality | 162.03 (7.33%) | 165.63 (7.49%) | 0.978 | 2.18% |

**Table II-7**. Main Markov model outcomes and estimated association measures

As shown in **Table II-7,** implementation of systematic genotyping reduced incidence of severe (grade 3-4) toxicity events from 24.72% to 24.18% and toxicity-related mortality from 0.14% to 0.11%. when compared to the current scenario in Portugal where the average test prescription rate is 78.63%. This represents a relative risk reduction of 2.18% for severe toxicity and 21.43% for toxicity-

related mortality. The preventive fractions for severe toxicity and toxicity-related mortality indicate that systematic genotyping could prevent 2.2% of severe toxicity cases and 23.6% of deaths related to toxicity.

The impact of systematic *DPYD* genotyping on 5-year mortality in CRC patients was also estimated by the model. The implementation of systematic genotyping reduced 5-year mortality from 7.49% to 7.33%, representing a relative risk reduction of 2.14%. The preventive fraction is 2.18%, indicating that systematic genotyping could have prevented such proportion of 5-year mortality cases, if it had been in place.

These results suggest that systematic *DPYD* genotyping has the potential for improving overall patient outcomes, with a reduction in the incidence of toxicity events, the toxicity-related mortality, and the 5-year mortality rates among colorectal cancer patients.

| Outcome | Scenario 1<br>Systematic *DPYD* genotyping;<br>n (%) | Scenario 2<br>Current *DPYD* genotyping;<br>n (%) |
|---|---|---|
| **Female** | | |
| Severe (grade 3-4) toxicity | 224.19 (24.18%) | 229.17 (24.72%) |
| Toxicity-related mortality | 1.00 (0.11%) | 1.30 (0.14%) |
| 5-year mortality | 67.96 (7.33%) | 69.47 (7.49%) |
| **Male** | | |
| Severe (grade 3-4) toxicity | 3010.28 (24.18%) | 317.18 (24.72%) |
| Toxicity-related mortality | 1.38 (0.11%) | 1.80 (0.14%) |
| 5-year mortality | 994.06 (7.33%) | 96.155 (7.49%) |

**Table II-8**. Markov model - outcomes by sex

**Tables II-8 and II-9** present the secondary outcomes of the analysis by sex and age group, with the input data provided by the national cancer registry (**Table II-6**) and the same assumption for national mean *DPYD* genotype prescription rate of 78.63%.

| Outcome | Scenario 1<br>Systematic *DPYD* genotyping;<br>n (%) | Scenario 2<br>Current *DPYD* genotyping;<br>n (%) |
|---|---|---|
| **Age group: ≤ 64 years** | | |
| Severe (grade 3-4) toxicity | 192.99 (24.18%) | 197.28 (24.72%) |
| Toxicity-related mortality | 0.86 (0.11%) | 1.12 (0.14%) |
| 5-year mortality | 58.51 (7.33%) | 59.81 (7.49%) |
| **Age group: 65 to 74 years** | | |
| Severe (grade 3-4) toxicity | 150.91 (24.18%) | 154.26 (24.72%) |
| Toxicity-related mortality | 0.67 (0.11%) | 0.88 (0.14%) |
| 5-year mortality | 57.78 (7.33%) | 59.06 (7.49%) |

| | | |
|---|---|---|
| **Age group: ≥75 years** | | |
| Severe (grade 3-4) toxicity | 190.57 (24.18%) | 194.81 (24.72%) |
| Toxicity-related mortality | 0.85 (0.11%) | 1.11 (0.14%) |
| 5-year mortality | 57.77 (7.33%) | 59.06 (7.49%) |

**Table II-9**. Markov model - outcomes by age group

### 3.1.2.3. Sensitivity analysis

A probabilistic sensitivity analysis for the main model was conducted to explore parameter uncertainty and demonstrate robustness of the results. The list of estimate ranges tested in the sensitivity analyses was based on relevant literature **(Annex I).**

The results indicate that systematic genotyping consistently results in fewer cases of severe (grade 3-4) toxicity compared to the current genotyping strategy across the range of outcomes. The analysis also shows that systematic *DPYD* genotyping results in significantly lower toxicity-related mortality across all quartiles and the median compared to current genotyping.

The sensitivity analysis confirms that systematic *DPYD* genotyping (scenario 1) consistently reduces both severe (grade 3-4) toxicity events and toxicity-related mortality compared to the current genotyping strategy (scenario 2). The reductions are evident across the entire range of outcomes, demonstrating the robustness and reliability of the systematic *DPYD* genotyping approach in improving patient outcomes. These findings underscore the potential benefits of adopting systematic *DPYD* genotyping in clinical practice for colorectal cancer patients undergoing fluoropyrimidine therapy.

Likewise, the sensitivity analysis conducted examined the robustness of the results for both systematic *DPYD* genotyping (Scenario 1) and current genotyping (Scenario 2) in terms of 5-year mortality (**Figure II-5**)**.** The analysis confirms that systematic *DPYD* genotyping reduces 5-year mortality, as it results in significantly lower mortality at the 3rd quartile, maximum, and mean values compared to current *DPYD* genotyping. These findings support the effectiveness of systematic *DPYD* genotyping in improving long-term survival outcomes for colorectal cancer patients undergoing FP therapy.

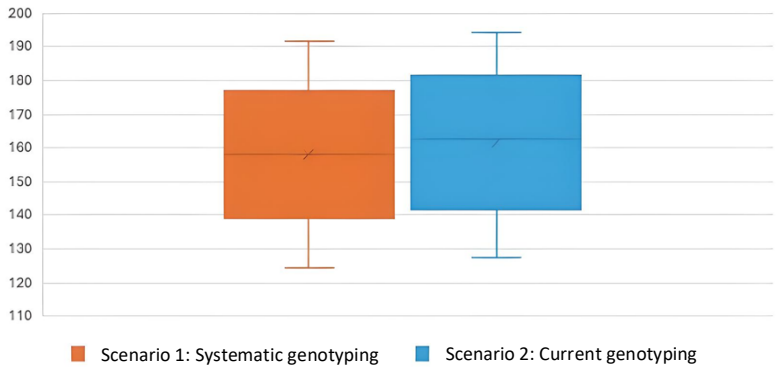



**Figure II-5**. Sensitivity analysis for 5-year mortality outcome

### 3.1.2.4. Markov Model - expanded analysis with a focus on equity

In order to shed some light in how the policy could affect some population subgroups differently, the Markov model was used to simulate the impact considering effect distribution according to hospital dimension (**Table II-10**) and workplace sector (**Table II-11).**

In this analysis, the impact of implementation of systematic *DPYD* genotyping on hospitals of different sizes (small, medium, or large) was evaluated, based on their average *DPYD* genotype testing rate. As presented in Table 4, the mean *DPYD* genotyping rate is significantly lower in small hospitals [x̄=61,40% (SD 34,8621) vs. x̄=83,61% (SD 31,8797) and x̄=81,76% (SD 36,4019) in medium and large-sized hospitals, respectively].

| Scenario 1: Systematic genotyping | | Scenario 2: Current genotyping | | | | | |
|---|---|---|---|---|---|---|---|
| | | Hospital dimension: Small | | Hospital dimension: Medium | | Hospital dimension: Large | |
| | n (%) | n (%) | RR; PF | n (%) | RR; PF | n (%) | RR; PF |
| Grade 3-4 Toxicity | 241.84 (24.18%) | 251.55 (25.16%) | 0.961; (3.86%) | 245.96 (24.60%) | 0.983; 1.68% | 246.42 (24.64%) | 0.981; 1.87% |
| Toxicity-related mortality | 1.074 (0.11%) | 1.674 (0.17%) | 0.641; 35.84% | 1.329 (0.13%) | 0.808 19.18% | 1.357 (0.14%) | 0.791 20.9% |
| 5-year Mortality | 73.32 (7.33%) | 76.26 (7.63%) | 0.961; 3.86% | 74.57 (7.46%) | 0.983 1.68% | 74.71 (7.47%) | 0.981; 1.87% |

RR- relative risk; AR- attributable risk; PF- preventive fraction

**Table II-10.** Expanded Markov model outcomes according to hospital dimension

RR- relative risk; AR- attributable risk; PF- preventive fraction

In terms of severe (grade 3-4) toxicity events, small hospitals would see a reduction from 25.16% to 24.18% with a relative risk (RR) of 0.9614, while medium and large hospitals would see more modest reductions with RRs of 0.983 and 0.981, respectively (Table 10). As the testing rate is lower in small hospitals, those could have the most significant reduction in toxicity-related mortality with an RR of 0.642, indicating a 35.84% reduction in risk. Regarding 5-year mortality, all hospital sizes experienced similar reductions, with small hospitals having an RR of 0.914 and medium and large hospitals having RRs of 0.983 and 0.981, respectively. These results suggest that systematic *DPYD* genotyping is most effective in reducing toxicity-related mortality, particularly in smaller hospitals, while also providing modest reductions in severe toxicity and 5-year mortality across all hospital sizes.

The analysis also explored the impact of systematic *DPYD* genotype testing across different workplace sectors (exclusively NHS vs. exclusively private sector) [**Table II-11**].

As we can remember from Table 4, the mean *DPYD* genotype prescription rate is higher in prescribers who claim to only work in the public sector (NHS) than in those who report to be exclusively employed in the private sector [x̄=79.86% (SD 35.173) vs. x̄=64.00% (SD 36.949)].
In the NHS sector, systematic genotyping reduced severe (grade 3-4) toxicity from 24.68% to 24.18% and toxicity-related mortality from 0.14% to 0.11%, with a preventive fraction (PF) of 2.02% and 22.28% respectively. In the private sector, the intervention reduced severe toxicity from 25.09% to 24.18% and toxicity-related mortality from 0.16% to 0.11%, with a PF of 3.61% and 34.29% respectively. For 5-year mortality, both sectors showed modest reductions, with the private sector having a slightly higher PF. These results indicate that systematic *DPYD* genotyping is effective in reducing severe toxicity and mortality, particularly in the private sector where the preventive impact is more pronounced.

| Scenario 1: Systematic *DPYD* genotyping | | Scenario 2: current *DPYD* genotyping | | | |
|---|---|---|---|---|---|
| | | Workplace sector: exclusively NHS | | Workplace sector: exclusively private | |
| | n (%) | n (%) | RR; PF | n (%) | RR; PF |
| Grade 3-4 Toxicity | 241.84 (24.18%) | 246.81 (24.68%) | 0.98; 2.02% | 250.90 (25.09%) | 0.964; 3.61% |
| Toxicity-related mortality | 1.074 (0.11%) | 1.38 (0.14%) | 0.78; 22.28% | 1.63; (0.16%) | 0.657; 34.29% |
| 5-year Mortality | 73.32; (7.33%) | 74.82; (7.48%) | 0.98; 2.01% | 76.06; (7.61%) | 0.964; 3.62% |

**Table II-11**. Expanded Markov model outcomes according to workplace sector
RR- relative risk; AR- attributable risk; PF- preventive fraction

### 3.1.2.5. Impact of *DPYD* genotype testing at the organizational level

Recent literature highlights possible significant capacity-related challenges in the implementation of *DPYD* genotype testing. Key barriers identified include inadequate infrastructure, insufficient financial reimbursements, and the need for additional resources (22–24). The need for dedicated personnel, such as pharmacists trained in pharmacogenetics, to coordinate the testing process and manage patient follow-up was also recommended (22–24). Furthermore, the necessity of improving laboratory capacity and infrastructure to handle increased testing volumes was a recurring theme (24,25).
Indeed, the necessity for laboratories to improve their capacity and facilities to meet increased testing demands is crucial. It is therefore important to understand the context-specific baseline

laboratory capabilities, logistical framework, and infrastructure situation to successfully scale up *DPYD* genotype testing.

**Figure II-6** displays the results from the survey done to laboratory personnel regarding *DPYD* genotype testing. The survey was distributed online to a convenient sample of 20 public (NHS-funded) and privately-funded genetic laboratories, and it collected responses from a total of 12 different laboratories throughout Portugal.

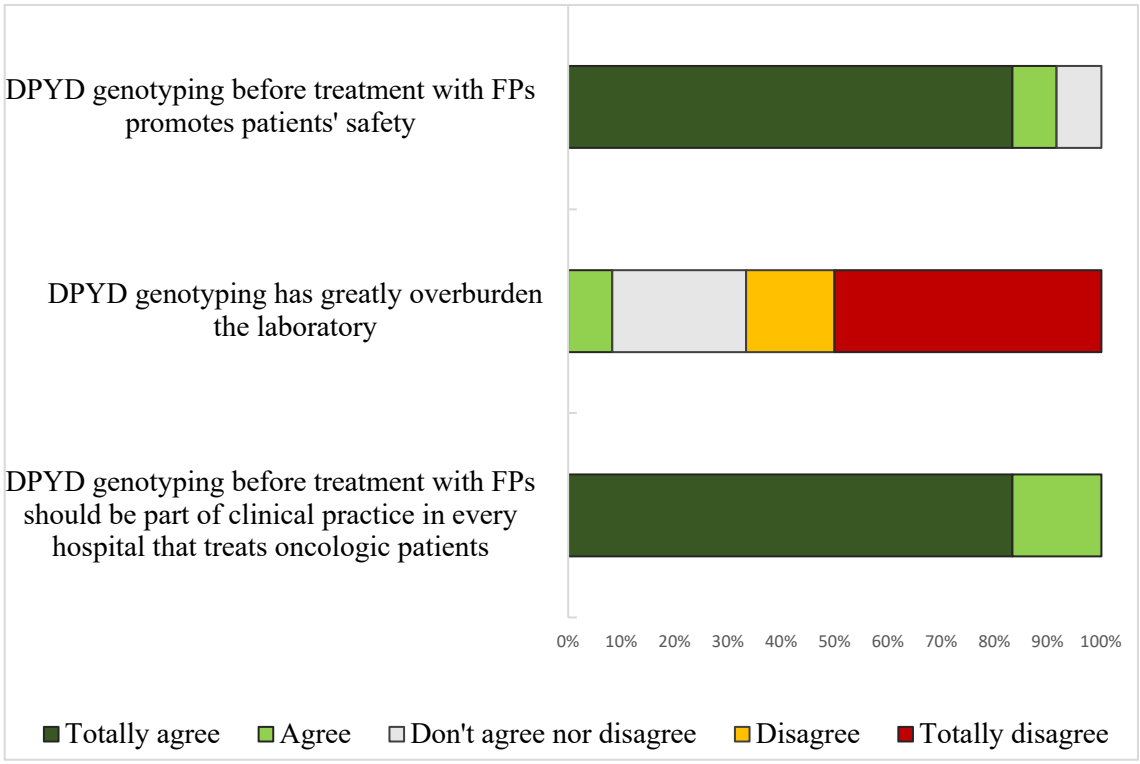



**Figure II-6.** Results of survey to genetic laboratory personnel (capacity and acceptability)

It was found that only a minority (10%) of lab personnel in Portugal agrees that *DPYD* genotyping has greatly overburdened the laboratory (Figure II-6).

To explore the potential barriers to *DPYD* genotype testing from the prescribers' perspective, oncology physicians in Portugal were asked to rank the most frequent motivations for non-prescription of the *DPYD* genotyping to cancer patients before FP therapy. **Figure II-7** illustrates the perceptions on their own motives for non-prescription of the *DPYD* genotype test to cancer patients' candidates for FPs. The "delay in receiving the test results" was the most appointed reason, with at nearly 80% of respondents considering this important, very important or extremely important. Then, "concerns about the cost for the healthcare system" and "low prevalence of polymorphisms associated with DPD activity deficiency", were the next most selected motives for non-prescription of pre-treatment *DPYD* genotype test, considered to be important by the majority. These were

followed by “lack of guidelines recommending *DPYD* genotyping” and “doubts about usefulness of the test” (**Figure II-7**).

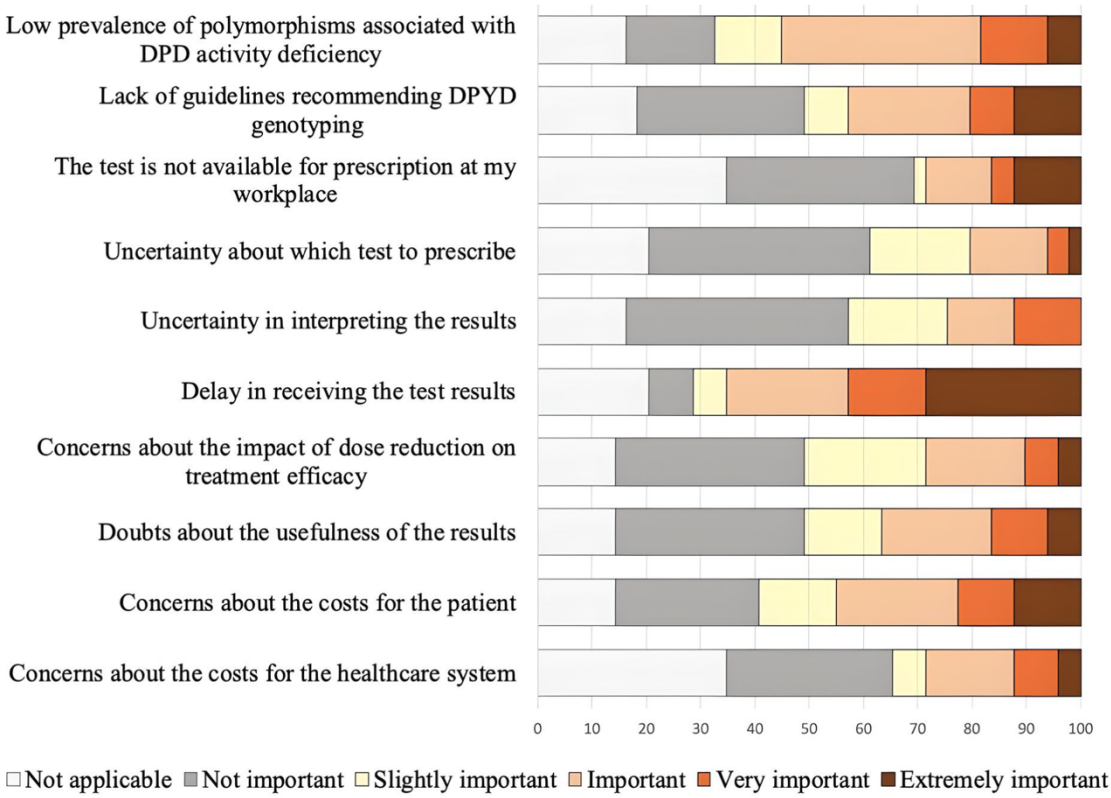



**Figure II-7**. Self-reported motivations for non-prescription of DPYD genotype testing

Despite growing interest in personalized medicine, there are relatively few studies in the literature that specifically address the acceptability of *DPYD* genotype testing.

In 2022, Glewis et al. conducted a cross-sectional survey to explore the acceptability of a pharmacogenetics screening program among healthcare professionals (HCPs) and patients, focusing on *DPYD* genotyping before chemotherapy with fluoropyrimidines. The study revealed that both HCPs and patients accepted the test and the consequent dose adjustments. The turnaround time for test results, which was 5 to 7 days, was considered acceptable by both groups, and they were comfortable with results being delivered by a pharmacist. The majority of HCPs (96%) were willing to offer pharmacogenetic testing beyond the trial, although they identified barriers such as lack of financial reimbursements and infrastructure (22).

Although not specific to *DPYD* genotyping, in Spain, Zubiaur et al. evaluated the perspectives on overall pharmacogenetic testing in two cohorts: one group of patients who had received any type of pharmacogenetic test and another group of healthy volunteers enrolled in a clinical trial for research purposes. Both groups found pharmacogenetic testing beneficial and believed that they should be informed of the results, not only for disease management but also for other relevant

future implications. The study highlighted the broad acceptability of pharmacogenetic testing and the desire for comprehensive communication of test results (23).

In Ontario, a HTA report assessed the clinical and economic impact of *DPYD* genotyping in cancer patients undergoing treatment with fluoropyrimidines. The HTA included surveys and interviews with both patients and healthcare professionals to gauge their acceptability of the *DPYD* genotyping. The results indicated strong support for the genotyping intervention, with a high percentage of patients (over 80%) and HCPs (around 90%) favoring the implementation of systematic *DPYD* testing. Patients appreciated the potential to avoid severe toxicities, which enhanced their overall confidence in the treatment process. Healthcare professionals valued the improved patient safety and treatment outcomes, recognizing the test's role in personalizing treatment plans. Despite the positive feedback, barriers such as financial and logistical challenges were noted, particularly the need for funding support and integration into existing clinical workflows (25).

In order to investigate the acceptability of *DPYD* genotype testing in Portugal, the survey to colorectal oncology physicians in Portugal gathered data on perceptions of acceptability based on the seven-component constructs of the Theoretical Framework of Acceptability (TFA). Results are presented in **Figure II-8**.

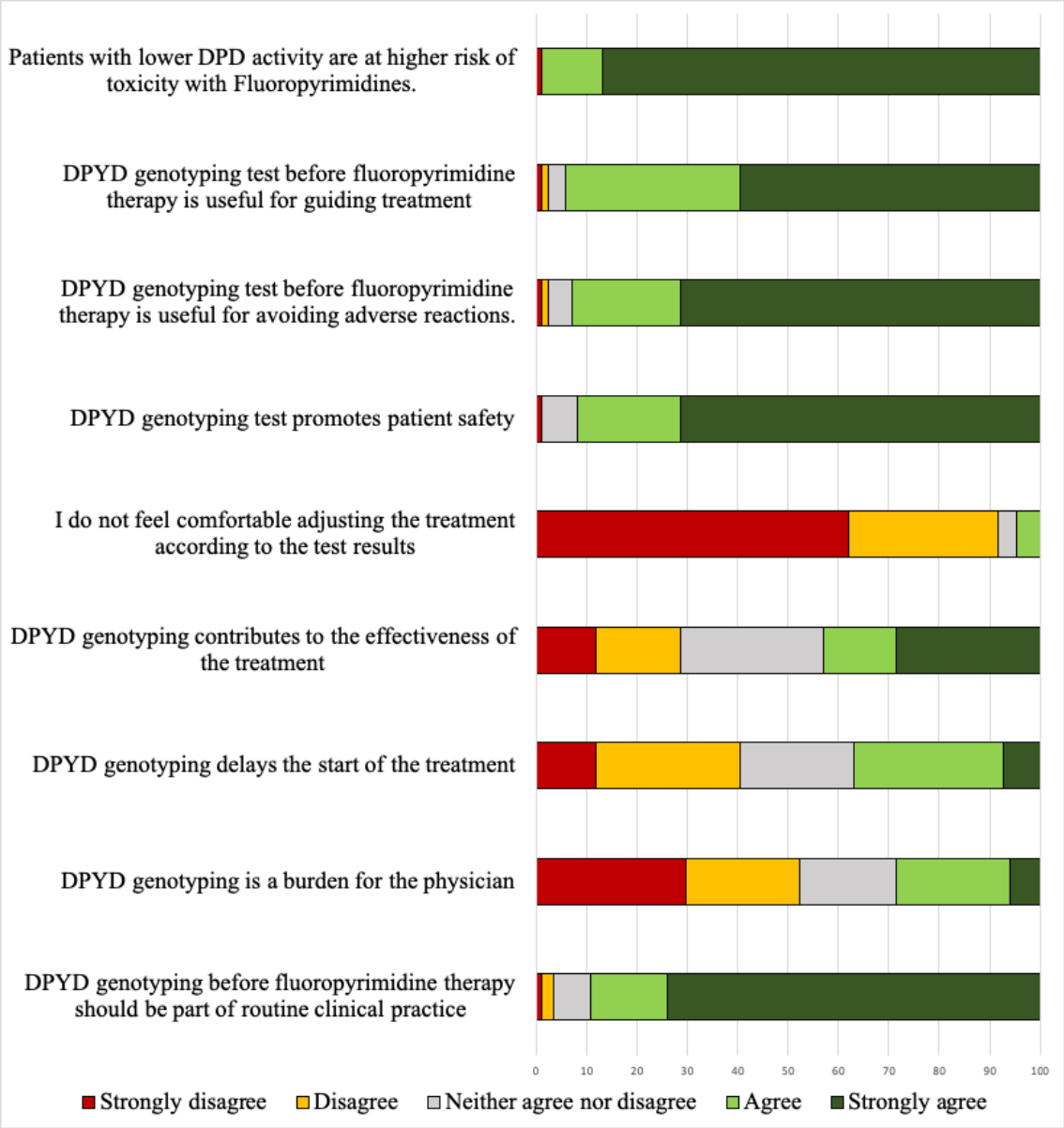



**Figure II-8**. Results of survey to oncology physicians on acceptability of DPYD

There was a strong consensus among oncologists that patients with lower DPD activity are at higher risk of toxicity with Fluoropyrimidines, that pre-treatment *DPYD* genotyping is useful for both guiding treatment and avoiding adverse reactions, and that *DPYD* genotyping promotes patient safety. Additionally, interpreting *DPYD* genotyping results or handling the additional workload associated with it was not a concern for the majority of oncologists: over 90% of respondents felt confident in adjusting treatments based on test outcomes, and more than 70% disagreed that *DPYD* genotyping is burdensome (**Figure II-8**).

Among genetic laboratory staff, there was near-uniform agreement that *DPYD* genotyping before starting fluoropyrimidine therapy promotes patient safety, and that it should be part of the routine laboratory practice in hospitals with Oncology Departments (**Figure II-7**).

### 3.1.2.5. Economic impact of *DPYD* genotype testing

The literature review assessed the cost-effectiveness of implementing systematic *DPYD* gene genotyping before administering FPs in CRC patients. A total of 12 studies were found and a summary of relevant findings is presented in **Table II-12**. The analysis revealed that systematic *DPYD* genotyping consistently demonstrated cost savings and improved patient outcomes across the ten studies reviewed. Most studies reported significant reductions in severe toxicity and associated healthcare costs. The cost savings primarily resulted from decreased hospital admissions and lower costs of managing severe toxicities, making the upfront costs of genotyping justified. Incremental cost-effectiveness ratios (ICERs) and other economic measures showed that systematic genotyping was a worthwhile investment, with studies indicating favorable cost-effectiveness thresholds. Overall, systematic *DPYD* genotyping was found to be cost-effective, enhancing patient safety and optimizing healthcare resource allocation

| Authors (Year), Country | Variants tested | Type of economic evaluation | Population | Intervention | N | Costs considered | Key findings |
|---|---|---|---|---|---|---|---|
| **Deenen et al (2015); Netherlands (26)** | *DPYD*2A* | Cost-minimization analysis using a decision analytical model | CRC patients | Upfront *DPYD* genotyping: analysis of prospective *DPYD* genotyping and subsequent dose adjustment vs. no genotyping (historical cohort) treated with standard dose (SD) of FP | Prospectively genotyped: n=2038; Historical cohort: n=3974 | Genotyping costs, costs of managing severe toxicities, hospitalization costs | Costs of screening and treatment: €2,772 per patient; Costs of nonscreening and treatment: €2,817 per patient; Cost saving: €45 per patient. Upfront *DPYD* genotyping is cost-effective and reduces severe toxicity events. |
| **Cortejoso et al (2016); Spain (27)** | *DPYD*2A* c.2846A>T c.1679T>G | Cost benefit analysis | CRC patients | Compared costs of screening for *DPYD* using real-time PCR and TaqMan probes vs. costs of treating neutropenia | n = 20 (CRC patients treated with FPs who had severe neutropenia) | Genotyping (equipment & personnel) costs, costs of managing severe neutropenia, hospitalization costs | Cost of *DPYD* genotyping 1000 patients: €6400; Cost of treating severe neutropenia: €3044 per patient. *DPYD* genotyping is cost-effective by genotyping the three *DPYD* variants in at least 2.21 cases per |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | 1000 treated CRC patients. |
| **Toffoli et al (2018); Italy (28)** | *DPYD*2A* c.1679T>G c.2846A>T c.1236G>A | Cost benefit analysis | CRC patients | CRC patients treated with SD-FPs who developed toxicities were retrospectively genotyped for *DPYD* and costs associated with toxicity management of wild-type and carriers of *DPYD* variants were compared | n = 550 CRC patients who had severe toxicity (37 carried *DPYD* variants) | Genotyping costs, costs of managing severe toxicities, hospitalization costs, treatment costs | Genotype-guided dosing is cost-saving. Toxicity management costs for wild-type: €825 Toxicity management costs for carriers of at least one *DPYD* variant: €2,972 |
| **Murphy et al (2018); Ireland (29)** | *DPYD*2A* 2846A>T, 1601G>A 1679T>G | Cost benefit analysis | CRC patients | Private hospital performed cost analysis of anticipated cost of implementing screening for *DPYD* mutations versus its usual practice (i.e., prospective *DPYD* testing was compared with reactive screening) | n = 134 CRC patients treated with FP in a 3yr period (30 had severe toxicity, 5 were *DPYD* variant carriers) | Genotyping costs, costs of managing severe toxicities, hospitalization costs, costs of delayed treatments | Costs related to hospitalization due to toxicity: €46,412 per case (total: €232,060); Cost per test: €177; Genotyping all 134 patients prospectively would have cost €23,718, being cost-saving. If at least 60% of patients identified with a *DPYD* mutation were prevented from experiencing severe |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | toxicity resulting in hospitalization, €120 000 would have been saved over the 3-year period. |
| **Fragoulakis et al (2019); Italy**<br><br>**(30)** | *DPYD*2A*<br>c.1679T>G<br>c.2846A>T<br>c.1236G>A | Cost benefit analysis | CRC patients | Patients with CRC who received FPs were retrospectively genotyped for *DPYD* and a comparison of severe toxicity management costs was done between wild-type and carriers | n = 571 (528 wild-type and 43 carriers) | Genotyping costs; Costs associated with severe toxicity, including cost of hospitalization and treatment | Pharmacogenomic-guided dosing is cost-saving.<br>Costs for toxicity management in the wild-type group: €1,150<br>Costs for toxicity management in the carriers group: €3,712 |
| **Henricks et al (2019); Netherlands**<br><br>**(31)** | *DPYD*2A*<br>c.1679T>G<br>c.2846A>T<br>c.1236G>A | Cost-minimization analysis using a decision analytical model | Cancer patients (including CRC) | Prospective clinical trial to compare prospective screening of *DPYD* with no screening: identified heterozygous *DPYD* variant carriers received FP dose reduction were compared to *DPYD* wild-type patients who received SD FP. | Prospectively genotyped: n=1,103 (1018 wild-type and 85 carriers of *DPYD* variants) | Genotyping costs; Costs associated with severe toxicity | Total costs for screening strategy: €2599 per patient; Costs for non-screening: €2650 per patient; Net cost savings of €51 per patient<br>Sensitivity analysis demonstrated the screening strategy was most likely cost-saving |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | or, in the worst-case scenario, cost-neutral. |
| **Ontario Health (2021), Canada (25)** | *DPYD2A* *DPYD13* c.2846A>T c.1236G>A | Cost-utility analysis | Cancer patients (including CRC) | Pre-treatment *DPYD* genotyping was compared with usual care to evaluate impact of *DPYD* genotyping on costs and outcomes. In the *DPYD* genotyping strategy, all patients candidates for FP therapy received upfront *DPYD* genotyping and dose adjustment as appropriate. In the usual care strategy, no *DPYD* genotyping is conducted, and all patients receive SD FP | N/A | Genotyping costs, costs associated with managing severe toxicities, hospitalization costs, costs of dose adjustment | The incremental cost-effectiveness ratio (ICER) was estimated at $12,000 per QALY. The study found that implementing *DPYD* genotyping could result in a net saving of $134 per patient due to reduced hospitalizations and toxicity management costs. Genotyping could also prevent ~28 cases of severe toxicity per 1,000 patients tested. The findings indicate that upfront costs of genotyping are offset by savings from avoided severe toxicities and associated healthcare expenses, and support the integration of *DPYD* |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | genotyping into clinical practice. |
| **Brooks et al (2022); USA**<br><br>**(32)** | *DPYD*2A*<br>c.1129-5923C>G<br>c.1679T>G<br>c.2846A>T | Cost-effectiveness analysis | Stage III CRC patients | Comparison between *DPYD* genotype screening before FP-based chemotherapy and subsequent FP dose adjustment vs. no screening leading to universal SD-FP treatment. Primary outcome was the incremental cost-effectiveness ratio (ICER) for *DPYD* genotyping. | N/A | Genotyping costs, costs of managing severe toxicities, hospitalization costs | Compared with no screening, *DPYD* genotyping increased per-patient costs by $78 and improved survival by 0.0038 quality-adjusted life years (QALYs), leading to an ICER of $20,506/QALY. |
| **Tsiachristas et al (2022); UK**<br><br>**(33)** | ToxNav® (20 SNPs commercial test panel) | Cost-effectiveness analysis | Cancer (including upper and lower GI tumors) patients treated with FPs | Propensity score matching (with GLM) comparison of cost savings and toxicity outcomes of prospective *DPYD* genotyping with dose adjustment vs. historical cohorts treated with SD FPs | Prospective *DPYD* genotyping: n=466; Historical cohort: n=1556 | Genotyping costs, costs of managing severe toxicity, hospitalization, treatment, critical care, equipment & diagnostics | Upfront *DPYD* genotyping is cost-effective: reduces moderate and severe toxicity, reduces chemotherapy costs by 12% (£9765 per patient), non-elective hospitalization costs by 23% (£2331 per patient), and critical care costs by 21% (£1219 per patient), thereby lowering hospital costs |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Fariman et al (2023); Iran (34)** | *DPYD*2A* c.1679T>G c.2846A>T c.1236G>A | Cost-effectiveness analysis | Advanced and metastatic CRC patients | Comparison of prospective *DPYD* genotyping and subsequent dose adjustment vs. analysis of nonscreening studies | N/A | Genotyping costs, costs of managing severe toxicities, hospitalization costs | With an estimate of $7,4 per test and considering the average of direct medical costs for normal metabolizers ($493), intermediate metabolizers ($770) and poor metabolizers ($937), upfront genotyping of *DPYD* was associated with lifetime ICER of $253. *DPYD* genotyping strategy is deemed cost-effective as long as test cost<$49 |
| **Fragoulakis et al (2023); Italy (35)** | *DPYD*2A* c.1679T>G c.2846A>T c.1236G> UGT1A1*27 UGT1A1*28 | Cost-utility analysis | Stage II-IV CRC patients | Cost-utility analysis of pre-emptive PGx genotyping for *DPYD* and UGT1A1 to compare PGx-guided treatment strategy to the standard-of-care | n =366 stage II-IV CRC patients (Control: 211; PGx guided:155) | Genotyping costs, costs of managing severe toxicities, hospitalization and emergency room costs | PGx guided treatment: €380<br>Standard of care: €565<br>ICER was estimated at €13418 (~ US$14695) per QALY |

CRC - colorectal cancer; FP- Fluoropyrimidine; GI - Gastrointestinal; GLM- Generalized linear models; ICER- incremental cost-effectiveness ratio; N/A- Not applicable ; QALY- Quality-adjusted life years; SD- standard dose

**Table II-12.** Summary of results from the literature review on economic evaluation of implementing systematic DPYD gene genotyping

## 3.2. Italy

### 3.2.1. Process

#### 3.2.1.1 Working Group

Following the definition of the context and objectives of the evaluation, the Technical Group and the Steering Committee were formed. The main professional figures needed to constitute the Steering Committee were identified. The Technical Team (**Table II-13**) was composed of Public Health professionals from the Università Cattolica del Sacro Cuore. The team also collaborated with international partners from the PROPHET Project, with progress on the HIA in all the three countries being regularly assessed through online meetings.

Specifically, the tasks performed by the technical team include:

- Conducting the screening and scoping phases, with the preparation of an initial report aimed at describing the policy under review, the potential impacts, and the methodologies used in the activity.
- Triangulating the evidence required to assess the identified impacts and drafting a second summary report.
- Preparing a final report.

Given the significant expertise required for developing the approach and the need to account for all potential policy impacts, the establishment of a Steering Committee formed by all the necessary stakeholders, was deemed necessary. With the Steering Committee, the impacts and methodologies for evaluating them were discussed, including the selection and retrieval of data to be included in the model. They were also specifically consulted regarding the assessment of barriers and organizational challenges.

| **Technical Team** | | |
|---|---|---|
| UCSC | Stefania Boccia (coordinator) | Full Professor of Hygiene and Preventive Medicine |
| UCSC | Roberta Pastorino | Assistant Professor of Biostatistics |
| UCSC | Angelo Pezzullo | Assistant Professor of Hygiene and Preventive Medicine |
| UCSC | Angelica Valz Gris | Public Health Researcher |
| UCSC | Francesco di Bernardino | Public Health Researcher |
| UCSC | Diego Tona | Public Health Researcher |
| UCSC | Erika Giacobini | Public Health Researcher |
| UCSC | Vittoria Tricomi | Public Health Researcher |

| | | |
|---|---|---|
| UCSC | Antonio Cristiano | Public Health Researcher |
| ***Steering Committee*** | | |
| ISS | Mauro Biffoni | National Institute of Health |
| CPE | Antonella Cardone | Patient Association |
| UNISA | Valeria Conti | Pharmacy Department |
| UniCamillus | Maria Rosaria Gualano | Health Impact Assessment Expert |
| INT Pascale | Piera Maiolino | Medical Oncology |
| UNI Federico II | Umberto Malapelle | Department of Laboratory Medicine and Molecolar Pathology |
| AIFA | Simona Montilla | Drug regulatory institution |
| UNISA | Francesco Sabbatino | Medical Oncology |
| AGENAS | Manuela Tamburo De Bella | National Agency for the Organization of Health Service |
| CRO AVIANO | Giuseppe Toffoli | Pharmacy Department |

**Table II-13**. Composition of the technical team and the steering committee for the health impact assessment on *DPYD* genotyping in Italy

### 3.2.1.2 Identified impacts

The potential impacts of the policy were identified by the Technical Team through a narrative literature review aimed at characterizing the approach. Subsequently, the identified impacts and their assessment methodologies were validated by the Steering Committee. The impacts and corresponding assessment methodologies are summarized in **Table II-14**.

| **Impact** | **Assessment methods** |
|---|---|
| Impact on patients health and well-being:<br>• Toxicity and mortality | • Markov model<br>• Steering Committee consultation<br>• Literature review |
| Impact on patients acceptability | • Literature review<br>• Steering Committee consultation |
| Economic impact | • Literature review |
| Organizational impact | • Literature review<br>• Steering Committee consultation<br>• Survey |

**Table II-14**. Impact and assessment methodologies identified during the scoping phase

### 3.2.1.2 Literature review

A narrative literature review was conducted on all the impacts identified using different strategies and inclusion criteria. For all the literature reviews the main database used was Pubmed. The search was focused on collecting the evidence necessary for evaluating the impact of the policy.. Given the scarcity of literature, both specific studies on the impact of *DPYD* and more general studies on the use of pharmacogenomics for the personalization of cancer therapy were investigated.

### 3.2.1.3 Markov Model

The health impact analysis was complemented by a Markov Model developed by INSA and described in the previous chapter. The model explores two distinct scenarios:

- **Systematic Genotyping Scenario:** Assumes that all patients with stage III CRC undergo mandatory *DPYD* testing. This estimate was calculated using the *I numeri del cancro* report, which provides data on the incidence of CRC patients in 2023, and Italian studies that detail the percentage of CRC patients diagnosed at stage III (36-38).
- **Concurrent Genotyping Scenario:** Represents the current use of *DPYD* testing in Italy for the personalization of stage III CRC therapy. The model, for simplicity, was limited to stage III patients, as they have a clear indication for fluoropyrimidine use. Since no data are available on fluoropyrimidine use in Italy, the current state of implementation was estimated based on the opinions of the Steering Committee and other experts in the field.

### 3.2.1.4 Survey

We conducted a survey to investigate some organizational aspects of the implementation of the *DPYD* test in the Oncology Units and to assess the level of the implementation. The invitations to participate were sent by a member of the technical team to the Complex Operating Units of Medical Oncology (n = 347) registered in the 13th Edition (2023) of the AIOM White Book of Oncology Unit via email. Where publicly available, the email addresses of the Directors of the Units were contacted. In cases where these were unavailable, the secretariats of the respective departments were contacted.

The study was approved by the Ethical Committee "*Comitato Etico Territoriale Area 3 Regione Lazio*" (ID7150). Targeted emails detailing the questions listed under the variables and procedures section were sent to the Directors of the Units or their secretariats. Written informed consent was obtained alongside the collected data. These documents were stored securely on a restricted-access section of the OneDrive platform for a duration of seven years, accessible only to the researchers involved in the study.

In closer detail, we asked:

- How many CRC patients were treated with fluoropyrimidines in 2023 in your department?
- Is the *DPYD* test prescribed in your department before administering fluoropyrimidines to CRC patients?
- If not, why is the test not prescribed?

- If yes, how many patients treated in 2023 underwent the *DPYD* test?
- Which laboratory performs the test?
- On average, how much time passes between the request for the test and the receipt of the report?
- Through which regional catalog code is the test requested?
- Does the report include only the presence/absence of the pathogenic variant, or does it also provide recommendations on fluoropyrimidine dosage?

The collected data were centralized and analyzed to ensure the accuracy and reliability of the information. Descriptive statistics were used to present the characteristics of the collected variables. Categorical variables were presented as absolute and relative frequencies, while quantitative variables were summarized using mean and standard deviation or median and interquartile range, as appropriate. The results are reported in paragraph **3.2.2.3**.

#### 3.2.1.5 Steering Committee Consultation

The input and opinions of the Steering Committee were also crucial for assessing many of the evaluated impacts, particularly in all organizational impacts. The Steering Committee was consulted in two ways: through an open-ended questionnaire and via three 90-minute online meetings.

The questions investigated through the questionnaire were:

1. Access and Logistics for the *DPYD* Test: What are the general experiences regarding waiting lists for the *DPYD* test? What logistical challenges are encountered in accessing the service?
2. Waiting Times and Clinical Management: Are the waiting times between the test prescription and chemotherapy utilized in any way (e.g., vaccinations, diagnostic tests)? On average, how long is the wait between the test prescription and the start of chemotherapy? What is the average time from sample collection to the delivery of test results?
3. Technological Support: Are computerized systems available for managing reminders related to the *DPYD* test? Are the test results automatically integrated into oncologists' electronic medical records?
4. Follow-Up Protocols for Ambiguous Results: In cases of ambiguous *DPYD* test results, what follow-up protocols are generally adopted? Is the phenotypic test used as the next step?
5. Ethnicity: For patients belonging to ethnic groups with genetic variants not covered by the available genetic test, is the phenotypic test used, or is no testing performed?
6. Patient Reactions and Therapeutic Implications: What are the typical reactions of patients to the proposal of the *DPYD* genetic test? Do they express concerns about the implications for their treatment options?
7. Oncologists' Knowledge of the Test and Medico-Legal Implications: Are oncologists generally informed and comfortable with the use and interpretation of *DPYD* test results? What are the current medico-legal implications of not performing the test?

### 3.2.2. Findings

#### 3.2.2.1 Impact on morbidity and mortality

As anticipated in paragraph 3.2.1.3, the impact of the approach on morbidity and mortality was estimated by comparing health outcomes between a *Concurrent Genotyping* scenario, reflecting the current level of test use on colorectal stage III patients in Italy, and a *Systematic Genotyping* scenario, assuming 100% utilization of the test on this population due to its mandatory implementation. The target population was estimated to be 11,817 CRC stage III Italian patients based on "I Numberi del Cancro Report 2023" (36). The average current *DPYD* genotype test prescription rate was estimated to be 70% for Italy based on the consultation with the Steering Committee and the preliminary results of the survey conducted on the Italian Oncology Units. **Table II-15**. displays the outcomes of expected serious (grade 3+) toxicity events, number of toxicity-related deaths, and number of deaths at 5 years follow-up for the scenario 1 (systematic *DPYD* genotyping) and scenario 2 (current *DPYD* genotyping).

| **Outcome** | **Scenario 1 Systematic *DPYD* genotyping;** n (%) | **Scenario 2 Current *DPYD* genotyping;** n (%) | **Relative risk (RR)** | **Preventive fraction** |
|---|---|---|---|---|
| Severe (grade 3-4) toxicity | 2837.02 (24.01%) | 2912.96 (24.65%) | 0.974 | 2.6% |
| Toxicity-related mortality | 12.56 (0.11%) | 17.25 (0.15%) | 0.733 | 26.7% |
| 5-year mortality | 860.06 (7.28%) | 883.085 (7.47%) | 0.974 | 2.6% |

**Table II-15.** Main Markov model outcomes and estimated association measures

As shown in **Table II-14**, the implementation of systematic genotyping can reduce the incidence of severe toxicity events from 24,65% to 24,01% and toxicity-related mortality from 0,15% to 0,11%. The correspondingpreventive fractions for severe toxicity and toxicity-related mortality indicate that systematic genotyping could prevent 2,6% of severe toxicity cases and 26,7% of deaths related to toxicity.

The 5-year mortality observed in the systematic DPYD genotyping scenario was also slightly reduced, with a relative risk of 0,974. It was estimated that the systematic genotyping could prevent about 2,6% of deaths that would occur under the current scenario at 5 years. The reductions, while modest, could have crucial implications for improving meaningful patient outcomes, particularly over a large population.

**The results of this model suggest that, although relatively modest due to the already substantial level of *DPYD* implementation in Italy, introducing a mandatory policy for the use of the test could have a significant impact on population health.** Furthermore, it is likely that the level of implementation is not uniform across centers, as partially highlighted by our survey detailed in paragraph **3.2.2.3**. The health gains for patients treated at centers where *DPYD* testing is poorly or not implemented could therefore be substantial. Additionally, this policy could contribute to reducing health inequalities stemming from the varying levels of *DPYD* implementation among different healthcare centers.

### 3.2.2.2 Patients acceptability

The literature review identified only 5 studies evaluating the acceptability of pharmacogenomic testing among patients, highlighting a significant gap in research, particularly when considering specifically *DPYD* testing (39-43). In fact, among these, only one study explicitly focused on *DPYD* testing, and no studies were conducted in Italy. Key findings of the included studies are reported in **Table II-16**. This scarcity underscores the need for further exploration into patient attitudes and experiences with pharmacogenomic testing in the Italian population.

The studies reported generally high levels of patient acceptance for pharmacogenomic testing. For instance, Cuffe et al. found that 97.4% of metastatic cancer patients were willing to undergo pharmacogenomic testing to detect the risk of severe toxicity, even with associated costs and moderate turnaround times (41). Similarly, Di Dong et al. reported a predicted uptake rate of 65% for pharmacogenomic testing, which increased when recommended by a physician (39). Glewis et al. emphasized the role of pharmacist-led education, with 71% of patients finding the process acceptable and clear (43). Concerns such as insurance coverage, turnaround times, and clarity of information were occasionally raised but did not significantly affect overall acceptance. However, Ming Lee et al. highlighted concerns about insurance and employment discrimination as potential barriers (42). Collectively, these findings suggest that while there seems to be a general acceptance of pharmacogenomic testing among patients, the provision of clear information and addressing logistical and ethical concerns remain fundamental.

Feedback from the Steering Committee provided further insights into the acceptability of *DPYD* testing specifically. Three members with experience in using *DPYD* testing in oncology reported generally positive acceptance of the test among patients, who did not express significant concerns or resistance. While the data from both the literature and expert consultation suggest good overall acceptability, the limited number of studies and anecdotal nature of the committee's insights preclude definitive conclusions about the potential impact of a policy mandating *DPYD* testing prior to fluoropyrimidine prescriptions. However, no evidence from the existing studies raises major concerns regarding patient acceptability in this context. This suggests that implementing such a policy could be feasible, provided adequate communication and support systems are in place.

| Title | Authors (Year), Country | Type of study | Key findings |
|---|---|---|---|
| **Measuring High-Risk Patients' Preferences for Pharmacogenetic Testing to Reduce Severe Adverse Drug Reaction: A Discrete Choice Experiment** | Di Dong et al (2016), Singapore | Discrete choice experiment | Overall, the predicted take-up rate for the test is 65% at a price of SGD400. If the test was recommended by a physician or was chosen by most of the patients, the take-up rate for the test would increase by 8.5 and 1.5 percentage points, respectively. |
| **Healthcare provider and patient perspectives on the implementation of pharmacogenetic-guided treatment in routine clinical practice** | Kaur et al., (2018), Canada | Survey | 52% of patient respondents were aware of PGx testing, with a significant association between awareness and positive opinions toward PGx. Both healthcare providers and patients recognized the value of PoC PGx testing devices, with 98% of healthcare providers and 71% of patients believing PoC devices would improve the accessibility and implementation of PGx testing. |
| **Cancer patients acceptance, understanding, and willingness-to-pay for pharmacogenomic testing** | Cuffe et al., (2014) | Survey | Among the 97% of 121 metastatic patients accepting chemotherapy, 97.4% wanted pharmacogenomic testing that could detect the risk of severe toxicity, accepting median incurred costs of $1000 (range $0-10,000) and turnaround time for results of 14 days (range 1-90 days). The majority of patients wanted to be involved in decision-making on pharmacogenomic testing; however, one in five patients lacked a basic understanding of pharmacogenomic testing. |
| **Assessment of patient perceptions of genomic testing to inform pharmacogenomic implementation** | Ming Lee et al., (2017) USA | Qualitative study | Participants agreed that pharmacogenomics could inform prescribing and help identify problem prescriptions but expressed concerns over insurance coverage and employment discrimination. |
| **Patient and healthcare professional acceptability of pharmacogenetic screening for *DPYD* and *UGT1A1*: A cross sectional survey** | Glewis eta t., (2023) Australia | Survey | The majority of patients 71% found the pharmacist education on serious side effects acceptable. 71% did not feel that undergoing PGx testing had caused unacceptable delays to treatment and 69% found the turnaround time for PGx results acceptable. Most patients 98% reported "extremely" or "quite a bit" acceptable for pharmacist to inform of the PGx results .The majority of |

| | | | |
|---|---|---|---|
| | | | patients felt that the information given about the PGx screening program has prepared them to undergo PGx testing (large extent, 52%, 151/288) The majority of patients found the information provided to them regarding the relevance of PGx testing in deciding their cancer treatment was clear 70% and valuable 71%. |

**Table II-16**. Literature review results on patients' acceptability

#### 3.2.2.3 Organizational barriers

The literature review identified 6 studies that provide insights into the organizational barriers to implementing *DPYD* testing in clinical practice (43-49). Key funding of the included studies are summarized in **Table II-17**. Common barriers highlighted across studies include a lack of clear national and international pharmacogenetic guidelines (mentioned in two studies), inadequate financial reimbursements (reported in three studies), prolonged test turnaround times (discussed in three studies), and limited IT infrastructure for managing genetic data (noted in two studies). Additionally, stakeholders frequently cited insufficient education and awareness among healthcare professionals about the clinical utility of *DPYD* testing (reported in four studies) and a lack of consensus on testing approaches or standard protocols (discussed in two studies). Facilitators of implementation, such as dedicated coordinators and resources for professional training, were also acknowledged.

Healthcare professionals' knowledge and familiarity with pharmacogenetics were emphasized as critical factors. Two studies, including Gurvere et al. and Morris et al. underscored limited awareness of pharmacogenetic testing and its interpretation as significant barriers (46,47). Gurvere et al. found that only 64% of healthcare providers had some familiarity with pharmacogenomics, and both studies highlighted the need for more educational initiatives (46). Furthermore, Glewis et al reported that clinicians identified education resources and the presence of a program coordinator as key enablers for successful implementation (43).

The only Italian publication by Bignoculo et al., offered a detailed perspective on the barriers specific to *DPYD* testing in Italy (49). These included the absence of standardized national guidelines, limited availability of reliable genotyping technology, and IT systems to integrate genetic data into clinical workflows. Financial reimbursement was highlighted as a critical barrier, alongside prescribers' limited awareness of the test's clinical relevance. This study highlights the need for systemic improvements, including better infrastructure and clinician education, to support the implementation of *DPYD* testing in Italy.

| Title | Authors (Year), Country | Type of study | Key findings |
|---|---|---|---|
| **Preemptive pharmacogenetic testing to guide chemotherapy dosing in patients with gastrointestinal malignancies: a qualitative study of barriers to implementation** | Lau-Min et al. 2022 USA | Qualitative study: | Sixteen medical oncologists and nine oncology pharmacists interviewed cited as the main barriers of implementation a mistrust in evidence on PGx and a lack of knowledge of clinicians. Clinicians cited a general lack of knowledge as a barrier that could impact not only their initial decision to perform PGx testing but also their ability to counsel patients on the risks, benefits, and alternatives to preemptive PGx-guided chemotherapy dosing |
| **DPD Testing Before Treatment With Fluoropyrimidines in the Amsterdam UMCs: An Evaluation of Current Pharmacogenetic Practice** | Martens et al., 2020 Netherlands | Qualitative study | Facilitating factors for stakeholders to implement testing included the existence of clear protocols, (anecdotal) evidence of the utility, being aware that peers are adhering to standard practice and clear and simple procedures for ordering and reporting. Main barriers included the lack of clear divisions of responsibilities, the lack of consensus on a test approach, long turn-around times and non-user-friendly IT-infrastructures. More professional education on the utility and limitations of pharmacogenetic testing was desired by most stakeholders. |
| **Healthcare provider and patient perspectives on the implementation of pharmacogenetic-guided treatment in routine clinical practice** | Gurvere et al., 2024 Canada | Survey | The results revealed that 64% of healthcare providers had some level of familiarity with PGx, however, PGx testing in clinical practice was low. The primary challenges identified by healthcare providers included limited access to testing and lack of knowledge on PGx test interpretation. Both healthcare providers and patients recognized the value of PoC PGx testing devices, with 98% of healthcare providers and 71% of patients believing PoC devices would improve the accessibility and implementation of PGx testing. |
| **Addressing barriers to increased adoption of *DPYD* genotyping at a large multisite cancer center** | Morris et al., 2023 USA | Qualitative study | Relevant stakeholders reported that the main barriers of *DPYD* implementation were limited education/awareness of clinical utility, lack of testing recommendations by oncology professional organizations, testing cost, lack of accessibility to a comprehensive in-house test and service, and prolonged test turnaround time. |

| | | | |
|---|---|---|---|
| **Patient and healthcare professional acceptability of pharmacogenetic screening for *DPYD* and *UGT1A1*: A cross sectional survey** | Glewis et al., (2023) Australia | Survey | HCPs were overall accepting of the program, with the majority (96%) willing to offer PGx testing to their patients beyond the trial. HCPs identified that lack of financial reimbursements (62%) and lack of infrastructure (38%) were the main reasons likely to prevent/slow the implementation of PGx screening program into routine clinical care. Survey data have shown overall acceptability from patients and HCPs participating in the PGx Program. |
| **Pharmacogenetics testing (*DPYD* and *UGT1A1*) for fluoropyrimidine and irinotecan in routine clinical care: Perspectives of medical oncologists and oncology pharmacists** | Glewis et al., (2023) Australia | Survey | Barriers to implementation included: lack of financial reimbursements (82%) and perceived lengthy test turnaround time (76%). Most Clinicians identified a dedicated program coordinator, i.e., PGx pharmacist (74%) and availability of resources for education/training (74%) as enablers to implementation. |
| **Ten-year experience with pharmacogenetic testing for *DPYD* in a national cancer center in Italy: Lessons learned on the path to implementation** | Bignoculo et al. (2023) Italy | Position Paper | The adoption of *DPYD* testing in hospitals has been hampered by several barriers, such as the need for common national and international pharmacogenetic guidelines, reliable genotyping technology with acceptable turnaround time, and IT technologies suitable for managing genetic data as part of standard clinical workflow. Prescribers' awareness of the clinical relevance of the tests is considered another relevant barrier to upfront *DPYD* testing in the clinical practice. The management of genetic data in a clinical context could be another barrier to straightforward implementation of PGx testing in clinical practice. The lack of clear reimbursement strategies remains a critical barrier to the implementation of pharmacogenetic testing in |

**Table II-17.** Literature review results on organizational barriers of *DPYD* genetic testing

The online survey to the Oncology Units provided us with insights about the Italian context. Overall, 35 out of 347 (10%) responded, of which 21 were located in the North, 3 in the Center, and 11 in the South of Italy. Ten units were categorized as small, treating fewer than 150 patients, while 25 were medium or large-sized units.
The total number of CRC patients treated with fluoropyrimidines reported by these hospitals was 3,878, and for 3,476 patients (89.6%), the DPYD test was performed. Among the responding oncology units, 27 reported conducting the test for 100% of their patients, 5 for over 90% of patients, and 3 for less than 70% of cases. Results are reported in **Table II-18**. The percentage of CRC patients tested was 99% in the North, 77% in the Centre and 90% in the Souths. In small hospitals the percentage of patients tested was 89%, and in medium/large hospitals was 9.
The average waiting time for test results was 8.03 days. However, excluding an outlier from Lazio, which reported an average waiting time of 35 days, the adjusted average was 7.11 days. Twenty-nine units (82.9%) reported waiting times under 10 days. Additionally, 24 oncology units (68.6%) indicated that the laboratory provides both the genetic variant result and the recommended fluoropyrimidine dosage.

| **Department Unit (n=35)** | **Test (%)** |
|---|---|
| Geographic area | |
| North | 99% |
| Centre | 77% |
| South | 90% |
| Unit dimension | |
| Small (<150 patients) | 89% |
| Medium/Large (>150 patients) | 96% |

**Table II-18.** Proportion of CRC patients treated with fluoropyrimidines tested with *DPYD* from the online survey conducted in Italy.

The response rate for the survey was very low, with only 10% of the contacted oncology departments participating. While the reported percentage of *DPYD* testing appears to be very high on average, with many units conducting the test on 100% of their patients, it is important to note that this percentage is significantly higher than the estimate provided by the consulted experts. This discrepancy strongly suggests that these results are likely influenced by selection bias, as units with better testing practices might have been more inclined to respond to the survey. Additionally, the reported data were provided directly by oncology departments rather than being collected from centralized databases, which could further limit the reliability of the findings. Despite these limitations, the results are still valuable as they highlight notable variability in *DPYD* testing practices across different regions of Italy. For example, the majority of responding units reported performing

the test routinely, but there remain a few that conduct it on less than 70% of patients. Moreover, geographic differences emerged, with most responding units located in the north, while fewer responses were received from the center and south of the country. This regional disparity raises questions about potential inequities in access to *DPYD* testing and its implementation. The finding that 29 out of 35 units reported test result turnaround times of less than 10 days is encouraging, as it suggests that timely testing is achievable in most settings. However, the outlier in Lazio, which reported a much longer average turnaround time of 35 days, underscores the need for more consistent practices nationwide. Furthermore, while 68.6% of units stated that laboratories provide both the genetic variant results and recommended fluoropyrimidine dosages, this still leaves room for improvement to ensure that all oncology departments receive actionable information to guide personalized treatment. In conclusion, while these results should be interpreted with caution due to potential biases and data collection limitations, they offer useful insights into the current state of *DPYD* testing in Italy. They highlight the need for continued efforts to standardize practices, address regional disparities, and ensure equitable access to this important pharmacogenetic test across the country.

In addition to the online survey, consultations with experts from the Steering Committee provided further details on the status of test implementation and on some perceived barriers. Steering Committee highlighted a significant variability in the organizational aspects of *DPYD* testing implementation across different institutions. In some centers, the test is routinely performed for all eligible patients without major logistical barriers or waiting lists. Patients can schedule the test through a centralized system and complete it within specific days set aside for sample collection. However, in other centers, logistical hurdles, such as limited availability of testing slots or the need for patients to travel for sample collection, may complicate access. Turnaround times for *DPYD* test results also vary widely. In certain institutions, results are available within one to three days in urgent cases, enabling timely adjustments to therapy plans. In other settings, longer wait times might delay the initiation of chemotherapy, although these periods can sometimes be used productively for other preparatory procedures, such as vaccinations or additional diagnostic tests. Technological support for the integration of test results into electronic health records is another area with noticeable discrepancies. While some centers are working to implement shared electronic systems between oncology and pharmacology units, others rely on manual processes that can slow communication and decision-making. This gap highlights the broader need for standardized IT infrastructure to facilitate streamlined workflows. For ambiguous test results, some institutions adopt follow-up protocols that include repeating tests with alternative methodologies or exploring phenotypic testing approaches, such as evaluating the UH(2)-U ratio. However, these practices are not consistently implemented nationwide, leaving room for improvement in follow-up procedures for inconclusive cases. The Steering Committee also noted variability in the level of familiarity and confidence among oncologists in using and interpreting *DPYD* test results. While some institutions provide robust support to oncologists through pharmacology units, others may lack sufficient

resources for education and training. Additionally, at the regional level, systemic barriers persist, such as the absence of *DPYD* testing in some healthcare service catalogs, which complicates access and funding in certain areas. Overall, the Steering Committee emphasized that while some centers have established efficient workflows and minimized logistical challenges, there is a clear need for more standardized regional and national policies. Such policies would ensure equitable access to testing, reduce logistical barriers, and foster the full integration of pharmacogenetic testing into routine clinical workflows across the country.

#### 3.2.2.3 Economic impact

Adopting a personalized approach not only optimizes the clinical management of patients but also has considerable economic implications for the national healthcare system. In Italy, the costs of *DPYD* gene genotyping vary across regions. For instance, in Latium, the total cost for the test and analysis is €215 (€60 for the test and €155 for the analysis), while in Lombardy, the total cost is €235 (€48 for the test and €187 for the analysis) (50,51). These initial costs represent a relatively modest investment compared to the potential savings from preventing fluoropyrimidine-related toxicities. It is important to note that the costs associated with implementing the test extend beyond the test fee itself, encompassing the additional workload for geneticists and oncologists, who often face delays of several days to receive reports with recommended dosages. However, current literature does not provide precise estimates of these direct costs.

Patients treated with fluoropyrimidines face a substantial risk of severe adverse events, with additional hospitalization costs ranging from €636 to €2015 per patient. Furthermore, costs for managing toxicity-related complications are significant, with grade 3 events incurring baseline costs of €234 and grade 0 to 2 events incurring €86 (52). Considering that approximately 600,000 patients worldwide develop severe toxicity due to these treatments annually, the potential economic savings from genotyping are substantial (53). In Italy, an estimated 513,500 individuals live with CRC, with an incidence of 50,500 new cases in 2023 (36). *DPYD* gene genotyping could reduce the risk of severe toxicity, which affects about 30% of patients treated with standard doses of fluoropyrimidines (54). This approach not only improves patients' quality of life but also alleviates the economic burden associated with complications. Severe grade 3-4 toxicities, including nausea, vomiting, diarrhea, stomatitis, leukopenia, neutropenia, and hand-foot syndrome, often necessitate costly and prolonged treatments, further increasing healthcare expenditures. Additionally, the total expenditure on cytostatic antineoplastic agents, including antimetabolites such as capecitabine and fluorouracil, was estimated at €79.9 million in the 2022 OSMED report. This underscores the importance of optimizing the use of these drugs through screening practices like genotyping, ensuring that only patients with a reasonable likelihood of tolerating and benefiting from the therapy receive standard doses.

As highlighted in the systematic literature review included in the Portugal case study, systematic *DPYD* genotyping consistently demonstrated cost savings and improved patient outcomes across the ten studies reviewed (26 - 35). Three of these economic analyses were conducted in Italy and provided insights into the financial and clinical implications of implementing this pharmacogenomic approach. The study by Toffoli et al. retrospectively genotyped 550 CRC patients who experienced severe toxicities associated with FP treatments, comparing the costs of managing toxicities in wild-type patients and those carrying *DPYD* variants (28). The findings demonstrated a significant difference in costs, with toxicity management for wild-type patients averaging €825, compared to €2,972 for *DPYD* variant carriers. This analysis concluded that genotype-guided dosing is cost-saving, emphasizing the financial benefits of preemptive genotyping in reducing the economic burden of severe toxicity management. Similarly, Fragoulakis et al. conducted a cost-benefit analysis on 571 CRC patients who received FP treatments, including 528 wild-type individuals and 43 *DPYD* variant carriers (30). This study found that pharmacogenomic-guided dosing is cost-saving, with toxicity management costs significantly lower for wild-type patients (€1,150) compared to €3,712 for carriers. The analysis reinforced the economic advantage of integrating genotyping into clinical practice to mitigate severe toxicities and their associated costs. In a more recent study, Fragoulakis et al. performed a cost-utility analysis of preemptive pharmacogenomic genotyping for *DPYD* and *UGT1A1* in 366 stage II-IV CRC patients, comparing a pharmacogenomic-guided treatment strategy to standard care (35). The analysis included genotyping costs, severe toxicity management, hospitalization, and emergency room costs. The results showed that the pharmacogenomic-guided treatment incurred an average cost of €380 per patient, compared to €565 for standard care. The ICER was estimated at €13,418 (~US$14,695) per quality-adjusted life year (QALY), demonstrating the cost-effectiveness of the pharmacogenomic approach in this setting.

In conclusion, the mandatory implementation of *DPYD* gene genotyping before fluoropyrimidine treatment in Italy represents a sustainable strategy that could result in significant economic savings and improved patient quality of life. Investing in this policy would not only align Italy with international best practices but also contribute to a more efficient and responsible healthcare system. Preventing severe toxicities and personalizing cancer treatments offer not only clinical benefits but also economic advantages, ensuring the long-term sustainability of the Italian healthcare system.

## 3.3. Finland

The report utilizes the Health Impact Assessment (HIA) framework, adapted from the World Health Organization (WHO) (36), to assess Finland's implementation of *DPYD* genotyping in colorectal cancer (CRC) treatment prior to fluropyrimidine-based chemotherapy. As a pilot study, it focuses on evaluating health outcomes, social equity, clinical practices, laboratory workflows, economic implications and patient well-being and acceptability. By addressing these dimensions, this study explores how the framework can inform innovative healthcare approaches and policies, including personalized prevention strategies, to promote equity and improve healthcare delivery across Europe.

### 3.3.1. Process

The HIA assessed the feasibility and potential impacts of implementing a policy to make *DPYD* genotyping mandatory for CRC patients before fluoropyrimidine chemotherapy. While this practice is widely accepted in Finland and guided by institutional and regional guidelines (37) following European Medicines Agency (EMA) recommendations in 2020 (15), the absence of a national policy posed a potential for variability in implementation, raising concerns regarding equitable access across different regions. Conducting the HIA enabled us to systematically evaluate the health impacts, organizational impacts, clinical practice influences, economic impacts, equity and overall patient wellbeing and acceptability.

We utilized the NCCHPP Internal Tool: Health Impact Assessment Screening Grid (July 2014 version) to guide us in the screening process, which allowed for a structured assessment, ensuring that the decision to proceed with the HIA was evidence based and aligned with best practices (38).

The scoping phase of the HIA focused on identifying priority issues, engaging stakeholders, and developing a conceptual framework to guide the assessment of a policy mandating pre-fluoropyrimidine chemotherapy *DPYD* genotyping for CRC patients.

#### 3.3.1.1. Stakeholder Engagement and Governance

A Finnish steering committee was formed, comprising representatives from the HIA expertise, the Finnish Cancer Registry (FCR), oncologists, laboratory professionals, patient associations, and the Finnish Medicines Agency (Fimea) as presented in **Table II-19** (39,40). Members were invited via email, followed by a debriefing meeting to introduce the project's objectives and scope. The meeting provided an opportunity to gauge their initial opinions and interest in participating. A subsequent follow-up meeting included a presentation of the conceptual and logic models, validating the identified impact categories and indicators, discussing next steps.

This committee operated as an advisory body, offering expert insights and guidance at every stage of the HIA process. Its primary aim was to validate the study design and planned outcomes, supporting the identification of priority issues, and providing scientific and technical advice. Key contributions included:

1. **Validating priority issues and indicators**: Ensuring the relevance and appropriateness of selected health determinants, indicators, and impacts identified during the scoping phase.
2. **Guidance on data collection**: Offering inputs on methodology, scope, and feasibility of data collection tools, including surveys and interviews.
3. **Ongoing support**: Providing feedback and expertise at key stages of the HIA, ensuring the scientific integrity of the findings.

Stakeholders emphasized that, while pre-chemotherapy *DPYD* genotyping in CRC patients is included in practice guidelines and considered similar to policy, this HIA would assess if its implementation would be equitable, sustainable, and accessible to all population groups.

| | | |
|---|---|---|
| **Technical Team** | | |
| THL | Markus Perola (Work package leader) | Research Professor, MD, PhD,<br>Public Health Consultant |
| THL | Pragathy Kannan | Public Health Researcher, M.Sc. Student |
| THL | Helena Kääriäinen | Research Professor, MD, PhD,<br>Clinical Geneticist |
| ***Steering Committee*** | | |
| HUS | Anna-Kaisa Anttonen | Chief Physician, Genetics, and clinical pharmacology |
| TAYS | Kaisa Lehtomäki | Oncologist, Colorectal cancer expertise |
| TAU | Meri Koivusalo | Public Health Consultant, HIA expertise |
| FCR | Juha Pekka Turunen | Secretary General, Cancer Prevention expertise |
| Fimea | Janika Nättinen | Health Economist, HTA expertise |
| Fimea | Tiina Karonen | Senior Physician, Pharmaceutical safety expertise |
| Colores | Mervi Kaartoaho | Patient representative |

THL-The Finnish Institute for Health and Welfare, HUS-Helsinki University Hospital, TAYS-Tampere University Hospital, TAU-Tampere University, FCR-Finnish Cancer Registry, Fimea-Finnish Medicines Agency, Colores-Finnish Colorectal Cancer Association

**Table II-19:** Composition of Stakeholder Committee in Finland

#### 3.3.1.2. Geographic Scope and Governance

The analysis was geographically scoped to Finland, in alignment with our collaborative framework with Portugal and Italy. An intersectoral platform was created with defined terms of reference to frame governance issues, guide stakeholder participation, and outline methodologies. Funding was provided by the PROPHET project, supporting necessary research and data collection activities.

### 3.3.1.3 Conceptual and Logic Models

The conceptual model, previously presented in this document, was adapted specifically for Finland's healthcare context to identify key health outcomes, indicators, and their interrelationships. This model was the foundation for planning the subsequent phases of the HIA, including the assessment and recommendations. Complementing this, the logic model, presented in **Table II-20**, outlines the expected impacts.

| Aspect | Description |
|---|---|
| Characteristics of the Proposal | Mandatory Pre-Chemotherapy *DPYD* Genotyping Policy for Colorectal Cancer Patients |
| | Target Population: Colorectal cancer patients scheduled for chemotherapy |
| | Genetic Screening Infrastructure: Establishment or enhancement of genetic testing infrastructure |
| | Regulatory Framework: Development or adaptation of regulations for compliance |
| | Healthcare Provider Training: Programs for effective interpretation of genotyping results |
| | Information Dissemination: Educational campaigns for patients and healthcare providers |
| Proximal Effects | Increased Genotyping Rates: Higher proportion of patients undergoing *DPYD* genotyping |
| | Identification of *DPYD* Variants: Allows personalized treatment adjustments |
| | Tailored Chemotherapy Dosing: Adjustments to mitigate adverse reactions |
| | Reduced Chemotherapy Toxicity: Decrease in treatment-related toxicities |
| | Improved Treatment Efficacy: Enhanced treatment outcomes |
| Intermediate Effects on Health Determinants | Access to Genetic Testing: Addressing disparities in healthcare access (IF they exist) |
| | Healthcare Equity: Ensuring equal access to personalized medicine |
| | Health Literacy: Improvement in understanding of personalized medicine |
| | Healthcare Resource Utilization: Optimal allocation of resources |
| | Quality of Life: Enhanced well-being during treatment |

| | |
|---|---|
| Health Repercussions | Reduced Chemotherapy Complications: Decrease in treatment-related morbidity and mortality |
| | Enhanced Patient Well-being: Improved overall patient experience |
| | Improved Treatment Adherence: Increase in treatment completion rates |
| | Long-Term Outcomes: Better survival rates and disease management |

**Table II-20:** Logic Model

**Identifying Priority Issues**

The following key issues were identified, with the steering committee playing a critical role in validating these findings and identifying any potential gaps:

1. Equitable access across socio-economic, geographic, and demographic groups.
2. Healthcare infrastructure and laboratory capacity to meet genotyping demand.
3. Perceptions and acceptability amongst oncologists and patients.
4. Potential health inequities in vulnerable populations
5. Organizational impacts, including laboratory capacity, healthcare provider training, and clinical workflow integration.

### 3.3.1.4. Literature Review in the Finnish context

A recent study involving 167 cancer patients in Finland investigated the integration of *DPYD* genotyping analysis, enzyme activity measurements, and plasma uracil concentrations prior to fluoropyrimidine administration (41) (**Table II-21).**

- 7.8% of patients were carriers of pathogenic *DPYD* variants, including the extensively studied *DPYD**2A and c.1129–5923C>G, both associated with DPD deficiency (41).
- A novel intragenic deletion in *DPYD* was identified which includes exon 4 in 31 % of patients carrying a pathogenic variant, highlighting Finland's unique *DPYD* gene profile (41).
- The C.2846A> T variant, common in Caucasian populations, was notably absent in the study cohort (41).
- The data from the study shows that a full gene analysis beyond the testing of the 4 common variants should be conducted as additional patients at risk may be missed. The study concluded that comprehensive genotyping along with enzyme activity measurements improves patient safety by preventing severe toxicities (41).

| *DPYD* variant | Europeans | Finns | Activity score (CPIC) |
|---|---|---|---|
| *DPYD**2A(c.1905+1G>A) | 1.6 | 2.3(2.4) | 0 |
| *DPYD**13(c.1679T>G) | 0 | 0.01(0) | 0 |

| | | | |
|---|---|---|---|
| c.2846A>T | 0.7 | 0.03(0) | 0.5 |
| HapB3(c.1129-5923>G, c.1236G>A) | 4.7 | 1.3(3.0) | 0.5 |
| A variant that works normally | | | 1 |

**Table II-21:** The allele frequencies of the four most known DPYD variants in the European and Finnish population and their activity scores according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) international (37).

#### 3.3.1.5. Data Collection

A mixed-methods approach was adopted to address identified issues:

- **Quantitative Analysis**: As previously described, a Markov model was utilized to estimate morbidity and mortality associated with *DPYD* genotyping implementation across Finland.
- **Qualitative Insights**: Anonymous web-based surveys were conducted via Webropol to gather insights from oncologists and laboratory professionals about clinical practices, perceived challenges, and their perspectives on the integration of *DPYD* genotyping into routine care. Interviews were conducted with patient representatives to understand their perspectives on genetic testing, its acceptability, and perceived barriers to access.

Outcome of the Scoping Process:

The Scoping phase resulted in a structured plan for assessing health impacts, including the methodology, stakeholder roles, and identified indicators.

### 3.3.2. Findings

#### Stakeholder Inputs and Engagement

Stakeholder inputs from the scoping phase were essential in guiding data collection and shaping the focus of the assessment. Their contributions provided practical context and helped prioritize key issues, ensuring that the results reflect real-world challenges and align with clinical and laboratory practices. These insights are integrated into the findings for each impact in this report.

#### 3.3.2.1. Markov Model Analysis: Morbidity, Mortality and Toxicity outcomes

#### Patient population and study design

In Finland, the total population diagnosed with colon cancer (ICD-C18) in 2019 was 2,367 cases, according to the Finnish Cancer Registry (39). Using data from the FinRegistry database, **496** patients were identified as having been treated with fluoropyrimidines

(Fluorouracil and Capecitabine) (42). These patients were matched using ATC codes for fluoropyrimidine therapies (L01BC02 for fluorouracil and L01BC06 for Capecitabine). This cohort constitutes the base population for the Markov model analysis, with 2019 data utilized as a proxy for 2023. Additionally, ATC code searches were extended to 2020 and 2021 to identify patients that started their treatment later, ensuring no eligible cases were excluded.

**Key Assumptions and Parameters**

1. **Prevalence of the *DPYD* variants**
   - The model assumes, based on estimates from the literature, that 7.8% of the population carry clinically significant *DPYD* variants that predispose then to severe toxicity from fluoropyrimidine therapy (41).
2. **Current testing Practices**
   - The current genotyping prescription rate is assumed to be 94.7%, which reflects the existing clinical practice in Finland for DPYD genotyping.
3. **Toxicity and dose adjustments**

   The Markov model simulates outcomes for **496** colon cancer patients treated with fluoropyrimidines under two scenarios:
   - Scenario 1: Systematic *DPYD* Genotyping - 100% testing coverage
   - Scenario 2: Current *DPYD* Genotyping - 94.7% testing coverage

   For both scenarios, two dose adjustment strategies were tested for patients carrying *DPYD* variants, as derived from literature findings: a reduction of 31% resulting in a severe toxicity probability of 32.5% and a reduction by 50%-75%, leading to a reduced toxicity probability of 22.5% (41).

**Markov Model outcomes**

This section presents the key outcomes from the Markov model analysis of colon cancer patients treated with fluoropyrimidines, focusing on toxicity, treatment-specific mortality, and the 5-year mortality rates under Scenario 1 (100% genotyping) and Scenario 2 (94.7% genotyping). Results are provided for both 32.5% probability and 22.5% probability of Grade 3 toxicity, ensuring a comprehensive analysis **(Table II-22).**

| Probability of Grade 3 Toxicity | Outcome | Scenario 1 - Systematic *DPYD* Genotyping; 100% | Scenario 2 -Current *DPYD* Genotyping; 94.7% | Relative Risk (RR) |
|---|---|---|---|---|
| 32.5% | Severe(grade 3-4) toxicity | 117.75(23.74%) | 118.58(23.91%) | 0.993 |
| | Toxicity-related mortality | 0.53(0.11%) | 0.58 (0.12%) | 0,914 |

| | | | | |
|---|---|---|---|---|
| | 5-year mortality | 35.70 (7.20%) | 35.95 (7.25%) | 0.992 |
| 22.5% | Severe(grade 3-4) toxicity | 113.89 (22.96) | 114.92 (23.17%) | 0.990 |
| | Toxicity-related mortality | 0.53 (0.11%) | 0.58 (0.12%) | 0.914 |
| | 5-year mortality | 34.53 (6.96%) | 34.84 (7.02%) | 0.991 |

**Table II-22**: Markov Model Outcomes

As shown in Table *4* implementing systematic *DPYD* (Scenario 1) genotyping leads to a marginal reduction in severe (grade 3-4) toxicity, treatment-related mortality and 5-year mortality.

**32.5% Probability of Grade 3 Toxicity**:

Under Scenario 1: 100% genotyping coverage-

- Severe (grade 3-4) toxicity decreased from 23.91% to 23.74%, representing a relative risk reduction of approximately 0,7% and absolute reduction of 0.17%.
- Toxicity-related mortality decreases from 0.12%to 0.11% achieving a relative risk reduction of 8,6% and an absolute reduction of 0.01%.
- Furthermore, 5-year mortality decreases slightly from 7.25% to 7.20%, representing a relative risk reduction of 0.7%. and an absolute risk reduction of 0.05%.

**22.5% Probability of Grade 3 Toxicity**:

Under Scenario 1: 100% genotyping coverage-

- Severe (grade 3-4) toxicity decreased from 23.17% to 22.96%, representing a relative risk reduction of approximately 0.91% and absolute reduction of 0.21%.
- Toxicity-related mortality decreases from 0.12%to 0.11% achieving a relative risk reduction of 8.6% and an absolute reduction of 0.01%.
- Furthermore, 5-year mortality decreases slightly from 7.02% to 6.96%, representing a relative risk reduction of 8.6% and an absolute risk reduction of 0.06%.

Implementing systematic *DPYD* genotyping at 100% coverage results in slight reductions in severe toxicity, treatment-related mortality, and 5-year mortality across both probability assumptions. However, the incremental benefit of moving from 94.7% to 100% genotyping is minimal, given Finland's already well-adopted *DPYD* genotyping practices.

### 3.3.2.2. Oncologist's Survey

To assess the adoption of *DPYD* genotyping in colorectal cancer treatment, a survey was distributed to oncologists across Finland through our stakeholder committee, specifically targeting those treating colorectal cancer. Despite attempts to reach both oncology clinics and national associations of oncologists, the survey yielded 21 responses in total, representing approximately 9.7% of the 217 oncology specialists in Finland (based on a 2019 report by the Finnish Medical Association) (43).

However, the number of oncologists actively treating colorectal cancer within this group is unknown.

The survey revealed a **94.7%** mean prescription rate for *DPYD* genotyping, affirming its integration into routine oncology practices in Finland. However, challenges such as test turnaround times, equity concerns and the need for broader stakeholder engagement were also identified.

**Key Findings**

**Demographics**

- Gender: Equally distributed between males and females.
- Age group: The largest group of respondents (9/21) fell within the 30-39 age group, followed by those aged 50-59 (6/21).
- Geographically, the largest proportion of participants (8/21) came from Etelä-Savo, North Karelia, or North Savo followed by Pirkamaa, Kanta-Häme, Central Finland, Päijät-Häme, or Ostrobothnia. Other regions included Uusimaa, Kymenlaakso or South Karelia and smaller representations from Varsinais-Suomi and Kainuu, Keski-Pohjanmaa, Lappi or Pohjois-Pohjanmaa.
- 19/21 were employed in public institutions, with minimal representation from the private sector.

**Implementation of *DPYD* Genotyping and Associated Challenges**

- One key finding is **the mean prescription rate of 94.7% for *DPYD* genotyping** among responding oncologists. This finding reaffirms the integration of *DPYD* genotyping into standard oncology practices in Finland. To explore the oncologistsperspectives on these issues, we included a set of Likert-scale questions in the survey as shown below (**Figure II-9**).

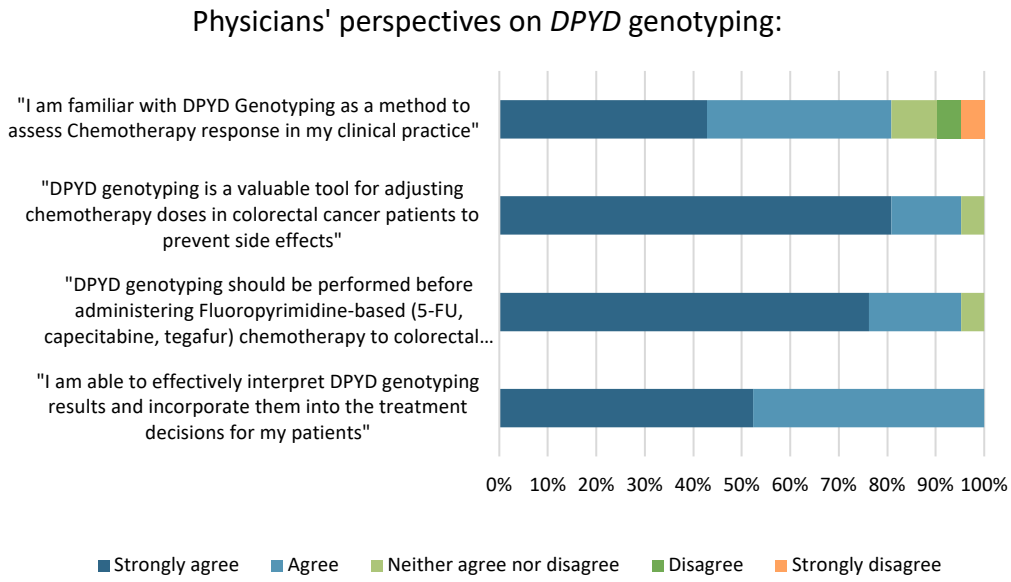



**Figure II-9:** Physicians' perspectives

However, the response rate suggests a need for further engagement with a broader cross-section of oncologists to validate these findings. The survey also included a question to identify the challenges oncologists face in integrating this genetic test into routine care **Figure II-10**. Respondents were given a predefined list of potential challenges and allowed to select multiple options, as well as provide input in an open text field for any "other" challenges not listed.

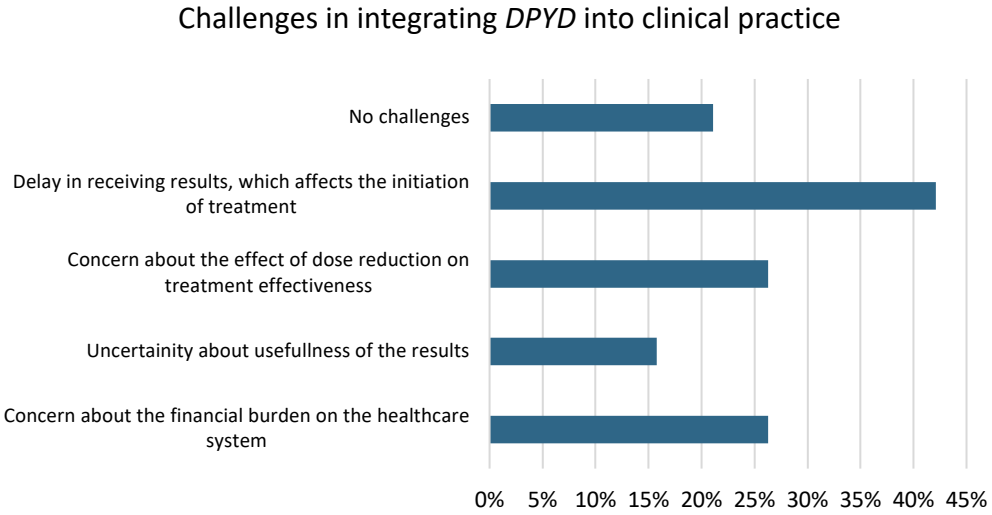



**Figure II-10:** Challenges in integrating *DPYD* into clinical practices

In addition to the predefined options, two respondents provided open-text comments under "other" challenges, one noted potential concerns about the correlation between DPD enzyme activity scores and drug tolerance which may impact perceptions of the test's clinical reliability. Another highlighted the broader issue of *DPYD* genotyping being "part of a wider gene panel (PGx), where the interpretation and application of other results is not standardized,". This highlights the challenge of integrating *DPYD* genotyping into broader PGx panels, where inconsistent interpretation and application due to lack of standardization emphasize the need for clear, consensus-driven guidelines.

**Turnaround Time for *DPYD* Genotyping Results**

Among 20 respondents, the reported time periods for receiving *DPYD* genotyping results varied:

- 3/20 reported 3-5 working days
- 11/20 indicated 5-10 working days.
  A significant portion, 5/20, experienced delays exceeding 10 working days.

**Equity Considerations**

To assess equity in the use of *DPYD* genotyping, oncologists were asked whether they had observed differences in its availability or use amongst different patient groups. 95% of respondents (18/19

oncologists) stated that there were no differences, indicating equitable access across patient demographics.
An open-text question further explored fairness in decisions regarding *DPYD* genotyping, considering factors such as age, frailty, and socio-economic status. Out of the 8 respondents to this question, all stated that treatment decisions are fair and equitable, with no observed disparities.

**Stakeholder Inputs**

During our scoping phase, an oncologist from the stakeholder committee described instances in which cultural and linguistic barriers, including those experienced by patients from different ethnic backgrounds, affected their understanding and acceptance of treatment options. These situations emphasize the importance of clear communication and culturally sensitive approaches to patient counseling, particularly in cases where the trust in medical authorities or understanding of treatment options vary. Such disparities, although rare in Finland are crucial to address to ensure equity not just in access to testing but also in treatment decision-making and outcomes.
A laboratory expert noted that the current *DPYD* genotyping does not cover all gene variants. She shared plans for introducing more comprehensive testing to address variations across ethnic backgrounds, including the Finnish population.

**Impact of *DPYD* Genotyping on Treatment Decisions**

Out of 19 respondents, 100 % of them said they would adjust chemotherapy dosages based on genotyping results. Additionally, 4/19 reported that they would consider alternative medications if possible. One respondent elaborated in an open-text field, stating that they would opt for alternative medications only if the *DPYD* activity score was 0.
However, responses to another survey question, which pertained to the involvement of another healthcare professional in addition to the oncologist, revealed that clinical pharmacologists or pharmacists are rarely involved in dosing decisions based on *DPYD* genotyping results in Finland, with 15/18 respondents indicating no involvement. Despite this, stakeholder input from a laboratory expert, who is also a practicing physician, suggested that ward pharmacists or pharmacologists may sometimes assist with dose adjustments in specific facilities, pointing to regional variability in practice.

**Impact of *DPYD* Genotyping on Treatment Outcomes:**

Oncologists were asked:
“Have you seen significant improvements in treatment outcomes or patient experience since incorporating *DPYD* genotyping into your practice?” (Multiple answers allowed; additional open-text responses under “other”)

**Key Findings (No. of respondents; 18/21)**

- Reduction in side effects: 13/18 respondents reported noticing a reduction in treatment-related side effects.

- Improvement in treatment efficiency: None of the respondents indicated improvements in treatment efficiency
- Improvement in patient satisfaction: 4/18 respondents observed improved patient satisfaction in their practice.
- Open-text responses in "other"
    - *"In a few patients with a variant associated with severely reduced DPD activity, a normal dose of fluoropyrimidine would probably have resulted in life-threatening harm, since even a small dose caused harm"*
    - *"The dose intensity of the treatment has decreased"*
    - *"I have not noticed a significant improvement in treatment results or patient experiences. In the past, we started with a reduced dose and then increased the doses if there were no problems in the previous treatment cycle".*

**Stakeholder Inputs**

An oncologist from our stakeholder committee identified that dose escalation based on genotyping results is challenging to implement uniformly due to factors such as varying clinician interpretation and patient-tolerability concerns. They noted that escalating doses requires consistent follow up and coordination, which is sometimes hindered by staff changes in university hospitals which could be a common occurrence. These challenges are compounded by the absence of systematic pharmacologist or pharmacist involvement in the majority of clinical settings.
The oncologist further emphasized that while laboratory reports typically provide very clear dosage guidance in most cases, complex or rare variants may require additional interpretation or consultation. These challenges highlight the potential need for further consultation, which could benefit from the involvement of pharmacologists or other specialists.

**Patient Trust in Oncologist's Recommendations**

An interesting finding of the survey was that 19/20 oncologists reported that patients trust the opinion of their doctor when asked about if patients express any concerns or preferences regarding DPYD genotyping and its impact on treatment decisions. This was part of a predefined list of potential patient behaviors, which also included options such as expressing anxiety, actively seeking information elsewhere, having specific treatment preferences, or belonging to vulnerable groups with unique concerns.

**Stakeholder Inputs**

An oncologist from our stakeholder committee corroborated this finding, emphasizing that Finnish patients generally exhibit a high level of trust in healthcare authorities and doctors. This cultural characteristic facilitates the acceptance of genetic testing and treatment recommendations, creating a favorable environment for integrating *DPYD* genotyping into routine healthcare.

#### Key Insights and Future Directions for *DPYD* genotyping

In conclusion,

- 14/20 oncologists highlighted the need for further research into long-term outcomes of *DPYD*-guided treatment
- 12/20 indicated the impact of dose reduction on chemotherapy efficacy.
- 7/20 advocated for identifying additional genetic markers to enhance treatment precision.
- 12/20 emphasized the importance of improving patient education and counselling about *DPYD* genotyping.

While genetic testing is widely integrated into practice, operational challenges, such as delays in receiving test results remain a concern as highlighted by an oncologist in an open text response.

### 3.3.2.3. Laboratory Survey

To assess the implementation of *DPYD* genotyping in Finland, a survey was conducted among laboratory professionals involved in genetic testing. Insights from the stakeholder committee and expert consultations revealed that the HUS diagnostic Center initiated *DPYD* genotyping in 2019, with other hospital labs adopting it over time (37).

#### Key Developments

Currently, genotyping is offered nationwide as part of a pharmacogenetic panel using next-generation sequencing (NGS) (44). Testing volumes have risen significantly since the EMA's 2020 recommendation for *DPYD* genotyping prior to fluoropyrimidine treatment. A professional from the Uusimaa region reported a growth from 220 results in 2019 to approximately 2100 tests by 2021. Starting in 2022, testing transitioned to a pharmacogenetic panel format, reflecting the expanding role of pharmacogenetics in personalized medicine.

#### Operational Impact of *DPYD* Genotyping on Laboratory Practices

#### Turnaround times for *DPYD* genotyping results

Laboratory professionals shared insights into the practical time required to produce DPYD genotyping results after receiving a sample.

Amongst 8 respondents:

- One professional reported a rapid turnaround time of 1-2 days.
- Three professionals mentioned that it took 3-4 days.
- Three others reported longer times exceeding 4 days.

These findings reveal regional differences in processing timelines.

#### Stakeholder Inputs

An oncologist from our stakeholder committee identified practical challenges, such as delays in initiating chemotherapy due to prolonged test turnaround times and human errors in conducting or documenting tests.

### Challenges in *DPYD* genotyping

Laboratory professionals identified specific challenges in *DPYD* genotyping through predefined options (multiple selection allowed) and open-text responses.
Amongst five respondents:

- Delays in results and lack of resources were the most cited challenges, reflecting operational constraints in certain areas.
- One professional highlighted variability in reagent quality.

### Stakeholder Inputs

A laboratory expert in our stakeholder committee identified that delays in genetic testing often stem from logistical issues, such as sample collection and transportation. She also noted that laboratory systems do not always integrate seamlessly with hospital patient record systems, which could lead to inefficiencies in data access and result interpretation.

### Impacts on Laboratory Workflow and Resource Allocation

Amongst 8 respondents:

- Four noted that it led to a reorganization of tasks
- Two mentioned changes in personnel arrangements to accommodate the testing process
- Interestingly, two respondents reported no changes to their workflows.

When asked if the "recommendation given by EMA 2020 had positive or negative effects on the operation of your laboratory, out of seven respondents:

- Three indicated an increased workload
- Two mentioned the development of new protocols to accommodate testing.
- One noted improved accuracy in testing.
- Another stated via an open-text response, that implementing *DPYD* genotyping has no significant impacts as the recommendations were promptly integrated into existing workflows.

These findings indicate how implementation impacts vary depending on laboratory resources and pre-existing practices.

### Stakeholder Inputs

Insights from an oncologist in our stakeholder committee highlighted the importance of high-quality, interpretable laboratory reports in clinical decision making. They pointed out that there could be variability in the quality of reports across laboratories. Survey responses indicated uncertainty regarding consistency of *DPYD* genotyping result instructions across healthcare facilities, with only 5/18 respondents confirming consistency and a majority unsure. This variability highlights the need for further standardization and training to ensure uniformity in reporting practices, ultimately enhancing clinician confidence in test results.

A laboratory expert highlighted significant efforts to automate genetic testing processes, reducing turnaround times. She noted that automation also enables simultaneous testing of multiple patients, enhancing laboratory capacity. However, she pointed out that there could be variability in test result formats across laboratories, which can cause confusion when interpreting results from external providers.

**Suggestions on Improving Laboratory operations**

When asked about potential improvements or changes to help optimize laboratory operations, respondents provided the following insights. Three laboratory professionals suggested that better training programmes would enhance operational efficiency. Three indicated the need for more up-to-date equipment, while two mentioned the importance of improved software to streamline processes.

**Enhancing the Clinical Utility of *DPYD* Genotyping**

When asked about improvements or developments needed to enhance the clinical utility of *DPYD* genotyping, respondents emphasized the need for a faster response rate and others suggested that testing should include a larger number of variants or broad range of genetic markers to improve comprehensiveness of results.

#### 3.3.2.4. Patient Representatives: Phone Interviews

We collaborated with Colores, a cancer patient association in Finland (49). Six patients, ranging in age from 47 to 72 (two males, four females), volunteered to participate. Over the course of a week, Helena Kääriäinen from our technical team conducted in-depth phone interviews with each patient. This qualitative approach provided valuable insights into patient experiences with fluoropyrimidine-based chemotherapy and their views on genetic testing for *DPYD*-related enzyme deficiencies.

- **Genotype testing awareness:** None of the patients believed they had undergone *DPYD* genotyping, though one patient discovered later from her files that she had been tested. This reflected a lack of communication about this aspect of their treatment. Some patients confused *DPYD* genotyping with cancer predisposition testing, indicating a general misunderstanding about the purpose of the test.

- **Attitudes toward testing:** five patients out of six said they would have accepted the test if offered, while one preferred to avoid delays in starting treatment.
    - When asked about potential waiting times of 1-2 weeks for the test results, most expressed a desire for immediate treatment initiation, with dose adjustments made later if necessary.
    - Three out of six patients said they still prefer the standard chemotherapy dose even if identified as high- risk.
- **Knowledge gaps**: The interviews highlighted a lack of patient education about *DPYD* testing and its implications. Four out of six patients did not recall being informed about side effects

risks before treatment. Most felt that organizations like the Cancer Society or Colores should play a stronger role in providing information but noted that they only contacted them later in their treatment journey.

**Stakeholder Inputs**

A member of our stakeholder committee, with direct experience as a cancer patient and active involvement in patient advocacy, highlighted several key areas for improvement:

- Psychosocial support: A greater collaboration with cancer associations was recommended to provide timely peer support, addressing delays and stigma some patients associate with seeking psychiatric care.
- Patient education: Clearer communication is required to guide patients to available resources early in their treatment. Associations like" Kaikki syövästä" and "Minä ja syöpä" were cited as valuable but underutilized due to limited awareness.
- Advocacy and awareness: The stakeholder, currently documenting her experiences in a book, stressed the importance of integrating patient perspectives with expert insights to raise awareness and improve care.

### 3.3.2.5. Economic Impact of *DPYD* Genotyping

The economic benefits of *DPYD* genotyping have been extensively documented in the literature, including cost savings from reduced toxicity-related hospitalizations and lower toxicity management costs (28,31,32,33,34,35). Given that a detailed economic assessment is already conducted by INSA, we have chosen not to replicate these analyses in this report. Instead, we acknowledge that existing evidence strongly supports the cost-effectiveness of *DPYD* genotyping in reducing adverse outcomes and healthcare costs, aligning well with Finland's healthcare objectives of efficiency and patient safety.

# 4. Discussion of results

The systematic implementation of *DPYD* genotyping prior to administering fluoropyrimidine-based chemotherapy for CRC patients is designed to identify individuals at risk of severe, potentially life-threatening toxicities due to DPD deficiency. This approach enables tailored therapeutic adjustments, underscoring the potential of personalized preventive medicine within pharmacogenetics and cancer treatment. This HIA, conducted in Portugal, Italy, and Finland, examined the clinical, organizational, and economic impacts of introducing systematic *DPYD* testing in these distinct healthcare contexts. By comparing outcomes across the three countries, we can draw broader insights about the potential for harmonizing policies around systematic genotyping.

In Portugal, the implementation of systematic *DPYD* genotyping led to measurable reductions in severe toxicity and mortality. A national survey estimated a baseline genotyping prescription rate of 78.63%. Following implementation, severe toxicity events decreased from 24.72% to 24.18%, corresponding to a relative risk reduction of 2.2%. Toxicity-related mortality fell from 0.14% to 0.11%, achieving a relative risk reduction of 23.6%. Additionally, five-year mortality experienced a slight decline from 7.49% to 7.33%, representing a preventive fraction of 2.18%. In Italy, where the baseline genotyping rate was estimated at 70%, outcomes of similar magnitude were observed. Systematic genotyping reduced severe toxicity from 24.65% to 24.01%, reflecting a relative risk reduction of 2.6%. Toxicity-related mortality dropped from 0.15% to 0.11%, achieving a preventive fraction of 26.7%. Over a five-year period, the risk of mortality declined by 2.6%, highlighting the positive impact of systematic genotyping on patient outcomes.

In Finland, where baseline *DPYD* genotyping adoption was already high at 94.7%, the benefits of systematic implementation were understandably marginal. Severe toxicity decreased slightly from 23.9% to 23.6%, corresponding to a relative risk reduction of 0.7%. Toxicity-related mortality fell from 0.12% to 0.11%, and five-year mortality saw a minimal decline from 7.25% to 7.20%. These findings reflect the already optimized nature of existing practices in Finland, leaving limited scope for further improvements.

The results from Portugal and Italy highlight clinically meaningful reductions in morbidity and mortality, supporting findings from similar international studies. These studies consistently demonstrate that pharmacogenetic testing is crucial for enhancing chemotherapy outcomes and mitigating adverse drug reactions. Finland's results, while indicative of diminishing returns at high adoption rates, still validate the importance of systematic *DPYD* genotyping in achieving population-wide health benefits.

The organizational impact of *DPYD* genotyping demonstrates notable differences in acceptability and laboratory capacity across the three countries.

In Portugal, a survey of healthcare professionals shows high levels of acceptability for DPYD testing. The majority of oncologists showed strong support for the integration of genotyping into routine protocols and disagreed that systematic genotyping would impose an excessive workload on them.

Laboratory staff similarly recognized its value for patient safety and small preoccupation with the policy's burden on genetic laboratories. However, some logistical challenges such as delays in receiving results, lack of specific guidelines and cost concerns persist. Addressing these barriers through improved infrastructure and workflows would enable smoother integration of DPYD testing into routine oncology care.

In Italy, *DPYD* genotyping acceptability is less well-documented. Feedback from the Steering Committee provided insights into acceptability of DPYD testing, reporting generally positive acceptance of the test among patients. Broader pharmacogenomic research suggests that both patients and healthcare professionals generally support genotyping initiatives. While the data from both the literature and expert consultation suggest good overall acceptability, the limited evidence precludes definitive conclusions about acceptability of the DPYD genotyping in the Italian context. However, systemic challenges, including the lack of standardized national guidelines, limited prescriber awareness, and regional disparities, could complicate implementation. Laboratory capacity and turnaround times vary significantly, with some centers establishing efficient workflows while others face significant delays. The collected data underscores the need for consistent protocols and reporting practices, at a national level.

In Finland, *DPYD* genotyping is well-integrated into oncology practice, with a reported prescription rate of 94.7% among oncologists. Laboratories utilize next-generation sequencing (NGS) panels to ensure comprehensive testing. Despite this progress, regional differences in turnaround times and operational capacity persist. As concluded from the survey data, the perspectives on *DPYD* genotyping reveal high acceptability among physicians and laboratory personnel. While delay in receiving test results was the most cited challenge among physicians, lack of resources and delays in providing results were the most cited challenges among laboratory personnel, reflecting operational constraints in certain areas. While acceptability among healthcare professionals is high across all three countries, laboratory capacity to implement *DPYD* testing varies significantly. Portugal and Finland report manageable laboratory workloads, whereas Italy experiences substantial regional disparities.

The economic analyses across the three countries underscore the value of *DPYD* genotyping. Although specific cost-related data for Portugal and Finland are limited, extensive literature on systematic genotyping consistently demonstrates cost savings. By reducing severe toxicities associated with fluoropyrimidine-based chemotherapy, genotyping offsets its upfront costs through decreased hospital admissions and lower toxicity management expenses. In healthcare systems constrained by budgets, these findings present a compelling case for integrating *DPYD* testing into routine cancer care. The potential for reducing treatment-associated costs aligns with the broader goals of cost-effective, patient-centered care.

This study has several limitations that should be acknowledged. Reliance on self-reported data and survey-based methodologies introduces potential biases, such as selection bias and inaccuracies in

reporting. Limited response rates in certain countries, such as Finland, further restrict the generalizability of these findings.

Additionally, differences in healthcare systems and implementation practices across the three countries complicate direct comparisons. Variations in baseline genotyping rates, infrastructure, and resource allocation mean that the observed outcomes may not fully represent the potential impact of systematic *DPYD* testing in other settings.

The focus on stage III colorectal cancer patients, or colon cancer patients in Finland, also limits the broader applicability of these findings. The absence of longitudinal data prevents the assessment of long-term outcomes, such as sustained reductions in toxicity-related mortality or improvements in overall survival.

Economic evaluations relied on retrospective analyses and assumptions, which might not capture real-world variables such as fluctuating costs or evolving healthcare policies. These limitations underscore the need for prospective studies, standardized data collection, and further research to refine economic assessments and inform policy development.

Despite these constraints, the evidence strongly supports the clinical and economic benefits of DPYD genotyping. Future efforts should focus on expanding patient populations, improving infrastructure, and creating standardized guidelines to maximize the impact of this policy.

# 5. Recommendations for Policy

Given the findings from the three HIA exercises that were summarized in this report, some key policy actions should be prioritized in order to improve the implementation and outcomes of systematic *DPYD* genotyping,

First, it is crucial to develop **comprehensive national guidelines** that ensure consistency in testing practices, reporting formats, and clinical workflows across different regions. These guidelines should address essential areas such as the selection of tests, recommendations for dosage adjustments, and follow-up protocols, in order to reduce regional disparities. By providing a standardized approach, these guidelines will help ensure that patients receive consistent, high-quality care, regardless of their location.

Next, **strengthening laboratory infrastructure** is essential. This includes investing in automation technologies which will help reduce testing turnaround times and allow laboratories to handle increased testing volumes. It would also be important to create standardized reporting systems that make it easier to integrate test results into clinical decision-making. This would improve the efficiency of laboratory operations and ensure that healthcare providers receive actionable insights in a timely manner.

Third, **raising awareness and providing targeted training** for healthcare professionals is key to ensuring the successful adoption of *DPYD* genotyping. Educational campaigns should be aimed at oncologists, pharmacists, and laboratory staff to highlight the clinical benefits of genotyping and how to properly interpret the results. Ensuring that healthcare providers are confident in using pharmacogenomic data will help integrate these insights into personalized treatment plans more effectively.

**Ensuring equitable access** to *DPYD* testing is another important priority. Efforts should be focused on addressing regional gaps in testing availability, particularly in underserved areas. Providing financial support, such as subsidies or insurance coverage for genotyping, will help reduce cost-related barriers and allow more patients to benefit from this technology.

Additionally, **improving data collection and access** is critical to making informed policy decisions. Creating national databases that track disease incidence, medication prescriptions, and testing rates will help monitor outcomes more effectively. Longitudinal studies and centralized data repositories will provide a solid evidence base to guide future policy decisions and fine-tune the implementation of *DPYD* testing.

Finally, **setting up monitoring and evaluation systems** will ensure ongoing improvement in the process. These systems should track genotyping rates, toxicity outcomes, and the economic impacts of *DPYD* testing. Regular monitoring will help identify areas that need attention and allow for timely adjustments, ultimately enhancing both patient safety and treatment effectiveness.

By adopting these measures, healthcare systems can maximize the clinical, organizational, and economic benefits of *DPYD* genotyping. These actions will not only improve patient safety and

treatment outcomes but also ensure that *DPYD* testing is integrated equitably and efficiently on a larger scale, making cancer care more personalized and cost-effective.

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# Section III: PROPHET Framework Validation Case Studies on *BRCA 1/2* testing and Pharmacogenetic Passport

# Section III-1: *BRCA 1/2* testing approach for the personalized prevention of breast and ovarian hereditable cancers in Italy

## 1. Background

### 1.1 Epidemiology of Breast Cancer

Breast cancer is one of the main public health challenges, with an estimated 666,000 deaths and 2.3 million new cases each year (1), making it the first malignancy in terms of incidence and mortality among women. In 2023, 55,900 new diagnoses were registered in Italy, bringing the total number of breast cancer cases in the country to 834,200. The high prevalence in the population is not only attributable to the high incidence, but also to the 88% 5-year survival (90% when the neoplasm is diagnosed at early stages) (2). Regarding mortality, it is estimated that in 2022 deaths due to breast cancer in Italy were about 15,500 (2). It is important to consider that breast cancer recurrence can occur up to 20 years after the diagnosis of the primary tumour, especially in some subpopulations with hormone receptor positive neoplasia (3). Although breast cancer presents in most cases as a 'sporadic' form occurring in women with no family history of the disease, about 15-20% of cases are familial forms, in which the tumour occurs in families with other already diagnosed cases (4). In 5-7% of cases breast cancer is linked to hereditary factors, as it is characterized by a strong genetic predisposition, in ¼ of cases due to pathogenic variants in the germinal DNA, involving the *BRCA1* and *BRCA2* genes (5, 6). Advancements in breast cancer screening and heightened awareness among women have led to the earlier detection of most breast cancers, often at a stage where conservative surgery and effective therapies can achieve high five-year survival rates. Early-stage breast cancer is typically managed with breast-conserving surgery followed by radiotherapy or mastectomy. Systemic adjuvant treatments, including hormone therapy, chemotherapy, or targeted therapies, are widely used post-surgery to significantly reduce the risk of recurrence and mortality. Treatment decisions are tailored to each patient, considering tumor biology, disease stage, and the potential benefit-risk ratio. For high-risk, hormone receptor-positive, *HER2*-negative early breast cancer, *CDK* 4/6 inhibitors like abemaciclib, combined with endocrine therapy, have emerged as a valuable option to further lower recurrence risk. Genomic tests, such as Oncotype Dx®

or Mammaprint®, assist in refining treatment decisions, particularly for patients with an intermediate risk of recurrence (2). While 6-7% of breast cancers are metastatic at diagnosis, most metastatic cases arise after recurrence of an earlier-stage tumor (2). Thanks to improved diagnostic and therapeutic strategies, innovative systemic therapies, and better integration of local and systemic treatments, survival outcomes for patients with metastatic breast cancer have significantly improved. The choice of systemic therapy is guided by tumor characteristics, prior treatments, and the patient's overall physical and psychological condition.

## 1.2 Epidemiology of Ovarian Cancer

Ovarian cancer is the second most common gynecological neoplasm, with an estimated incidence of 225,000 new cases per year worldwide. This disease is a great burden on public health, as it is often diagnosed at an advanced stage (75%-80% of cases) and has a 5-year survival rate of 42%, with approximately 140,000 deaths recorded annually, despite improvements in treatments (5, 6, 7). In Italy, about 6,000 new cases of ovarian cancer were identified in 2022, while data for 2023 are not yet available (2). Concerning prevalence, it is estimated that there are 49,800 women in Italy living after diagnosis (2). In 2022, the mortality associated with ovarian cancer in Italy was 3,600 deaths (2). A hereditary predisposition to epithelial ovarian cancer can be found in most patients, 25% of whom have germline mutations in the *BRCA1* or *BRCA2* genes (4). In early-stage ovarian cancer, surgery is curative in about 70% of cases (2). However, due to a recurrence risk of 25-30%, adjuvant chemotherapy is often advised. This typically involves carboplatin, either alone or in combination with paclitaxel. For advanced ovarian cancer (FIGO stages III and IV), radical surgery is considered the cornerstone of treatment (2). Achieving no residual tumor after surgery is a critical prognostic factor, closely linked to prolonged survival. Standard care usually includes six cycles of combined carboplatin and paclitaxel, potentially accompanied by interval debulking surgery. Recent years have seen a notable reduction in ovarian cancer mortality, likely influenced by the introduction of *PARP* inhibitors as part of first-line therapy. These drugs have shown significant survival benefits, particularly for patients with *BRCA1* or *BRCA2* mutations (2). Nevertheless, even with optimal surgical and chemotherapy approaches, approximately 70% of patients with advanced disease face recurrence within the first two years, highlighting the need for continued advancements in treatment strategies.

### 1.3 *BRCA1* and *BRCA2* genes

The genes *BRCA1* (BReast CAncer gene 1) and *BRCA2* (BReast CAncer gene 2) are two tumorsuppressor genes that play a key role in repairing damaged DNA. *BRCA1* encodes for a pleiotropic protein involved in the DNA damage response, acting in both checkpoint activation and DNA repair. On the other hand, *BRCA2* acts as a mediator in the central mechanism of homologous recombination (HoR) (8). These genes exhibit similar phenotypic pathological patterns as they encode proteins involved in HoR, a process that corrects DNA mutations using the sister chromatid. When these genes have specific modifications, called variants or pathogenic mutations, they lose

their function and favour cancer development (9). If a copy of either gene is mutated in the germ line, hereditary breast and ovarian cancer syndrome (HBOC) develops, which is transmitted in an autosomal dominant manner. This syndrome is associated not only with an increased risk of early breast cancer, but also with ovarian, pancreatic, stomach, larynx, fallopian tube and prostate cancer (8). Mutations in the *BRCA1* and *BRCA2* genes are responsible for approximately 3% of breast cancers (11). This value increases to 50% when the malignancy occurs in the presence of a family history of breast cancer and up to 90% in the presence of a family history of breast and ovarian cancer.

Depending on the population, the probability of carrying a pathogenic mutation in *BRCA1* or *BRCA2* is estimated to be between 1 in 400 and 1 in 800 (13, 14), with carriers having an average cumulative risk of breast cancer in the first 80 years of 72% [95% CI, 65% - 79%] for a pathogenic *BRCA1* variant and 69% [95% CI, 61% - 77%] for a *BRCA2* variant (14). Furthermore, the presence of pathogenic variants of *BRCA* genes increases the age-specific risk of contralateral breast cancer after first diagnosis (15). Similarly, heterozygous carriers of *BRCA1* or *BRCA2* germline mutations have been found to have an increased lifetime risk of developing ovarian cancer (*BRCA1* 40%-60%; *BRCA2* 11%-30%) (16). Current evidence indicates that *BRCA1/2* pathogenic variants (PVs) are also associated with pancreatic cancer, and that *BRCA2* PVs are associated with prostate cancer risk, but with lower penetrance.

### 1.4 *BRCA1/2*-Related Cancer Prevention

The clinical utility of BRCA testing in high-risk populations has been proven since 2003 by authoritative agencies for genetic test evaluation, such as the CDC's Office of Public Health Genomics through the ACCE framework (17). Over the years, various strategies regarding testing criteria, sequencing methods, and prevention approaches have also been evaluated (18-20), with constant updates to both international and national guidelines.

#### 1.4.1 *BRCA* 1/2 testing strategies

Early identification of *BRCA1/2* mutation carriers offers the opportunity to implement effective strategies for preventing hereditary breast and ovarian cancer. These strategies include earlier, more frequent, or intensive screening, as well as surgical and medical interventions to reduce risk.

To ensure timely identification of *BRCA1/2* mutation carriers, four primary testing approaches have been investigated: (i) population-based genetic screening targeting individuals without cancer; (ii) genetic screening based on family history, focusing on those without cancer but with a family history indicative of *BRCA1/2* mutations; (iii) familial mutation-based screening, which tests cancer-free individuals for a confirmed familial *BRCA1/2* mutation; and (iv) cancer-based genetic screening, aimed at individuals diagnosed with *BRCA*-associated cancers (21).

The population-based genetic screening model has gained attention due to its ability to identify a greater number of *BRCA1/2* mutation carriers and because it addresses disparities in access. However, most expert guidelines recommend genetic screening based on a thorough evaluation of personal and family history, followed by risk assessment and genetic counselling (22).

**The National Institute of Health and Clinical Excellence (NICE) advocates for genetic testing among family members of individuals with confirmed *BRCA* mutations, enabling access to genetic counseling and preventive testing for familial pathogenic variants (23).** In cases of a positive result, relatives are directed toward programs aimed at early cancer diagnosis and reducing the risks of associated cancers, such as breast and ovarian.

**The US Preventive Services Task Force (USPSTF) further reinforces these recommendations, advocating for *BRCA1/2* testing in individuals with personal or family histories suggestive of hereditary cancers (24).** Genetic counseling plays a pivotal role in guiding patients through result interpretation and subsequent therapeutic or screening measures. The USPSTF guidelines highlight the need for cascade testing within families, starting with affected relatives when available. Particular attention is given to populations with common ancestral mutations, such as the Ashkenazi Jewish community. More recently, the National Comprehensive Cancer Network (NCCN) updated its 2024 guidelines, extending *BRCA* testing recommendations to include family members of patients with prostate carcinoma, reflecting a broader approach to identifying and managing hereditary cancer risks (25).

In Italy, 14 scientific societies have jointly issued a position paper on the implementation of *BRCA* testing for the prediction and prevention of breast, ovarian, pancreatic, and prostate cancers (26). This document aligns with both national and international guidelines, emphasizing that eligibility for *BRCA1/2* mutation testing should be determined based on personal and family medical histories. Key factors include the number of affected relatives, the types of cancers, the occurrence of multiple primary tumors, age at diagnosis, sex, and the immunohistochemical and molecular characteristics of the tumors (**Figure III- 1**).

| |
|---|
| **Personal history:**<br>Male breast cancer<br>Woman with breast cancer and ovarian cancer<br>Woman with breast cancer <36 years<br>Woman with triple negative breast cancer <60 years<br>Woman with bilateral breast cancer <50 years<br>Woman with non-mucinous and non-borderline ovarian cancer at any age<br>Metastatic pancreatic adenocarcinoma<br>Metastatic prostate cancer |
| **Personal history of breast cancer <50 years and first-degree familiarity[a,b] for:**<br>Breast cancer <50 years<br>Non-mucinous and non-borderline ovarian cancer at any age<br>Bilateral breast cancer<br>Male breast cancer<br>Locally advanced or metastatic pancreatic cancer<br>Metastatic prostate cancer |
| **Personal history of breast cancer >50 years and family history of breast cancer, ovarian cancer, metastatic prostate cancer or locally advanced/ metastatic pancreatic cancer in 2 or more first-degree relatives[a,b] among them (including one in first degree with her[a,b])** |
| **Personal history of prostate cancer and familiarity[c]:**<br>At least one first-degree relative[a] with non-Grade Group 1 prostate cancer aged <60 years<br>At least two family members with non-Grade Group 1 prostate cancer aged <50 years |
| **Family history of pancreatic cancer:**<br>At least two first-degree relatives[a] with pancreatic adenocarcinoma[d]<br>At least three family members with pancreatic adenocarcinoma[e] |
| **If present, testing eligibility criteria for genetic syndromes with an increased risk of pancreatic cancer** |
| **Family history of:**<br>**Known pathogenic variant in a predisposing gene in a family member** |

**Figure. III-1** Eligibility Criteria for *BRCA* testing from a position paper of Italian Scientific Societies, 2022 (26).

In 2023, AIOM published new breast cancer guidelines (**Table III-1**), which expanded the eligibility criteria for *BRCA* testing access in patients with breast cancer (27). The new guidelines expand access to genetic testing in the following ways:

- By extending the eligibility age from 36 to 40 years old.
- By including hormone receptor positive breast cancers with and CPS/EG scores ≥3;
- By including early-stage hormone receptor positive breast cancer with ≥4 lymph nodes
- By extending the triple-negative breast cancer eligible from only <60 years to any age
- By extending the family history criteria from patients with relatives with Pancreatic or Prostate metastatic cancers, to patients with relatives with Pancreatic or Prostatic cancer at any stage

| Category | Eligibility Criteria |
|---|---|
| **Clinical Characteristics with Increased Probability of *BRCA* Pathogenic Variant** | Woman with both breast and ovarian cancer |
| | Woman with breast cancer <40 years |
| | Woman with triple-negative breast cancer (any age) |
| | Woman with bilateral breast cancer <50 years |
| | Male breast cancer |
| **Without Clinical Characteristics but Eligible for Specific Treatments** | Patient with early-stage breast cancer, hormone receptor positivity, and ≥4 positive lymph nodes |
| | Patient with hormone receptor-positive breast cancer and prior neoadjuvant chemotherapy with residual disease and CPS/EG score ≥3 |
| **Family History Associated with Increased Probability of *BRCA* Pathogenic Variant** | Patients aged 41–50 with a personal history of breast cancer and first-degree relatives with: Breast cancer <50 years, non-mucinous and non-borderline ovarian cancer (any age), Bilateral breast cancer, Male breast cancer, Pancreatic cancer, Prostate cancer |
| | Patients with a personal history of breast cancer >50 years and a family history of breast, ovarian, or pancreatic cancer in ≥2 first-degree relatives |
| | Known *BRCA* pathogenic variant in a relative |

**Table III-1.** Eligibility Criteria to *BRCA* test for Breast Cancer patients from 2023 AIOM guideline (27).

Risk assessment, genetic counseling, and testing for *BRCA1/2*-related cancers have become integral components of public health initiatives in Italy. However, despite the progress made with the National Prevention Plan (NPP) 2020-2025, the implementation of the *BRCA* testing remains uneven between the different regions. The NPP, which places a strong emphasis on cancer prevention, has encouraged the regions to develop PDTAs (care pathways) dedicated to screening for hereditary-familial cancers such as breast, ovarian, pancreas and prostate. Following the indications of the NPP

and the State-Regions Agreement, many Regions have started to adopt specific PDTAs for the prevention of *BRCA* related, for breast and ovarian cancers.

However, the adoption of these PDTAs has not been uniform across the country. Some regions, such as Emilia-Romagna, Lombardy, Piedmont, Liguria, Tuscany, Sicily, Basilicata, Campania, Marche, Molise, Veneto, Apulia, Abruzzo, Sardinia, Latium, Trentino-Alto Adige, the Valle d'Aosta and the autonomous province of Trento, have already developed and implemented specific pathways. However, other regions are still in the development or implementation phase of such pathways, generating a situation of disparities in access to testing and prevention. Although there are several differences among regional PDTAs, most prioritize *BRCA* testing for women at high hereditary risk, particularly those with a family history of breast or ovarian cancer. However, many of these PDTAs are not aligned with the latest guidelines. The eligibility criteria vary widely, and very few extend to include prostate and pancreatic cancers.

### 1.4.2 *BRCA* sequencing strategies

It is possible to determine the carrier status of mutations in the *BRCA1* and *BRCA2* genes using both blood and salivary samples, usually by NGS.

NGS test allows DNA sequences to be read in parallel, reducing both costs and waiting times for sequencing (29). Compared to the previous Sanger test method, which involved the amplification of single DNA strands by Polymerase Chain Reaction and modified nucleotides analysed by capillary electrophoresis (29), NGS allows the construction of a set of DNA fragments linked to a synthetic DNA sequence, called an adapter. These fragments serve as the basis for DNA amplification to create a DNA library (30). It is also important to consider the pre-analytical variability due to the way the DNA sample is taken. Studies have shown that NGS tests, especially when combined with reading software such as VIP, R and AVA, achieve a specificity of almost 100% and a sensitivity of at least 97.5% (31). The clinical validity of NGS tests refers to the test's ability to identify genetic variants related to the development of the malignancy, its prognosis or treatment. It is important to specify that NGS tests are able to identify both specific mutations that have a direct impact on the risk of developing the disease and mutations of uncertain significance. To address this challenge, specific gene panels have been developed to identify *BRCA* mutations associated with risk of developing specific cancers, following the criteria established by ClinGen (32) and PanelApp (33, 34). These panels may also include variants of other genes that confer a high breast cancer risk (e.g. *PALB2, ATM, CHEK2, PTEN*).

The French Genetic and Cancer Consortium has created specific panels for each type of neoplasm related to *BRCA* mutations. These panels define the genes (also other genes than *BRCA*) involved in each neoplasm and assign a weighted risk level for each gene (**Figure III-2, III-3**). The clinical validity of these tests is supported by evidence such as the increased cumulative risk of contralateral breast cancer within 10 years being 23.9% for women under 41 years of age with mutations, compared to 2.7% in women without mutations. Mutation carriers have also been shown to have worse overall

survival (hazard ratio, HR 1.30, 95% CI: 1.11-1.52) and breast cancer-specific survival (HR 1.45, 95% CI: 1.01-2.07) than *BRCA* negative women (35).

In Italy, there are currently no precise indications regarding the technology to be used to conduct genetic analyses in at-risk populations. For example, in the PDTA dedicated to hereditary-familial tumors, drawn up by the oncological network of the Campania region in 2022, the use of NGS testing is recommended, without however excluding the use of other techniques, such as Multiplex Ligation-dependent Probe Amplification to identify approximately 10% of gene rearrangements (36). Moreover, in the PDTA, freedom is left to individual laboratories to choose the technique to be used: they can opt for the single-gene strategy, candidate genes or use more or less extensive panel genetic tests (36).

On 23 February 2023, the Ministry of Health published an outline of a ministerial decree, accompanied by a technical annex providing guidance on the establishment of Molecular Tumor Boards and the identification of specialized centers for the performance of extended genomic profiling tests using NGS. This document was submitted to the State-Regions Conference for approval on 10 May 2023 (37). It is hoped that a clear indication will be provided on the technology to be adopted to guarantee the highest possible sensitivity and specificity, as found in scientific literature.

| Genes | Tumours (Number of Genes) | | | | |
|---|---|---|---|---|---|
| | Breast (N=13) | Endometrium (N=10) | Ovary (N=12) | Pancreas (N=12) | Prostate (N=11) |
| ATM | X | | | X | X |
| BARD1 | X | | | | |
| BRCA1 | X | X | X | X | X |
| BRCA2 | X | X | X | X | X |
| BRIP1 | | | X | | |
| CDH1 | X | | | | |
| CDKN2A | | | | X | |
| CHEK2 | X | | | | X |
| EPCAM | | X | X | X | X |
| HOXB13 | | | | | X |
| MLH1 | | X | X | X | X |
| MSH2 | | X | X | X | X |
| MSH6 | | X | X | X | X |
| NF1 | X | | | | |
| PALB2 | X | | X | X | X |
| PMS2 | | X | X | X | X |
| PTEN | X | X | | | |
| RAD51C | X | X | X | | |
| RAD51D | X | X | X | | |
| STK11 | X | | | X | |
| TP53 | X | | X | X | |

**Figure III - 2**. Genes investigated by individual cancer-specific panels by *INESS,* 2022 (34).

| Gene | Tumour risk | Risk management | Conclusion |
|---|---|---|---|
| ATM | Elevated | YES | Included |
| BARD1 | Limited | YES | Included |
| BRCA1 | Very elevated | YES | Included |
| BRCA2 | Very elevated | YES | Included |
| CDH1 | Elevated | YES | Included |
| CHEK2 | Elevated | YES | Included |
| NF1 | Elevated | YES | Included |
| PALB2 | Elevated | YES | Included |
| PTEN | Elevated | YES | Included |
| RAD51C | Limited | NO | Included |
| RAD51C | Limited | NO | Included |
| STK11 | Elevated | YES | Included |
| TP53 | Elevated | YES | Included |
| NBN | Exclusively 657 of 5 | NO | Excluded |
| Lynch syndrome | Limited | NO | Excluded |
| BRIP1 | Limited | NO | Excluded |

**Figure III - 3.** Panel of genes involved in breast cancer and cancer risk *by INESS, 2022* (34).

### 1.4.3 Preventive strategies in *BRCA*+ patients

When *BRCA1/2* genetic testing yields informative results, the increased risk of developing breast or ovarian cancers in mutation carriers, whether healthy or already diagnosed, can be managed through three main approaches: intensive surveillance, pharmacoprevention studies, and prophylactic surgery (10). Given the relatively recent advances in understanding hereditary susceptibility to breast cancer, there is still no conclusive evidence on the optimal management strategies. The only approach proven to significantly reduce the risk of developing breast cancer is prophylactic surgery. Bilateral prophylactic mastectomy, which involves the removal of breast tissue, is estimated to reduce breast cancer risk by 90–100% (10). The type of mastectomy can range from total mastectomy to skin-sparing or nipple-skin-sparing mastectomy, which offer superior cosmetic outcomes. Although data are limited, these approaches do not appear to increase the risk of local recurrence, although a small residual risk remains in areas such as the axillary extension and retroareolar region. In *BRCA* mutation carriers, while the risk of ovarian cancer is lower than that of breast cancer, the absence of reliable early diagnostic methods and the poor prognosis of late-stage ovarian cancer make prophylactic bilateral salpingo-oophorectomy a recommended risk-reduction strategy (10). Moreover, this procedure is recommended as it also leads to a reduction in the risk of breast cancer (10). This procedure, typically advised for *BRCA1/2* carriers starting at age 35–40 or after childbearing is complete, involves the removal of the ovaries and fallopian tubes up to their attachment to the uterus (10).

For *BRCA* mutation carriers who opt out of prophylactic surgery, the US Preventive Services Task Force recently issued guidelines on surveillance strategies (8). Based on a systematic review, these guidelines found no clear benefit of intensive screening in genetically at-risk women. While annual MRI can result in higher false-positive rates, when combined with mammography, it achieves near

100% sensitivity. However, the impact of MRI on breast cancer mortality within surveillance strategies remains unproven. In Italy, some regions have issued guidelines for the surveillance of individuals with genetic mutations, but these vary significantly (10). Common recommendations including breast ultrasound every six months, annual mammography from age 35 to 69, then biennial mammography until age 74, annual breast MRI starting at age 25 until age 74, annual transvaginal ultrasound and CA125 testing starting at age 30 (10).

# 2. Methodology

## 2.1 Health Impact Assessment

The HIA approach implements and offers a number of different methods and approaches to gain the knowledge needed to identify the potential and actual impacts of a policy/programme/project (38). This process employs a wide range of quantitative and/or qualitative evidence, which may include epidemiological and/or demographic data, as well as information from public health and clinical cmedicine. It also takes into account the considerations, experiences and expectations of the community and other stakeholders regarding the likely interactions between a policy/programme/project and the health of a population (including both the general well-being of the population and that of its constituent groups). There are three main types of HIA (38):

- Prospective HIA: at the start of the development of a project, proposal or plan.
- Concurrent HIA: runs alongside the implementation of the project (or policy)
- Retrospective HIA: assesses the effect of an existing project or policy and can be used as an evaluation tool. Retrospective assessments can also be made of unexpected events, as a way of learning lessons for future similar events.

**In the context of the current PROPHET case study, we conduct a concurrent Health Impact Assessment. The primary goal of this HIA is to evaluate the impact of interventions aimed at standardizing and improving the implementation of *BRCA* tests for the prevention of hereditary breast and ovarian cancers across Italian regions, in alignment with the most recent Italian guidelines.**

Although there is no fixed and formally unambiguous way of producing an HIA, there is a growing consensus around the key elements and main steps in the process:

## 2.2 Screening phase

### 2.2.1 Policy definition

Given the significant health burden and notable prevalence of *BRCA1/2* mutations, there is a globally recognized need to implement effective screening strategies for individuals at high genetic risk of breast and ovarian cancers. However, as analyzed in the previous chapter, the current state of personalized prevention strategies in Italy for this population is highly inconsistent and often fails to adhere to the recommendations of major international guidelines. This variability not only leaves this vulnerable population inadequately protected but also creates significant geographical disparities in access to care and preventive services.

In many regions, the criteria for accessing *BRCA* testing, the pathways for risk-reducing surgeries, and surveillance programs are neither standardized nor equitable, resulting in unequal opportunities for early detection and risk mitigation. Some individuals may receive comprehensive

care aligned with best practices, while others are left without adequate preventive measures due to regional policy gaps or resource limitations. Such disparities underscore the urgent need for a systematic evaluation of how personalized prevention strategies are implemented across the country.

**To address this issue, we propose conducting a comprehensive HIA to evaluate the effects of a policy that includes a series of interventions aimed at improving the prevention of hereditary BRCA-related breast and ovarian cancers in Italy, based on the recommendations of the most recent guidelines.**

Specifically, the evaluated policy involves the following interventions:

- **Standardization of eligibility criteria for *BRCA* testing**: Establishing clear and uniform guidelines for determining who qualifies for genetic testing, ensuring equal access for all high-risk individuals regardless of their geographical location.
- **Harmonization of testing methodologies**: Implementing consistent protocols for *BRCA* testing, including quality standards for laboratory procedures and genetic counseling, to ensure accurate and reliable results nationwide.
- **Improving the cascade screening process** through the comprehensive identification of at-risk family members and the enhancement of genetic and psychological counseling services. This includes ensuring systematic testing of relatives, strengthening access to pre- and post-test genetic counseling, and providing structured psychological support to address the emotional burden associated with BRCA testing and preventive interventions.
- **Alignment of criteria for access to and reimbursement of prophylactic surgeries**: Creating a unified framework that governs eligibility and financial coverage for risk-reducing surgeries, such as prophylactic mastectomy and salpingo-oophorectomy, to eliminate financial and logistical barriers.
- **Standardization of active surveillance protocols**: Developing cohesive guidelines for ongoing surveillance in individuals with *BRCA* mutations who opt not to undergo prophylactic surgeries. This includes uniform recommendations for the use of imaging modalities such as mammography, MRI, and transvaginal ultrasound, as well as the frequency and duration of such interventions.

By implementing a standardized, evidence-based approach, we aim to reduce the disparities currently observed in *BRCA*-related cancer prevention in Italy and ensure that all individuals at risk receive the same high-quality care. This initiative would not only enhance the protection of this vulnerable population but also contribute to a more equitable and effective healthcare system, ultimately improving outcomes and reducing the overall burden of hereditary cancers in Italy.

**It is important to emphasize that, in the context of PROPHET, this HIA focuses specifically on evaluating the impact of implementing *BRCA* testing for primary prevention purposes, targeting**

**individuals who are currently healthy but carry a higher genetic risk for breast and ovarian cancers. The objective is to assess how this policy could enhance early detection and prevention in asymptomatic individuals, ultimately reducing the incidence (and mortality) of these cancers.** This HIA does not consider the impacts of such a policy on cancer patients themselves. While the potential benefits for this group are significant, including improved treatment planning and family risk assessment, these considerations fall outside the scope of this case study.

### 2.2.2 Resources needed

Once the policy was defined, the necessary skills for conducting the HIA were established, and two groups were identified. One of these is the technical group, whose responsibilities are outlined below.

Specifically, the tasks of the technical group, composed of Public Health professionals from UCSC, included:

- Conducting the screening and scoping phases, with the preparation of an initial report aimed at describing the policy under review, the potential impacts, and the methodologies used in the activity.
- Triangulating the evidence required to assess the identified impacts and drafting a second summary report.
- Preparing a final report summarizing the evidence collected on the approach and subsequent recommendations.

The identified necessary skills to perform this task included conducting literature reviews, developing decision-tree impact models and economic analyses, and expertise in evaluating preventive approaches and personalized prevention strategies.

Given the significant expertise required for developing the approach and the need to account for all potential policy impacts, the establishment of a Steering Committe was deemed necessary. With the Steering Committee, the impacts and methodologies for evaluating them were discussed, including the selection and retrieval of data to be included in the model. They were also specifically consulted regarding the assessment of barriers and organizational challenges.

## 2.3. Scoping phase

### 2.3.1 Definition of the roles and skills to include in the Steering Committee

Following the definition of the context and objectives of the evaluation, the main professional stakeholders needed to constitute the Steering Committe were identified. This selection was crucial to ensure qualified and multidisciplinary feedback, enriching the analysis process and contributing to a more comprehensive and informed evaluation. In this context, the main stakeholders of interest identified are:

- Medical Genetics Expert
- Oncologist
- Radiologist
- General Surgeon
- Plastic and Reconstructive Surgeon
- Professionals belonging to territorial prevention departments
- Professionals working in genetic laboratories
- Patients' associations
- Professionals from industry

Members of the panel are shown in **Annex III**.

### 2.3.2 Identification of Potential Impacts of the Policy

The potential impacts of the policy were identified by the Technical Group through a narrative literature review aimed at characterizing the approach. Subsequently, the identified impacts and their assessment methodologies were validated by the Steering Committe. The impacts and corresponding assessment methodologies are summarized in **Table III -2.**

| **Impacts of policy under study** | **Assessment methods** |
|---|---|
| Impact on patients' health and well-being:<br>• Breast and Ovarian Cancer Incidence<br>• Breast and Ovarian Cancer Mortality<br>• Quality Adjusted Life Years (QALYs)<br>• Psychological Wellbeing | • Decision tree comparative model<br>• Literature review |
| Impact on patients' acceptability, satisfaction and awareness | • Literature review<br>• Steering Committe consultation |
| Economic impact | • Decision tree comparative model<br>• Literature review |
| Organizational impact<br>• Prophylactic surgery feasibility<br>• Screening feasibility<br>• Genetic counselling feasibility<br>• Healthcare professionals' knowledge and attitude | • Literature review<br>• Steering Committe consultation |

**Table III-2:** Impact and assessment methodologies identified during the scoping phase

## 2.4. Evidence Assessment phase

### 2.4.1 Literature Review

A narrative literature review was conducted to collect the evidence necessary for evaluating the impact of the policy in the Italian context, using mainly Pubmed database. Each literature review was conducted by two members of the Technical Group independently. Specifically, we searched for evidence on:

- Efficacy of preventive strategies in *BRCA*+: systematic reviews and clinical guidelines were collected to gather data to develop the Decision Tree comparative model and evaluate the impact of the policy.
- Economic impact: systematic reviews were collected for gathering more information on the economic impact of different testing strategies. An additional search for economic studies in Italy was performed.
- For the organizational impact and impact of patient's knowledge and satisfaction the search was focus on studies developed in the Italian context.

### 2.4.2 Decision tree simulation model

The analysis was conducted by using a decision-tree model to assess the impact of the implementation of the proposed policy in Italy in terms of number of ovarian and breast cancer cases, number of related deaths, and costs. To this end we compared two different scenarios:

- The **current scenario** represents the state of *BRCA* testing implementation in Italy, where access criteria for high-risk patients vary across regions, not all eligible relatives undergo *BRCA* testing, and preventive strategies are not fully guaranteed or standardized according to the current guidelines.
- The **ideal scenario** assumes a national approach, testing all high-risk patients who meet the eligibility criteria defined in the most recent Italian guidelines (26, 27). In this scenario, all eligible family members undergo BRCA testing as indicated by guidelines, have an optimal uptake of prophylactic surgical interventions, and all remaining *BRCA+* individuals undergo through annual MRI.

The first step in developing the model was to estimate the population of patients identified as high-risk and therefore eligible for *BRCA* testing, from which cascade screening of healthy family members would begin. The ideal scenario population includes patients with breast, ovarian, prostate, or pancreatic cancer who are at high risk of being *BRCA+* carrier, as defined by the most recent Italian guidelines (26, 27).

Due to the lack of necessary data in Italian cancer registries on the prevalence of eligible parients to the test, the estimation was conducted in two phases:

- **Estimation of the proportion of cancer patients meeting each criterion:** the proportion of cancer cases meeting the personal history criteria for *BRCA* testing, as outlined in the guidelines, was estimated using data from the Surveillance, Epidemiology, and End Results (SEER) Program database of the U.S. National Cancer Institute (39). Cancer registry data from the past ten years (2012–2022) were analyzed, limited to cases of Caucasian ethnicity to approximate the Italian population. The use of the SEER database was necessitated by the need for individual-level data, given the significant potential overlap between some of the criteria in the guidelines and the lack of readily accessible Italian cancer registry data containing all required variables. For familial history criteria in breast cancer patients, due to insufficient detailed estimates covering all guideline-defined criteria, only the criteria reported in **Table III-3** were estimated using data available in the literature (40,41)). The eligible patients not included in the analysis due to a lack the data necessary to estimate them are:

    - Hormone receptor positive breast cancers patients with and CPS/EG scores ≥ 3;
    - Early-stage hormone receptor positive breast cancer patients with ≥4 positive lymph nodes;
    - Breast cancer patients < 50 years with a first-degree relative with male breast cancer or bilateral breast cancer;
    - Prostatic cancer patients with a first-degree relative with non-Grade Group 1 prostate cancer aged <60 year, or with two relatives with non-Grade Group 1 prostate cancer aged <50 year.

All the estimated proportions for each criterion are reported in **Table III-3**.

| **Category** | **Description** | **Proportion of cancer patients meeting each criterion*** | **Source** |
|---|---|---|---|
| **Personal history:** | Male breast cancer | 0,76% | SEER database (39) |
| | Woman with breast cancer and ovarian cancer | 0,60% | SEER database (39) |
| | Woman with breast cancer <40 years | 4,6% | SEER database (39) |
| | Woman with breast cancer <36 years (regional criterion)[#] | 2,6% | SEER database (39) |
| | Woman with triple-negative breast cancer | 8,6% | SEER database (39) |
| | Woman with bilateral breast cancer <50 years | 0,1% | SEER database (39) |
| | Woman with non-mucinous and non-borderline ovarian cancer | 97,2% | SEER database (39) |

| | | | |
|---|---|---|---|
| | Metastatic pancreatic adenocarcinoma | 49,4% | SEER database (39) |
| | Metastatic prostate cancer | 12,3% | SEER database (39) |
| **Personal history of breast cancer < 50 years** | First degree relative with Breast cancer <50 years | 0,44% | Rawal et al., 2006 (40) |
| | First degree relative with non-mucinous and non-borderline ovarian cancer | 0,1% | Rawal et al., 2006 (40) |
| | First degree relative with pancreatic cancer | 0,2% | Rawal et al., 2006 (40) |
| | First degree relative with prostatic cancer | 0,3% | Rawal et al., 2006 (40) |
| **Personal history of breast cancer > 50 years** | Family history of breast, ovarian, pancreatic or prostatic cancer in ≥2 first-degree relatives | 1,2% | Zhang et al., 2017 (41) |

**Table III-3** Criteria Applied to Establish the High-Risk Population Eligible for *BRCA* Testing

*The percentage is calculated relative to the reference cancer, e.g., male breast cancer is estimated to account for 0.78% of all breast cancer cases.

#This criterion was not used to calculate the population of high-risk patients eligible for testing according to the guidelines, but rather to calculate the percentage of high-risk patients tested in the current scenario.

- **Integration to Italian Cancer Incidence estimates:** The estimated proportion of high-risk cases was applied to Italian incidence estimates for breast, ovarian, prostate, and pancreatic cancers, sourced from the AIOM report "I numeri del Cancro 2023" (2).

To compare the ideal scenario with the current one, it was also necessary to estimate the current uptake of *BRCA* testing among high-risk patients in Italy. Due to the lack of relevant data, the number of high-risk patients currently undergoing *BRCA* testing was estimated by identifying those eligible for testing based on regional PDTAs. We then used the regional incidence rates to apply the proportions reported in Table III-3 to the regions that included the criteria in their PDTA. For breast cancer, the incidence rate reported in the Osservasalute 2022 report was used (42). For pancreatic and prostate cancer, which are included only in the criteria of the Campania region, the incidence rates indicated in the regional PDTA for these tumors were applied (43). Since regional data on ovarian cancer incidence were unavailable, we estimated the incidence for ovarian cancer in the seven regions that include this cancer in their eligibility criteria. This estimation was conducted by applying age-specific incidence rates per 100,000 inhabitants, which were calculated for five-year age groups using the 2022 European Cancer Information System database (44), to the population of each region based on ISTAT 2022 population data (**Table III-4**).

| **Category** | **Description** | **Regions reporting the criterion in the regional PDTA*** | **N° Region** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Personal history:** | Male breast cancer | Abruzzo, Aosta Valley, Apulia, Basilicata, Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, Marche, Piedmont, Sardinia, Sicily, Tuscany, Trentino-Alto Adige, Veneto. | 17 |
| | Woman with breast cancer and ovarian cancer | Abruzzo, Aosta Valley, Apulia, Basilicata, Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, Marche, Piedmont, Sardinia, Sicily, Tuscany, Trentino-Alto Adige, Veneto. | 17 |
| | Woman with breast cancer <40 years° | None | 0 |
| | Woman with breast cancer <36 years | Abruzzo, Aosta Valley, Apulia, Basilicata, Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, Piedmont, Sardinia, Sicily, Tuscany, Trentino-Alto Adige, Veneto. | 16 |
| | Woman with breast cancer <30years | Marche | |
| | Woman with triple-negative breast cancer | Abruzzo, Aosta Valley, Apulia, Basilicata, Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, Marche, Piedmont, Sardinia, Sicily, Tuscany, Trentino-Alto Adige, Veneto. | 17 |
| | Woman with bilateral breast cancer <50 years | Abruzzo, Aosta Valley, Apulia, Basilicata, Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, Marche, Piedmont, Sardinia, Sicily, Tuscany, Trentino-Alto Adige, Veneto. | 17 |
| | Woman with non-mucinous and non-borderline ovarian cancer | Calabria, Campania, Emilia-Romagna, Lazio, Lombardia, Marche, Trentino-Alto Adige | 7 |
| | Metastatic pancreatic adenocarcinoma | Campania | 1 |
| | Metastatic prostate cancer | Campania | 1 |
| **Personal history of breast cancer < 50 years** | First degree relative with Breast cancer <50 years | Abruzzo, Aosta Valley, Apulia, Basilicata, Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, Marche, Piedmont, Sardinia, Sicily, Tuscany, Trentino-Alto Adige, Veneto. | 17 |
| | First degree relative with non-mucinous and non-borderline ovarian cancer | Abruzzo, Aosta Valley, Apulia, Basilicata, Calabria, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, Marche, Piedmont, Sardinia, Sicily, Tuscany, Trentino-Alto Adige, Veneto. | 17 |
| | First degree relative with pancreatic cancer | Calabria, Campania, Toscana | 3 |
| | First degree relative with prostatic cancer | Calabria, Campania, Toscana | 3 |
| **Personal history of breast cancer > 50 years** | Family history of breast, ovarian in ≥2 first-degree relatives | Abruzzo, Calabria, Campania, Emilia-Romagna, Liguria, Puglia, Sardegna, Toscana, Valle d'Aosta | 9 |

**Table III-4** Eligibility Criteria for *BRCA* test on high-risk patients in the Italian region according to the Regional PDTA

*The regions of Friuli Venezia Giulia, Umbria, and Molise have not yet published a PDTA on BRCA screening

Once the populations of high-risk patients (HR patients) eligible in the ideal scenario and the population of high-risk patients tested in the current scenario were estimated, a Decision Tree model was constructed **(Figure III-4).**

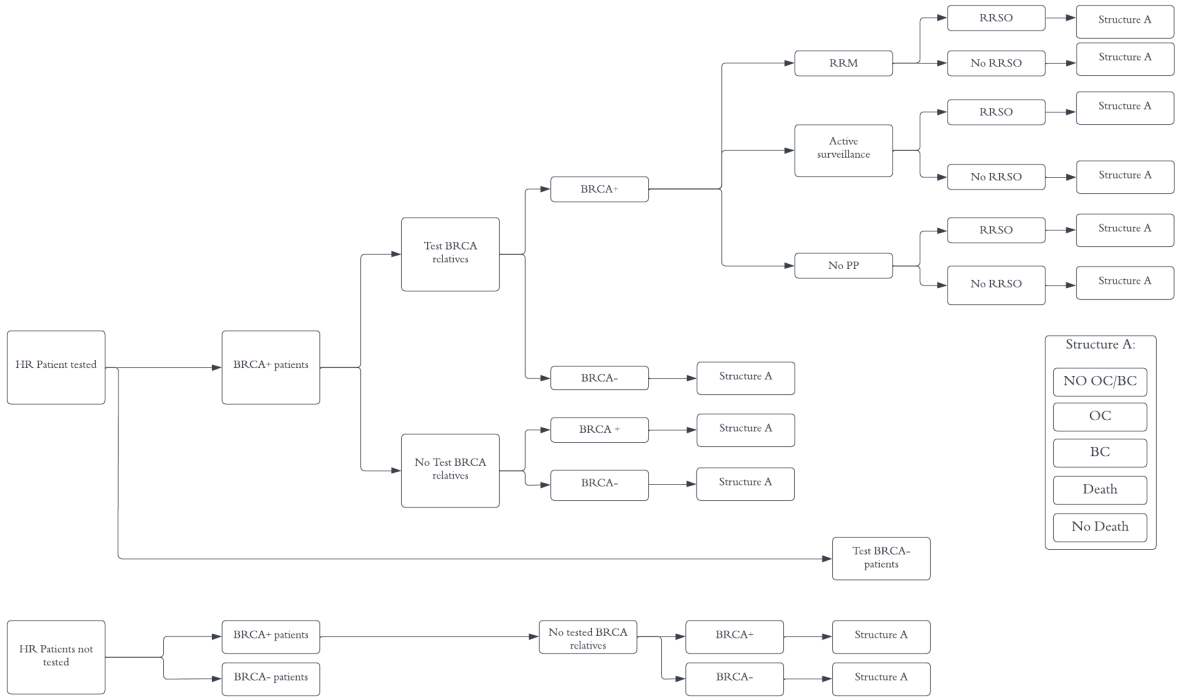


**Figure III-4.** Decision tree model

HR: high risk; RRM: risk-reducing mastectomy; RRSO: risk-reducing salpingo-oophorectomy; PP: personalized prevention; OC: Ovarian Cancer; BC: breast cancer

In the **current scenario** only the proportion of high-risk patients previously estimated based on the criteria reported in the regionals PDTA are tested. Healthy family members of the BRCA+ tested patients, may or may not undergo the test. Healthy family members who undergo BRCA testing may carry the mutations, with probabilities varying based on their degree of kinship (50% for first degree family members, 25% for second degree family members, etc). BRCA+ result for women initiates a decision-making pathway where individuals can choose between risk-reducing mastectomy (RRM), active surveillance through MRI, or foregoing personalized preventive interventions (No PP). Additionally, they may consider risk-reducing salpingo-oophorectomy (RRSO). Subsequent nodes in the decision tree model estimate probabilities for developing breast cancer (BC), ovarian cancer

(OC), or remaining cancer-free (No BC/OC). Finally, for breast and ovarian cancer patients, the model accounts for the possibility of cancer-related mortality within five years of diagnosis.

In contrast, the **ideal scenario** assumes the 100% of high-risk patients and subsequent healthy family members of BRCA+ patients undergo BRCA test, with all positive female individuals opting for preventive interventions, whether surgical or through active surveillance.

All the data and sources used in the decision model are reported with references in **Table III-5**.

It is important to emphasize that the model estimates the number of cancer cases and deaths in the two scenarios by considering only the effect of preventive approaches on the healthy population, which consists of the relatives of the high-risk patient population estimated through the previous analyses.

| **Description** | **Current Scenario** | **Ideal Scenario** | **Source** |
|---|---|---|---|
| Percentage of carriers in high-risk patients | 16,6% | | Alson et al., 2012 (45) |
| Estimated number of first-degree relatives per positive patients | 2,66 | | Trevisan et al., 2024 (46) |
| Estimated number of second-degree relatives per positive patients | 1,86 | | Trevisan et al., 2024 (46) |
| Estimate number of third-degree relatives per positive patients | 1,97 | | Trevisan et al., 2024(46) |
| Percentage of First degree relative tested | 44,4% | 100% | Trevisan et al., 2024(46) |
| Percentage of Second degree relative tested | 8,6% | 100% | Trevisan et al., 2024(46) |
| Percentage of Third degree relative tested | 7,1% | 100% | Trevisan et al., 2024(46) |
| Percentage of female carriers that undergo RRM | 10% | 35,9% | Metcalfe et al, 2019(47) |
| Percentage of female carriers that undergo active surveillance | 77,8% | 100% | Metcalfe et al, 2019 (47) |
| Percentage of female carriers that do not undergo to any personalized preventive intervention | 12% | 0% | Metcalfe et al, 2019 (47) |
| Percentage of female carriers that undergo RRSO | 52,5% | 55% | Metcalfe et al, 2019; (47)<br>Rebbeck et a, 2019;(48) |
| Reduction in risk of breast cancer from RRM with RRSO | 95% | | Machanda et al, 2015 (49) |
| Reduction in breast cancer risk from RRM without RRSO | 91% | | Machanda et al, 2015(49) |
| Reduction in risk of breast cancer from RRSO alone | 49% | | Machanda et al, 2015(49) |
| Reduction in risk of ovarian cancer from RRSO | 96,6% | | Machanda et al, 2015(49) |
| Reduction in risk of breast cancer deaths from active surveillance | 78,0% | | Machanda et al, 2015(49) |
| Probability that female carrier will get breast cancer | 53% | | Machanda et al, 2015(49) |
| Probability that a female noncarrier will get breast cancer | 13% | | Machanda et al, 2015(49) |
| Probability that a female noncarrier will get ovarian cancer | 1,9% | | Machanda et al, 2015(49) |
| Probability that a female carrier will get ovarian cancer | 29,90% | | Machanda et al, 2015(49) |
| Ovarian Cancer mortality 5 year from diagnosis | 61% | | Chirlaque et al, 2017(50) |
| Breast Cancer mortality 5 years from diagnosis | 13% | | Crocetti et al, 2017 (51) |
| Cost test BRCA | 1.026,20 € | | Lombardia Regional tariff (52) |
| Cost RRM | 5.954,00 € | | DRG (53) |

| | | |
|---|---|---|
| Cost RRSO | 6.791,00 € | DRG (53) |
| Cost Ovarian Cancer (per 5 year) | 83.523,33 € | Lazzaro et al 2015 (54) |
| Cost Breast Cancer (per 5 year) | 32.193,33 € | Mennini et al 2021 (55) |
| Cost Annual MRI (per 20 year) | 3.742,60 € | DRG (53) |
| Cost psychological counselling | 19,37 € | DRG (53) |

**Table III - 5.** Data and sources used in the decision tree model

### 2.4.2 Steering Committee consultation

The input and opinions of the Steering Committee were crucial for assessing impacts, particularly in shaping the decision tree model and check some of the probabilities used, as well as for all organizational impacts. The Steering Committee was consulted in two ways: through an open-ended questionnaire and via three 90-minute online meetings. The questionnaire is detailed in **Annex IV.**

## 2.5 Policies implementations and monitoring recommendations

The recommendations for the implementation were formulated and reported in this document based on the data provided by our literature reviews, the decision tree model results, and the input provided by the Steering Committee.

# 3. Evidence Impact Assessment

## 3.1 Impacts on female patients health and wellbeing

### 3.1.1 Impacts on cancer incidence and mortality

From our **literature review**, we identified six systematic reviews and two guidelines on prophylactic surgery, as well as two meta-analyses, three guidelines, and one cohort study on active surveillance that are relevant for evaluating the impact of our approach on mortality and incidence (56-64). A detailed description of the included studies and their key findings is provided in **Annex V**.

Prophylactic surgery RRM and RSSO, has been extensively studied and consistently shown to significantly reduce the incidence and mortality associated with *BRCA1/2*-related cancers. A systematic review and meta-analysis by Xia Li et al. demonstrated that RRM reduced breast cancer risk by approximately 90–100% (RR: 0.114; 95% CI: 0.041–0.317) in *BRCA1/2* mutation carriers (56). Similarly, RSSO was shown to reduce ovarian cancer risk by 69–100% and improve overall survival in both *BRCA* mutation carriers with and without a history of breast cancer (HR: 0.349; 95% CI: 0.190–0.639). The review by Ludwig et al. further confirmed the effectiveness of RRM, reporting a 90–95% reduction in breast cancer risk among BRCA mutation carriers, while RRSO significantly reduced both ovarian and breast cancer risks and translated into improved survival outcomes (57). Marchetti et al., in their meta-analysis, quantified the ovarian cancer risk reduction from RRSO, reporting a hazard ratio (HR) of 0.19 (95% CI: 0.13–0.27, $p < 0.00001$), along with an all-cause mortality reduction of 68% (HR: 0.32; 95% CI: 0.27–0.38, $p < 0.00001$) (58). The analysis also highlighted comparable survival benefits in patients with and without prior breast cancer diagnoses, underscoring its wide applicability. Additionally, a study by Xiao et al. noted also that RRO reduced breast cancer incidence in *BRCA* mutation carriers without a history of breast cancer (HR: 0.58; 95% CI: 0.37–0.78) and decreased recurrence risk in those with prior breast cancer (HR: 0.50; 95% CI: 0.31–0.69) (59). Bermejo-Pérez et al. highlighted that both RRSO and RRMM significantly decreased the incidence of gynecological and breast cancers in female BRCA carriers compared to active surveillance (60). The 2019 USPSTF guidelines further supported the role of prophylactic surgery, citing evidence of a 90–100% reduction in breast cancer incidence and an 81–100% reduction in mortality from RRM, alongside a similar reduction in ovarian cancer risk from BSO (63). These findings emphasize the central role of prophylactic surgery as the most effective intervention for *BRCA* mutation carriers. However, studies such as Honold et al. also cautioned about the potential adverse effects associated with RRM, highlighting the need for individualized decision-making and further research into long-term outcomes. (61)

The impact of MRI surveillance on breast cancer mortality and incidence in *BRCA* mutation carriers has been addressed in a limited number of studies. A cohort study by Lubinski et al. evaluated annual MRI surveillance in women with *BRCA1* and *BRCA2* sequence variations over a mean follow-up of 9.2 years. Among the cohort, 13.8% developed breast cancer, and 1.4% succumbed to the disease (62). The age-adjusted hazard ratio (HR) for breast cancer mortality was significantly

reduced for women with BRCA1 mutations who participated in MRI surveillance (HR: 0.20; 95% CI: 0.10–0.43; P < 0.001), whereas no significant reduction was observed for women with BRCA2 mutations (HR: 0.87; 95% CI: 0.10–17.25; P = 0.93).

The AIOM 2023 guidelines also emphasize the role of MRI in breast cancer screening for high-risk populations (10). Although annual MRI, when combined with mammography, achieves a sensitivity close to 100%, its direct impact on breast cancer mortality has yet to be conclusively demonstrated. Similarly, the US Preventive Services Task Force 2019 and the National Comprehensive Cancer Network reported no published effectiveness trials of intensive screening modalities, such as MRI, that specifically evaluate reductions in cancer incidence or mortality (63, 64). However, available evidence highlights that MRI alone or combined with mammography has higher sensitivity (63–70%) compared to mammography alone (25–62%) in detecting breast cancer among *BRCA* mutation carriers. While MRI shows promise in improving early detection, the limited data on its impact on mortality underscore the need for more prospective studies to establish its efficacy in reducing breast cancer-related deaths.

**Through the application of our decision tree model, we were also able to estimate the impact of implementing the proposed approach on the number of deaths from breast and ovarian cancer prevented, as well as the total number of cases prevented.**

In the **ideal scenario**, it was estimated that a total of 25,626 patients with breast, ovarian, prostate, or pancreatic cancer would undergo *BRCA* testing per year. Of these, 4,252 would test positive for a *BRCA* mutation. Through cascade screening 27,650 relatives were tested for *BRCA*, of whom 8,682 would test positive for a *BRCA* mutation. These identified individuals would then undergo preventive strategies, including prophylactic surgery or active surveillance with MRI. From the 27,650 healthy relatives tested for *BRCA* mutations, it was estimated that 6,272 would develop breast or ovarian cancer in their life, with an estimated number of deaths after five-year of 1,571. In the **ideal scenario**, it was assumed that 36% of female patients would undergo mastectomy, and 55% would undergo salpingo-oophorectomy.

In contrast, in the **current scenario**, only 8,807 individuals out of the 25,626 estimated to be at high risk according to the latest guidelines would undergo *BRCA* testing. Through the cascade screening of the high-risk patients resulted positive, a total of 9,503 health relatives were identified. Estimating a 23% acceptance rate (45), only 2,168 were tested, and 948 resulted positive. Among 2,168 health relative tested, 25,482 not tested in the concurrent scenario, it was estimated that 9,705 would develop in their life breast or ovarian cancer, with a five-year mortality of 2,588 (**Figure III-5, III-6)**.

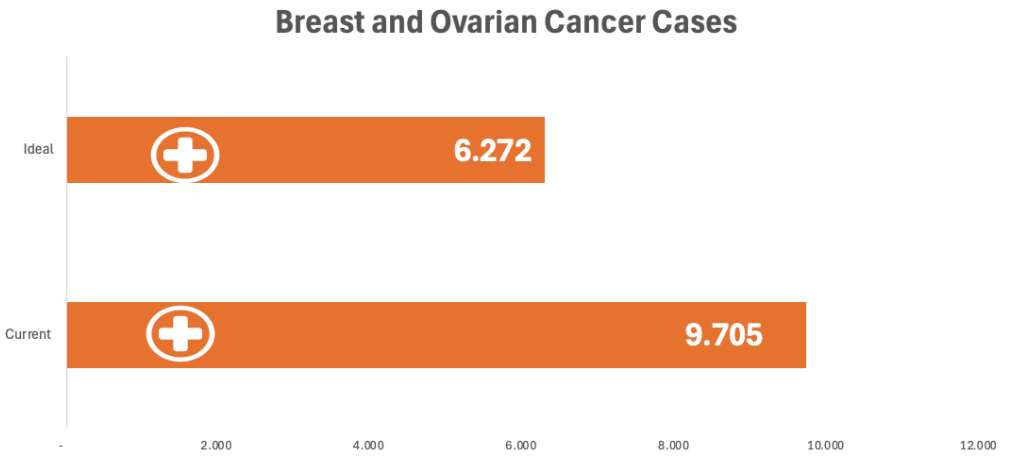


**Figure III-5.** Estimated absolute value of number of occurring Breast and Ovarian Cancer cases in the **ideal** and in the **current scenario**.

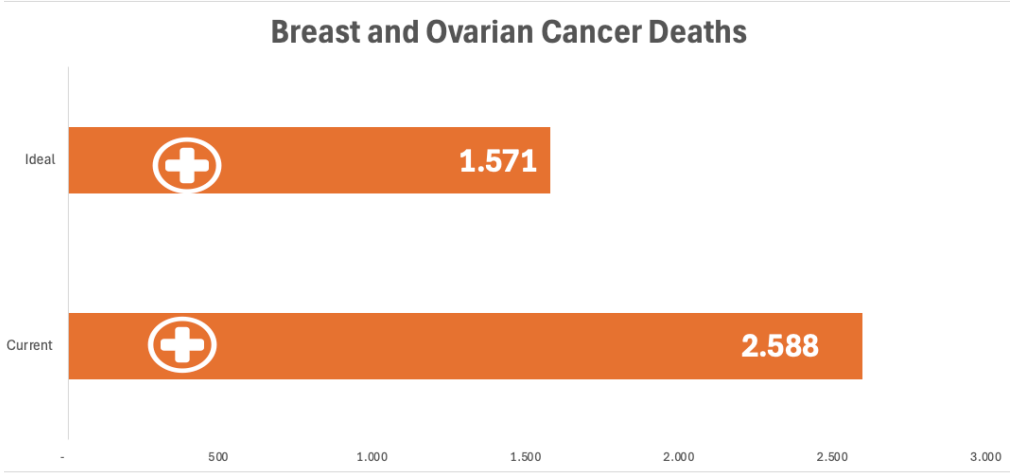


**Figure III-6.** Estimated absolute value of occurring Breast and Ovarian Cancer Deaths in the **ideal** and in the **current scenario**.

The comparison between the two scenarios highlights a significant delta in both cancer incidence and mortality. **In the ideal scenario, the broader implementation of *BRCA* testing and preventive measures results in a reduction of approximately 3,432 breast and ovarian cancer cases, representing a 35,4% decrease compared to the current scenario. Similarly, the five-year mortality rate is reduced by 1017 deaths, which translates to a 39,3% decrease.**

These reductions underscore the substantial benefit of expanding *BRCA* testing and implementing preventive strategies like prophylactic surgery and active surveillance.

The model has several limitations. The first limitations stem from estimating the two baseline populations: patients at high risk eligible for the *BRCA* test according to the guidelines and the estimated number of patients currently undergoing *BRCA* testing in Italy.

- Using the U.S. SEER database to estimate the proportion of patients corresponding to each criterion presents a limitation in terms of the accuracy of these estimates for Italy. To mitigate this limitation, we included in the analysis only Caucasian patients. Additionally, also estimates related to familial risk are derived from international, rather than Italian studies. Lastly, certain patient groups corresponding to specific guideline criteria could not be estimated, but we believe these groups should have a minimal impact on the overall estimate (e.g., women with breast cancer under 50 years old with a first-degree relative with male breast cancer or bilateral breast cancer).
- Regarding the estimation of patients currently undergoing *BRCA* testing, the primary limitation is that our estimates assume all patients eligible under regional PDTA are being tested. While it is assumed that regional PDTA are implemented in hospital settings, this may result in an overestimation. Furthermore, the most recent regional incidence data for breast cancer dates to 2019, and the regional distribution was considered analogous for the 2023 incidence data provided by AIOM and used in the analysis. In addition, for ovarian cancer, in the absence of regional data, the same regional distribution as breast cancer was assumed.

As for the limits related to the decision tree model, firstly it relies on generalized mortality assumptions, which oversimplify individual variability in the onset of ovarian and breast cancer. This approach may not accurately reflect the diverse genetic, demographic, and clinical profiles of patients. Second, the model applies a single efficacy reduction factor for preventive surgeries (RRM and RRSO), which limits its ability to capture the nuanced differences between early and late interventions or individualized patient risk profiles. Additionally, the assumption of a homogeneous population reduces the applicability of the model to settings with diverse healthcare infrastructures or patient characteristics. The model heavily relies on clinical trial data, which may not fully translate into real-world effectiveness, introducing uncertainty when applied outside controlled conditions. Furthermore, it does not integrate the potential impact of comorbidities, such as other chronic diseases, which could influence both health outcomes and costs for *BRCA*-positive individuals. These limitations underscore the need to interpret the results cautiously and consider the model's applicability to specific subpopulations and healthcare systems. Despite these constraints, the model provides valuable insights into the effectiveness and mortality benefits of systematic *BRCA* testing in Italy.

### 3.1.2 Impacts on patients wellbeing

Through **a literature review**, we identified five primary studies conducted in Italy on psychological and emotional impacts and one systematic review on sexual function (65-70). The studies included and key results are reported in **Annex VI.**

The psychological burden of preventive strategies was explored by Lombardi et al, who found that *BRCA* mutation carriers experience higher levels of anxiety and depression than non-carriers, particularly in the months following genetic test disclosure (65). However, protective factors, such as pre-test education, family communication, and decision-making regarding preventive strategies,

were found to mitigate these effects over time (65). In addition, Mella et al. examined the emotional impact on 91 women one month after receiving a positive *BRCA* test result (66). Their study revealed that fatigue and inertia were among the highest-reported mood states in BRCA+ patients, with variations linked to whether participants were probands or cancer patients. Furthermore, Borreani et al. noted that while anxiety and depression levels showed no significant changes over time, prophylactic surgery significantly reduced perceived cancer risk and associated worries, compared to surveillance strategies (67).

Regarding the role of preventing intervention Caruso et al. address psychophysical stress during genetic counseling was identified crucial for improving overall mental health of *BRCA*+ patients (68). Furthermore, Di Mattei et al. highlighted the role of pre-test genetic counseling in minimizing psychological distress, noting that most participants did not report distress attributable to the procedure (69).

Kershaw et al. conducted a systematic review and meta-analysis on the impact of risk-reducing bilateral RRSO on sexual function (70). Their findings reveal that 71% of studies reported a significant negative impact on sexual function post-RRSO (SMD -0.63, [-0.82, -0.44], $p = 0.03$), including increased vaginal dryness (SMD 9.25, [3.66, 14.83], $p < 0.00001$). These adverse effects were observed regardless of menopausal status, and hormone replacement therapy did not eliminate the negative outcomes.

Collectively, these studies underscore the complex psychological and emotional dynamics associated with *BRCA* testing and preventive interventions, highlighting the significant emotional burden that many patients face. The results demonstrate the critical importance of targeted counselling and support services to address the heightened levels of anxiety, depression, and psychological distress experienced by *BRCA* mutation carriers, particularly in the months immediately following test disclosure. These services not only improve patients' mental health and quality of life but also play a key role in empowering individuals to make informed decisions about their preventive strategies. Pre-test education, family communication, and proactive decision-making about preventive measures were identified as protective factors that can mitigate distress over time. Expanding and standardizing psychological support services, including pre-test and post-test counseling, could significantly reduce the emotional burden of genetic testing. Implementing comprehensive and uniform psychological counseling services across regions would ensure that patients receive consistent and evidence-based support, regardless of their geographic location or healthcare provider. These services could include dedicated sessions to address patients' concerns, structured emotional support during decision-making about preventive interventions, and long-term follow-up for mental health monitoring. Such an approach would not only reduce the immediate impact of anxiety and depression but also help patients navigate the complexities of living with a *BRCA* mutation, ultimately enhancing their overall well-being and resilience.

## 3.2 Economic impact

Through a **literature review**, we identified two primary studies conducted in Italy and three systematic review on the economic impact of *BRCA* testing strategies (71-75). The studies included and key results are reported in **Annex VII**.

The literature review highlights the economic implications of *BRCA* genetic testing and related preventive strategies, drawing insights from various cost-effectiveness analyses and systematic reviews. Koldehoff et al. conducted a systematic review to evaluate the cost-effectiveness of targeted genetic testing for breast and ovarian cancer (71). Their analysis highlighted that *BRCA* testing for high-risk women without cancer ICERs ranging from cost-saving (dominating) to $21,700 per QALY. Cascade testing, which involves testing high-risk individuals and extending testing to their relatives, proved to be a financially viable approach with ICERs between $6,500 and $50,200/QALY. D'Andrea et al. performed a systematic review of economic evaluations for *BRCA* genetic testing programs, shedding light on the cost dynamics across various testing strategies (65). The review found that population-based *BRCA* testing remains prohibitively expensive, exceeding $1 million/QALY even when prophylactic surgeries are included in the management of mutation carriers. However, family history-based testing, which targets high-risk individuals and incorporates cascade testing for their relatives, demonstrated promise. Unfortunately, the economic evaluations for this approach remain incomplete, particularly in terms of detailed cost assessments and selection criteria for high-risk populations. Cancer-based genetic testing, which focuses on identifying index cases among women diagnosed with specific breast or ovarian cancer subtypes, emerged as a more cost-effective strategy when combined with prophylactic interventions, especially for younger women. This underscores the importance of tailoring genetic testing programs to specific populations and clinical contexts to optimize their economic and clinical outcomes.

Regarding the two-study conducted in Italy Di Brino et al. conducted a cost-minimization analysis that provided compelling evidence of the economic sustainability of preventive genetic testing for relatives of patients with *BRCA*-mutated ovarian cancer (67). They estimated that such a strategy could result in cost savings of approximately €17.8 million for the Italian National Healthcare System, considering the high average cost of therapy for breast and ovarian cancers, which exceeds €90,000 per case.

Furthermore, Di Pilla et al. offered an innovative perspective by analyzing the cost-effectiveness of a clinical-radiogenomic screening program (66). Using clinical criteria and family history as a baseline, they demonstrated that integrating a radiogenomic model improved the detection of *BRCA* mutation carriers by 41.8%, resulting in a 23.7% reduction in *BRCA*-related cancer incidence. This model incurred an annual cost increase of €2.51 per person, yielding an ICER of €3,800 per year of healthy life expectancy gained over a 62-year observation period. When simulating an improved radiogenomic model with enhanced sensitivity (80%) and specificity (95%), the study found an even greater increase in *BRCA* detection (68.3%) and a 38.4% reduction in cancer rates, with a minimal cost increase of €0.70 per person annually. This refined approach demonstrated an ICER of €653 per

year of healthy life expectancy gained, illustrating the substantial potential for integrating radiogenomics into clinical practice to enhance cost-effectiveness and improve patient outcomes.

Collectively, these studies demonstrate the significant economic benefits associated with targeted and cascade genetic testing approaches. While population-based and multigene testing strategies present cost challenges, focusing on high-risk populations through family history-based and cascade testing offers a more cost-effective and impactful path forward. These findings also emphasize the critical role of prophylactic interventions, such as RRM and RRSO, in mitigating the long-term costs and health burdens associated with *BRCA*-related cancers. By prioritizing cost-effective approaches and integrating advanced screening technologies, healthcare systems can provide equitable and sustainable access to *BRCA* testing and preventive care.

**In addition, through the application of our decision tree model, we were able to estimate the impact of implementing the proposed approach on cost for the health care system.**

The estimated costs of genetic testing, preventive interventions, and costs related to ovarian and breast cancers management are presented in **Table III-5** in section 2.4.1. **Table III-6** shows the economic impact of the preventive strategy in the ideal and current scenarios. In the ideal scenario, the additional expenditure for genetic testing of patients and their relatives was estimated at 43.409.286,20 € with an additional 493.586,34 € for psychological counseling. These costs result from the application of eligibility criteria for genetic testing for patients, according to the latest guidelines, across all Italian regions, as well as a comprehensive screening of the relatives of patients who tested positive. The additional expenditure related to the ideal adherence to preventive treatments, including RRM, RRSO, and annual MRI-based active surveillance, was estimated at 65.143.900,80 €. Therefore, the implementation of cascade screening and subsequent preventive strategies in line with the guidelines, results in an estimated total increase in spending of 109.046.773,34 € in the ideal scenario. However, this expenditure is offset in the long term by the effectiveness of the preventive strategy in reducing ovarian (- 1228 estimated cases) and breast cancer (- 2204 estimated cases) incidences, as well as by the high management costs associated with these cancers. This leads to a total savings of € 173.520.760,00 € resulting from the reduction in the number of cancer cases. **The strategy results therefore cost-saving, with a differential economic impact between the ideal and current scenarios of -€64,473,986.66**.

| Cost | Ideal Scenario | Current Scenario | Difference |
|---|---|---|---|
| Test BRCA | 54.671.831,20 € | 11.262.545,00 € | 43.409.286,20 € |
| Psychological counselling | 535.580,50 € | 41.994,16 € | 493.586,34 € |
| RRM | 18.612.204,00 € | 565.630,00 € | 18.046.574,00 € |
| RRSO | 32.427.025,00 € | 3.361.545,00 € | 29.065.480,00 € |
| Active surveillance | 20.797.628,20 € | 2.765.781,40 € | 18.031.846,80 € |
| Ovarian Cancer | 131.549.250,00 € | 234.115.903,33 € | -102.566.653,33 € |
| Breast cancer | 151.212.086,67 € | 222.166.193,33 € | -70.954.106,67 € |
| Total Cost | 409.805.605,57 € | 474.608.122,07 € | -64.473.986,66 € |

**Table III-6.** Economic impact of the ideal scenario versus the current scenario.

RRM: risk-reducing mastectomy; RRSO: risk-reducing salpingo-oophorectomy.

However, it is important to highlight that the model has several limitations. In addition to those already discussed in section 3.1.1 regarding the estimation of the effectiveness of preventive strategies, there are also limitations related to the estimation of costs, particularly those associated with the management of ovarian and breast cancer. Specifically, the model uses average cancer management costs, which fail to capture the complexity of real-world cancer care, including geographic variations, differences in treatment regimens, and stage-specific care costs. Furthermore, the analysis is based on a static decision tree model, which does not account for the dynamic nature of disease progression and patient outcomes over time. This limitation could impact the accuracy of cost estimations, as it does not consider the costs associated with changes in disease states, recurrence, or patient survival.

## 3.3 Organizational impact

Through **a literature review** we collected a total of seven studies conducted in Italy that investigated different organizational challenges related to the implementation of *BRCA* testing (76-82). The included studies and key results are reported in **Annex VIII.**

McCary et al. examined the legislative framework and regulatory practices surrounding genetic counseling across EU member states, including Italy (76). The study identified two key regulatory documents: the General Authorization No. 8/2014 for the Processing of Genetic Data and the Guidelines for Medical Genetics (2004). While these regulations provide a framework for genetic counseling, the report emphasized the need for recognizing genetic counselors as healthcare professionals to address gaps in service delivery and improve population-level genetic literacy. As highlighted in **Table III-7,** they also provide detailed insights into the organizational framework for genetic counseling and testing in the European Union, with specific reference to Italy. According to their findings, clinical geneticists and oncologists are the primary providers of genetic counseling. In certain circumstances, laboratory scientists with medical genetics specializations may also deliver this service. Clinical geneticists and oncologists are authorized to order germline genetic tests, and genetics is formally recognized as a clinical specialty in Italy. However, the recognition of genetic counselors as healthcare professionals remains lacking, presenting a significant barrier to expanding these services. National regulations guide the content of genetic counseling, ensuring consistency and adherence to established protocols. Genetic counseling is mandatory both before and after genetic testing, reinforcing the importance of thorough patient education and support throughout the testing process. Telemedical counseling is acknowledged as a potential delivery method, though it remains infrequently used. The study also notes that there are no significant reimbursement barriers to counseling services in Italy, indicating that economic constraints are not a primary factor limiting access.

| Characteristics investigated | Italian genetic counselling characteristics |
|---|---|
| Who Provides Genetic Counseling | Clinical geneticists, oncologists; in specific circumstances, laboratory scientists with medical genetics specialization |
| Who is Allowed to Order Germline Tests | Clinical geneticists, oncologists |
| Is Genetics a Clinical Specialty? | Yes |
| Are Genetic Counselors Recognized? | No |
| What Guides Counseling Content | National regulation |
| When is Genetic Counseling Provided | Mandatory pre- & post-test |
| Where/How is Telemedical Counseling Conducted | Possible |
| Frequency of Telemedical Counseling | Minority |
| Reimbursement Barriers to Counseling | None |

**Table III-7.** Characteristcs of genetic counseling in Italy. Adapted from McCary et al. (2024) (76)

Tinterri et al. conducted a national survey of 109 breast centers in Italy to identify organizational barriers to *BRCA* testing (77). Over half (53.2%) of the centers reported challenges, including issues related to cost and reimbursement (11.9%), reporting timelines (35.7%), and pre-test counseling availability (13.8%). While most centers (78.9%) employed a mainstream-consent approach led by medical oncologists (85.3%) or breast surgeons (67.9%), these barriers highlight the need for systemic improvements in testing workflows. The survey also revealed that 70.6% of centers conducted *BRCA* testing before surgery, while 24.8% did so during early-stage treatment, and 4.6% during metastatic recurrence. Urgent testing was acknowledged by 87.2% of centers, with counseling and testing turnaround times varying widely. These findings underline inconsistencies in access and timing, further emphasizing the need for standardized practices across breast centers.

Regarding challenges related to laboratory testing, Capoluongo et al. underscore significant challenges in the implementation and standardization of NGS-based *BRCA* testing, despite its widespread adoption for both somatic and germline analyses in molecular diagnostic laboratories (78). One critical issue is the variability in molecular pipelines, as *BRCA* genes are frequently analyzed within larger gene panels rather than as standalone targets, leading to inconsistencies across laboratories. Additionally, the use of diverse bioinformatic tools presents a challenge, as some

platforms fail to reliably detect large genomic rearrangements or provide uniform coverage across all regions of the *BRCA* genes. The volume of samples processed in many laboratories further exacerbates these difficulties, limiting the ability of bioinformatic pipelines to identify large rearrangements or copy number variations effectively. Compounding these issues is the variation in sequencing machines, which can yield non-comparable results, particularly when contrasting somatic and germline analyses. These factors collectively highlight the lack of a fully standardized pathway for *BRCA* NGS-based testing, emphasizing the need for uniform protocols and tools to ensure accuracy, reproducibility, and comparability of results across diagnostic settings.

In addition, studies on the knowledge and attitudes of healthcare professionals toward genetic testing reveal notable gaps. Panic et al. through a survey found that only 70% of 364 Italian residents could correctly answer over 80% of questions on breast cancer genetic testing, with postgraduate training positively influencing knowledge (80). Similarly, Marzuillo et al. highlighted that less than half of 1079 surveyed physicians appreciated the importance of efficacy and cost-effectiveness evidence in selecting genetic tests (80). Both studies emphasize the urgent need for targeted education and training programs to enhance professional knowledge and confidence in offering genetic counseling and testing.

Lastly, two studies conducted by Cortesi et al. and Ricci et al. investigated the impact on participation of different screening strategies (81, 82). Cortesi et al. analyzed a regional population-based hereditary breast cancer screening program in Italy, examining the participation and outcomes for women at high hereditary risk (81). Of 60,040 women evaluated, only 3.5% (22,289) were referred for further genetic counseling, and just 25.2% (5,615) accepted the invitation to attend a Spoke evaluation. Overall, 11,667 women were assessed, of whom 5,554 advanced to the Hub evaluation. Ultimately, 42.8% (2,342) met the criteria for genetic testing, with 23.2% (544) testing positive for *BRCA1/2* mutations. These findings highlight significant attrition at each stage of the referral process, reflecting a need for better engagement and support mechanisms to ensure that high-risk individuals complete the testing pathway. Ricci et al. investigated the feasibility of integrating genetic counseling into routine oncology appointments for ovarian cancer patients (82). The study found that 31% of women diagnosed with ovarian cancer were referred for genetic counseling, with most referrals occurring during the initial oncology visit (54%) rather than follow-up appointments (22%). Of those referred, 76% attended counseling, and 95% underwent *BRCA* testing, resulting in a mutation detection rate of 19% (4/21). This study demonstrates the feasibility of integrating genetic counseling into oncology workflows but also underscores the need for improvements in referral rates and follow-up adherence.

In conclusion, while Italy has made notable progress in establishing *BRCA* testing programs, the findings from these studies highlight significant organizational challenges that continue to hinder the full realization of their potential benefits. Low referral rates for genetic counseling, especially for patients with ovarian cancer, suggest missed opportunities for early intervention and preventive

care. Inconsistent access to *BRCA* testing, variability in timelines for test results, and delays in urgent cases further exacerbate these inefficiencies, potentially leaving high-risk individuals without timely access to life-saving preventive strategies. Moreover, the evident knowledge gaps among healthcare providers, as demonstrated by the surveys, underline the critical need for targeted education and training programs. These gaps not only affect the quality of genetic counseling but also limit the integration of genetic testing into routine clinical practice, particularly in underserved or resource-limited areas.

## 3.4 Patients experience

Through **a literature review**, we identified five studies that analyzed patients' experience in the context of *BRCA* genetic testing (45,83-86). The included studies and key results are reported in **Annex IX.**

From the literature regarding patient satisfaction, evidence has been found related to genetic testing and RRSO, while unfortunately, there is a lack of evidence concerning RRM. Grandi et al. examined the satisfaction levels of 55 women who underwent RRSO, reporting exceptionally high satisfaction rates, with a mean score of 99.4 on a visual analog scale (0-100) (83). This high level of satisfaction was consistent across various subgroups, including pre- and postmenopausal women, cancer survivors, and hormone therapy users. These findings highlight the strong acceptance of RRSO as an effective preventive strategy and indicate that multidisciplinary counseling plays a crucial role in preparing patients for the procedure and managing their expectations (83). Additionally, Blondeaux et al. evaluated a nurse-driven genetic counseling pathway for women with uninformative *BRCA* test results (84). Their study revealed that 93.6% of the 299 participants reported a positive counseling experience, with 96% finding it helpful in addressing their concerns. This underscores the importance of effective communication in enhancing patient understanding and satisfaction within the context of genetic testing and preventive measures.

Evaluating the understanding of test results, Gavaruzzi et al. identified significant comprehension challenges among younger women aged 18-24 compared to those aged 30-45 (85). Younger participants demonstrated lower understanding of *BRCA*-related cancer risks, struggling to interpret key risk figures and providing less accurate responses to open-ended questions. These findings suggest the necessity of age-specific educational approaches to ensure younger women can fully grasp the implications of *BRCA* testing and preventive strategies. In contrast, Di Pietro et al. found high levels of perceived understanding among participants, with an average score of 9.27 out of 10 reported by 252 individuals, of which 87.3% were over 40 years old (86). These results reflect the effectiveness of counseling in fostering comprehension, particularly for older age groups. Furthermore, Blondeaux et al. revealed a positive impact of genetic counselling on patient understanding (84). Of the 299 participants, 93.6% reported a positive counseling experience, and 96% found it helpful in addressing their concerns. However, while 87.8% accurately understood

their negative test results and acted accordingly, only 22.4% were aware that a low residual risk of hereditary cancer persisted (84).

Effective communication of *BRCA*-related risks within families was found to be essential for encouraging cascade testing and promoting preventive care. Trevisan et al. reported a low cascade testing uptake rate of 22.8% among the families of 213 probands with *BRCA1/2* pathogenic variants 45). Factors such as female gender, age under 70 years, and first-degree relationships with the proband were associated with higher testing uptake, suggesting potential areas for targeted interventions to improve participation. Additionally, Di Pietro et al. found that 49% of *BRCA*-positive women intended to share their genetic test results with their offspring, while 27% planned to disclose this information to their partners (86). Familial relationships significantly influenced these decisions, with open and supportive family environments linked to more proactive communication. These findings highlight the importance of fostering family-centered strategies to facilitate discussions about genetic risks and encourage broader participation in testing programs.

Despite these positive findings, challenges remain in ensuring equitable access to and understanding of *BRCA* testing information. Younger women and those with uninformative test results appear to be at greater risk of misinterpreting or underestimating their cancer risks. Furthermore, while satisfaction with surgical interventions like RRSO is high, there remains a critical need for standardized communication protocols that address residual risks and facilitate informed decision-making. In conclusion, these studies collectively highlight the strengths and gaps within the current *BRCA* genetic testing and counseling framework in Italy. High levels of satisfaction and perceived understanding demonstrate that existing programs are effective for many participants. However, the data also reveal significant areas for improvement, particularly in addressing the unique needs of younger women, individuals with uninformative test results, and those navigating familial disclosure. Enhancing patient education through tailored counseling strategies, incorporating age-appropriate communication techniques, and fostering supportive familial environments could greatly improve both the psychological well-being and the preventive health outcomes of individuals undergoing *BRCA* genetic testing.

# 4. Recommendations

The findings of this HIA have underscored the need for multiple strategic interventions to fully implement a comprehensive *BRCA* screening program in Italy. A successful implementation would yield significant public health benefits, including a reduction in cancer incidence and mortality. The following recommendations, informed by literature reviews and Steering Committee consultations, outline key actions required across multiple categories.

## 4.1 Governance and regulations

Ensuring the effective and equitable implementation of *BRCA* testing and subsequent preventive strategies across Italy requires continuous updates to guidelines, mechanisms for national oversight, and financial coverage for all interventions. Specifically:

1. **Regularly update national guidelines and regional PDTA to align with the latest scientific evidence and clinical advancements**. This process should involve national scientific societies and multidisciplinary experts to ensure consistency, relevance, and applicability across all regions. In addition, PDTAs should be harmonized to reduce regional variability in *BRCA* testing eligibility, surveillance schedules, and referral pathways. These protocols should ensure equitable and consistent access across Italy and must include regular audits to monitor adherence and identify gaps or delays in implementation.
2. **Implement mechanisms for guaranteeing and monitoring regional adherence to national guidelines.** This can be achieved by including *BRCA* testing pathways and preventive interventions as part of the Livelli Essenziali di Assistenza (National Essential Level of Care) to ensure all regions comply with minimum standards of care.
3. **Guarantee that all interventions, including genetic testing, psychological counseling, cascade screening, and preventive surgeries, are reimbursed uniformly in all regions.** National funding and policies must be established to remove financial barriers and ensure equitable access to services for all eligible individuals.

## 4.2 Organizational and Structural Interventions

Strengthening organizational structures and standardizing pathways is essential to improve *BRCA* testing implementation and follow-up care, ensuring consistency, efficiency, and equitable access across all regions. The following actions are recommended:

1. **Establish and strengthen dedicated GOMs for hereditary cancers, including specialists such as oncologists, geneticists, surgeons, psychologists, and case managers.** The presence of case managers will ensure seamless coordination of care, facilitate scheduling, and improve communication between healthcare providers and patients. These groups should follow evidence-based protocols to optimize patient outcomes.

2. **Transition from monogenic to multigenic testing frameworks to detect a broader range of genetic alterations related to hereditary cancers.** Consider integration of advanced tools as next-generation sequencing technologies, to improve testing efficiency, cost-effectiveness, and detection accuracy.
3. **Ensure equitable and timely access to prophylactic surgeries, such as mastectomy and salpingo-oophorectomy, as well as subsequent reconstructive procedures.** This involves expanding surgical capacity in high-demand regions, streamlining appointment systems to reduce wait times, and guaranteeing full reimbursement for both prophylactic and reconstructive surgeries across all regions. Additionally, the integration of pre- and post-surgical counseling will address psychological concerns, enhance patient outcomes, and improve satisfaction with reconstructive results.
4. **Create national and regional registries to manage data on individuals with hereditary cancer syndromes.** These registries will enable structured follow-up, personalized preventive strategies, and consistent monitoring of the screening program. The data collected will also support research initiatives, policy planning, and monitoring program effectiveness.
5. **Develop a unified, interoperable digital platform to centralize patient data and streamline communication among healthcare providers.** This system will support multidisciplinary teams in decision-making and enable automated reminders for surveillance and follow-up care.
6. **Implement structured, ongoing training programs to address knowledge gaps among oncologists, geneticists, general practitioners, and other healthcare professionals.** These programs should focus on the latest testing protocols, preventive strategies, and psychosocial support approaches. In addition, it is important to develop clear, evidence-based guidelines for healthcare providers to ensure accurate and consistent communication with patients about BRCA testing eligibility, results, and preventive strategies. This will reduce misinformation and help manage patient expectations.

## 4.3 Ensuring Patient-Centered and Ethical Preventive Care

1. **Ensure uniform nationwide access to psychological support services integrated into the *BRCA* testing process.** Pre-test counseling should prepare individuals for testing outcomes and address emotional concerns, while post-test counseling must focus on managing anxiety, depression, and uncertainty. Long-term psychological follow-up should also be available to support patients throughout their journey.
2. **Enhance Pre-Test Education and Decision-Making.** It's important to implement structured educational programs to equip individuals with the knowledge needed to make informed decisions about *BRCA* testing and preventive measures. Decision aids, such as visual guides and online tools, can facilitate understanding of testing options and results.
3. **Provide support for BRCA-positive individuals to communicate results to at-risk family members through tailored counseling sessions and educational resources.** Encouraging family discussions can improve the uptake of cascade testing and foster a proactive approach to prevention.

4. **Invest in healthcare infrastructure in underserved regions, to ensure equitable availability of BRCA testing, genetic counseling, and preventive care services.** Increased funding should support workforce development and improve access to high-quality care.

## 4.4 Conclusion

The cascade screening for BRCA-related hereditary breast and ovarian cancers represents a pivotal step towards implementing precision prevention strategies in Italy. By identifying individuals at high genetic risk and enabling timely preventive interventions, cascade screening has the potential to significantly reduce cancer incidence and mortality, while improving patient outcomes and fostering a more equitable healthcare system. However, its success hinges on addressing several critical challenges spanning organizational, economic, and ethical dimensions.

First, achieving uniformity in the implementation of BRCA testing and cascade screening requires harmonized national guidelines and PDTA that align with the most recent evidence. Standardizing eligibility criteria, referral pathways, and follow-up protocols is essential to eliminate regional variability and ensure equitable access to care across Italy. Moreover, establishing robust national monitoring mechanisms, such as incorporating BRCA pathways into the Livelli Essenziali di Assistenza (National Essential Level of Care), will ensure that all regions adhere to consistent standards while enabling the evaluation of program effectiveness.

Second, the ethical implications of cascade screening must be carefully navigated. Ensuring informed decision-making and safeguarding patient autonomy are paramount, particularly in the context of genetic testing where outcomes can have far-reaching implications for both individuals and their families. Comprehensive pre- and post-test counseling services must be uniformly accessible to address the emotional burden of *BRCA* testing, support family communication, and facilitate informed decisions about preventive strategies. Without these supportive structures, the psychological and social dimensions of hereditary cancer prevention risk being overlooked.

Third, the economic sustainability of cascade screening requires strategic resource allocation. National reimbursement policies must guarantee full coverage for genetic testing, cascade screening, psychological counseling, and preventive interventions, including prophylactic surgeries and reconstructive procedures. Addressing geographic and socioeconomic disparities is equally critical, with investments targeted at underserved regions and populations to bridge existing gaps in access to care.

Finally, the success of cascade screening depends on the capacity and preparedness of the healthcare system. Comprehensive training programs for healthcare providers, including genetic counselors, oncologists, and general practitioners, are necessary to address knowledge gaps and ensure high-quality care delivery. National and regional registries for individuals with hereditary cancer syndromes should be established to enable structured follow-up and facilitate personalized prevention strategies. These registries would also provide invaluable data for research and policy development, ensuring the continuous evolution and improvement of screening programs.

While significant challenges remain, the potential benefits of cascade screening for *BRCA*-related cancers far outweigh the obstacles. By reducing cancer incidence and mortality, improving patient outcomes, and fostering equity, this approach has the power to transform cancer prevention in Italy. The insights gained from this HIA, combined with expert consultations and evidence from the literature, provide a clear roadmap for addressing these challenges. With sustained investment and coordinated efforts among policymakers, healthcare providers, and patient advocates, cascade screening can pave the way for a more ethical, effective, and equitable healthcare system in Italy, positioning the country as a leader in precision prevention.

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# Section III-2: Implementing a Population-Based Approach to Personalizing Therapy in Italy Through the Use of the Pharmacogenetic Passport

## 1. Background

### 1.1 Variability in Drug response and Pharmacogenetics

It is known that the pharmacokinetics and pharmacodynamics of drugs can be influenced by factors such as age, sex, disease characteristics, diet, and interactions with other substances. When these factors are not accurately assessed, therapeutic responses can vary considerably among patients, affecting drug efficacy or increasing the risk of ADRs (1). In clinical practice, for instance, this leads to the need to adjust the dose of certain drugs in patients with reduced kidney function (2), liver conditions (3), and in newborns and children (4, 5). Variants of so-called "pharmacogenes" genes involved in the pharmacokinetics and/or pharmacodynamics of various molecules, significantly contribute to individual variability in drug response. Several studies have highlighted how polymorphisms in genes encoding metabolizing enzymes and transporters affect the absorption, distribution, metabolism, and elimination of drugs, with significant consequences for therapy efficacy, safety, and tolerability (6). Moreover, genetic variants in components of the immune system, such as T cell receptors (TCRs) and human leukocyte antigens (HLAs), are associated with immune-mediated drug responses (7). The study of how someone's genetic variants influence responses to specific therapies is called pharmacogenetics. Pharmacogenomics, on the other hand, is a broader field that studies the influence of the entire genome on drug response, integrating data from transcriptomics, proteomics, or metabolomics to understand the interactions between multiple genes and their products in drug response (8). The clinical application of these disciplines promises to help understand and manage ADRs, leveraging genetic information to predict drug responses and optimize their use.

### 1.2 Impact of adverse drug reactions on Public Health

ADRs represent a public health issue, being a frequent cause of hospitalization (9, 10). A recent study by Kagagamine et al, from estimate that about 5% of hospitalizations are due to ADRs, and a similar percentage of patients experience ADRs while hospitalized (11). In an observational study conducted by the National University of Singapore, 8.1% of hospital admissions were attributed to ADRs, frequently manifesting as gastrointestinal disorders, electrolyte imbalances, and bleeding. Other studies report an incidence of ADR-related hospitalizations ranging from 2.7% to 8.8% (12).

According to a 2021 systematic review, the prevalence of ADRs in primary care settings was estimated at 8.32%. Preventable ADRs account for approximately 12.35–37.96% of cases, with variations related to factors such as age and patient comorbidities (13) especially in elderly patients and those with comorbidities (14). In Italy, a 2010 study found that the incidence of emergency hospitalizations was higher in patients who had taken medications (24.9%) compared to those who had not (16.4%) (15). Another Italian study reported ADRs in 3.3% of emergency room visits, with a higher hospitalization rate among patients with ADRs (30.7% vs. 23.7%) (16).

Certain types of drugs, such as cardiovascular medications, are associated with a higher risk of ADRs, especially in the elderly and people with comorbidities. A study showed that antiarrhythmics and antihypertensives have a relative risk of 5.75 and 2.97, respectively, of being associated with ADRs. Diuretics, on the other hand, can cause a range of ADRs, such as electrolyte imbalances and kidney failure. According to an observational study by the Liverpool University Hospital Foundation National Health Service (NHS) Trust, these account for 14.2% of ADRs (17). The same study found that anticoagulants are associated with 9.6% of reported ADRs, such as intracranial and gastrointestinal bleeding. Chemotherapy agents are also known for their high risk of severe ADRs, such as neutropenic sepsis and other complications, accounting for 7.3% of ADRs. Finally, proton pump inhibitors are associated with ADRs such as hypomagnesemia and Clostridium difficile infections, constituting 8.3% of reported ADRs.

These data demonstrate that some common medications are associated with a high risk of ADRs, both due to individual variability factors and their frequent use in patients of all ages, including the most vulnerable groups (**Table III - 8**).

| ATC group (n ADRs) | Subgroup | Drug | ADRs |
|---|---|---|---|
| Cardiovascular | Diuretics | Furosemide, hydrochlorothiazide, spironolactone, indapamide, amiloride | AKI, hypoK/hypoNa, hypoMg/hypoPO4, hypotension |
| | ARB | Losartan, candesartan, olmesartan | AKI, hypotension, hyperK |
| | ACEI | Enalapril, lisinopril, imidapril | AKI, hypotension, hyperK |
| | Beta blocker | Atenolol, bisoprolol, carvedilol | Bradycardia, hypotension |
| | CCB | Amlodipine, nifedipine | Hypotension, peripheral edema |
| | Nitrates | Isosorbide mononitrate, glyceryl trinitrate | Hypotension, headache |
| | Statin | Atorvastatin | Elevated creatine kinase, transaminitis |
| | Antiarrhythmic | Flecainide | QTC prolongation |

| | | | |
|---|---|---|---|
| Blood | Vitamin K antagonists | Warfarin, acenocoumarol | Supratherapeutic INR, bleeding, bleeding and supratherapeutic INR, bruising |
| | Antiplatelets | Aspirin, clopidogrel, ticlopidine | Bleeding, dyspepsia |
| | Heparin | Enoxaparin | Bleeding |
| | Anti-anemics | Fe fumarate, Fe gluconate, epoetin β | Constipation, elevated hemoglobin |
| Antineoplastic & immunomodulating | Antineoplastics | Cyclophosphamide, capecitabine, doxorubicin, prednisolone, carboplatin, carfilzomib, cisplatin, oxaliplatin, paclitaxel, others | Anemia/leucopenia/ thrombocytopenia, infection/sepsis, diarrhea, mucositis, AKI, rash, peripheral neuropathy |
| | Immunosuppressants | Cyclosporine, mycophenolate, prednisolone, leflunomide , methotrexate | Cytomegalovirus reactivation, transaminitis |
| Central nervous system | Analgesics | Morphine, tramadol, fentanyl | Constipation, N/V, respiratory depression, seizure, drowsiness |
| | Antiepileptics | Phenytoin, gabapentin | Rash, drowsiness/lethargy |
| | Anti-parkinson | Levodopa/benserazide | Diarrhea |
| | Antipsychotics | Quetiapine, risperidone | Giddiness, extrapyramidal side effects |
| | Antidepressants | Mirtazapine | Giddiness |
| | Antianxiolytics | Midazolam, unknown | Respiratory depression |
| Musculoskeletal | NSAIDs | Diclofenac, etoricoxib, naproxen | AKI, gastritis |
| | Muscle relaxants | Ophenadrine | Constipation |
| | Anti-gout | Allopurinol | Acute gout flare |
| | Bone | Strontium | Abd bloatedness/ diarrhea |
| Miscellaneous | Phosphate binders | Ca acetate, Ca carbonate, lanthanum | hypoPO4, hyperCa, abd bloatedness |
| | Resonium | Resonium | hypoK |
| | Vitamin D | Ergocalciferol | hyperCa |
| Hormones | Insulins | Insulin | Hypoglycemia |
| | Thyroid | Propylthiouracil, thyroxine | Transaminitis, elevated T4/suppressed TSH |
| | Steroids | Dexamethasone | Increased white cell count |
| | OHGA | Metformin | Lactic acidosis, N/V |

| | | | |
|---|---|---|---|
| Gastrointestinal & metabolism | Anti-diarrhoeals | Charcoal, loperamide, unknown* | Constipation |
| | Proton pump inhibitors | Esomeprazole | Diarrhea |
| | Laxative | Macrogol | Diarrhea |
| | Antispasmodic | Chlordiazepoxide/clidinium | Constipation |
| Anti-infectives | Antibiotics | Amoxicillin, clindamycin, metronidazole | Diarrhea, N/V, drug exanthema |
| | Antivirals | Acyclovir | N/V/diarrhea |
| Respiratory | Beta-agonists | Salbutamol | hypoK, tremors |
| | Theophylline | Theophyllline | Premature ventricular complex |
| Genitourinary | Alpha-blockers | Tamsulosin , terazosin | Hypotension/giddiness |

**Table III-8** Drugs causing most common adverse drug reactions (ADRs).

*Exact drug name could not be traced

Abd: abdominal, ACEI: angiotensin converting enzyme inhibitor, ADR: adverse drug reaction, AKI: acute kidney injury, ARB: angiotensin receptor blocker, ATC: anatomical therapeutic chemical, Ca: calcium, CCB: calcium channel blocker, Fe: ferrous, hyperCa: hypercalcemia, hyperK: hyperkalemia, hypoK: hypokalemia, hypoMg: hypomagnesemia, hypoNa: hyponatremia, hypoPO4: hypophosphatemia, INR: international normalized ratio, NSAIDs: non-steroidal anti-inflammatory drugs, N/V: nausea/vomiting, OHGA: oral hypoglycemic agents, TSH: thyroid stimulating hormone (Source: Chan, Sze Ling et al. "Prevalence and characteristics of adverse drug reactions at admission to hospital: a prospective observational study)(18)

## 1.3 Role of Pharmacogenetics in Reducing ADRs

The assessment of patients' ADR risk can be improved using pharmacogenetics (PGx) information. Therefore, the potential impact of PGx on public health is promising. According to the "Pharmacogenomics Knowledgebase" (19) over 90% of the population has at least one pharmacogenomic variant that influences drug response.

Given that single genes can interact with multiple drugs, it is estimated that about two-thirds of the population will receive a drug with a known pharmacogenetic association at some point in their lifetime. This percentage is even higher in high-risk groups, such as the elderly (20, 21).

Some examples of pharmacogenes associated with ADRs include *CYP2C9* for warfarin (22), *TPMT* and *NUDT15* for thiopurines (23), *DPYD* for fluoropyrimidines (24), and *UGT1A1* for irinotecan (25). Over the past 15 years, several scientific consortia have been established, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) (26), the Pharmacogenomics Knowledge Base and the Dutch Pharmacogenetics Working Group (19). The aim of these groups is to gather evidence and develop guidelines to apply pharmacogenetics in clinical practice, supporting professionals in personalizing therapy based on the results of genetic tests. Currently, over 90 gene-drug interactions have guidelines that recommend adjustments in prescriptions (19=.

### 1.4 PGx Panels and the "PGx Passport"

In recent years, the use of multigenic/multigene? panels has been proposed to simultaneously evaluate various genes involved in drug metabolism. It has been estimated that while the frequency of individual alleles associated with pharmacogenetic variants affecting drug response is relatively low, a panel including variants of the 12 most important pharmaco-genes could identify at least one relevant genotype in 90-95% of individuals across various populations (27). Therefore, the use of preventive pharmacogenetic test panels could represent an efficient strategy for the clinical implementation of pharmacogenetics. Several panels have been developed internationally (28, 29). The PGx Passport includes 58 germline variants across 14 key genes (*CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, UGT1A1*, and *VKORC1*) to optimize the prescription of 49 commonly used drugs (30).

# 2. Methodology Overview

## 2.1. Health Impact Assessment

The HIA approach implements and offers a number of different methods and approaches to gain the knowledge needed to identify the potential and actual impacts of a proposal (34). This process employs a wide range of quantitative and/or qualitative evidence, which may include epidemiological and/or ethnographic data, as well as information from public health, toxicology and medicine. It also takes into account the considerations, experiences and expectations of the community and other stakeholders regarding the likely interactions between a policy/programme/project and the health of a population (including both the general well-being of the population and that of its constituent groups). There are three main types of HIA (34):

- Prospective HIA: at the start of the development of a project, proposal or plan.
- Concurrent HIA: runs alongside the implementation of the project (or policy)
- Retrospective HIA: assesses the effect of an existing project or policy and can be used as an evaluation tool. Retrospective assessments can also be made of unexpected events, as a way of learning lessons for future similar events.

Although there is no fixed and formally unambiguous way of producing an HIA, there is a growing consensus around the key elements and main steps in the process (**Table III-9**):

| | |
|---|---|
| **1. Screening** | Definition of the policy to be tested and resources needed to conduct HIA |
| **2. Scoping** | • Definition of the technical skills required within the technical group. |

| | |
|---|---|
| | • Characterization of the policy under consideration and its possible impacts.<br><br>• Definition of methodologies for evidence collection and impact assessment. |
| **3. Evidence assessment** | Triangulation of qualitative and quantitative evidence to assess the impacts of the policy under consideration. |
| **4. Reporting and recommendation** | Preparation of the HIA report with results of the evidence assessment and the subsequent recommendation |

**Table III-9:** Main steps to produce an HIA report

In the context of these case studies, we will conduct a prospective HIA. The primary goal is to evaluate whether the potential implementation of this approach in Italy could be beneficial for the health of the Italian population, cost-effective, ethical, equitable, and feasible.

## 2.2 Screening phase

### 2.2.1 Policy definition

The objective of this HIA is to evaluate the impacts of implementing a population-based approach in Italy centered on the use of the Pharmacogenetic Passport an innovation for primary prevention in healthcare. The pharmacogenetic passport is a tool that consolidates information on allele variants of genes linked to the response to specific drugs. This information is obtained preemptively through a panel of pharmacogenetic tests, facilitating rapid access to critical genomic data and enhancing the timeliness and personalization of therapies.

This HIA aim to provide valuable insights for decision-makers, enabling them to:

- Identify the most effective and sustainable methods for implementing the pharmacogenetic passport in Italy, including the target population and delivery mechanisms.
- Determine the necessary actions to promote the adoption of the pharmacogenetic passport.
- Assess potential challenges and barriers to the implementation of this approach.
- Examine the ethical and equity implications of the preventive use of pharmacogenetic tests.

### 2.2.2 Definition of the skills required

Once the policy was defined, the necessary skills for conducting the HIA were established, and two groups were identified. The Technical Team was composed of Public Health professionals from Università Cattolica del Sacro Cuore. Specifically, the tasks of the technical group include:

- Conducting the screening and scoping phases, with the preparation of an initial report aimed at describing the policy under review, the potential impacts, and the methodologies used in the activity.
- Triangulating the evidence required to assess the identified impacts and drafting a second summary report.
- Jointly evaluating the impacts with the Steering Committee.
- Preparing a final report containing the evaluations conducted with the Steering Committee and recommendations for policy implementation and monitoring.

The identified necessary skills include conducting literature reviews, developing decision-tree impact models and cost-effectiveness analyses, and expertise in evaluating preventive approaches and personalized prevention strategies.

Given the significant expertise required for developing the approach and the need to account for all potential policy impacts, the establishment of a Steering Committee was deemed necessary. With the Steering Committee, the impacts and methodologies for evaluating them were discussed, including the selection and retrieval of data to be included in the model. They were also specifically consulted regarding the assessment of barriers and organizational challenges.

## 2.3. Scoping phase

### 2.3.1 Definition of the necessary figures to include in the Steering Committee

Following the definition of the context and objectives of the evaluation, the main professional figures needed to constitute the Steering Committee were identified. This selection was crucial to ensure qualified and multidisciplinary feedback, enriching the analysis process and contributing to a more comprehensive and informed evaluation. In this context, the main figures of interest identified are:

- Clinical Pharmacologist
- Pharmacogenetics Specialist
- Laboratory Medicine Specialists in Medical Genetics and Bioclinical Medicine
- Regulatory Agency Representative
- Pharmaceutical Company Representative
- Patient Representatives

- General Practitioner
- Clinical Physicians: Oncologist, Anesthesiologist, Cardiologist, Geriatrician

Members of the panel are reported in **Annex X**.

### 2.3.1 Identification of Potential Policy Impacts

The potential impacts of the policy were identified by the Technical Group through a narrative literature review aimed at characterizing the approach. Subsequently, the identified impacts and their assessment methodologies were validated by the Steering Committee. The impacts and corresponding assessment methodologies are summarized in **Table III-10:**

| **Impact** | **Assessment methods** |
|---|---|
| Impact on health | Literature review |
| Impact on patients' acceptability, satisfaction and awareness | • Literature review<br>• Steering Committee consultation |
| Economic impact | • Literature review |
| Organizational impact | • Literature review<br>• Steering Committee consultation |

**Table III-10** impact and assessment methodologies identified during the scoping phase

## 2.4. Assessment phase

### 2.4.1 Literature Review

A narrative literature review was conducted to examine all the identified impacts using various strategies and inclusion criteria. PubMed served as the primary database for all the literature reviews. The search focused on gathering the evidence necessary to evaluate the policy's impact. Specifically:

- Efficacy of the passport on health outcomes: Evidence from RCTs and guidelines.
- Economic impact: Systematic reviews of economic evaluation of pharmacogenetic tests. We also searched for economic evaluation conducted in Italy, and economic evaluation of multigenic/multigene? panels.
- Patient acceptability and organizational challenges: Initially, the search targeted primary studies conducted in Italy; however, the scope was broadened due to the limited availability of evidence.

Each literature review was conducted independently by two members of the Technical Group.

### 2.4.2 Steering Committee consultation

The input and opinions of the Steering Committee were crucial for assessing many of the evaluated impacts, particularly in defining the decision tree model and some of the probabilities used, as well as for all organizational impacts. The Steering Committee were consulted in two ways: through an open-ended questionnaire and via three 90-minute online meetings. The questionnaire is detailed in **Annex XI.**

## 2.5 Policies implementations and monitoring recommendations

The recommendations for the implementation were formulated and reported in this document based on the data provided by our literature reviews and the input provided by the Steering Committee.

# 3. Evidence Impact Assessment

## 3.1 Impact on health

In order to implement a genomic test, it is necessary to demonstrate its clinical utility, meaning the test's ability to provide useful information for the diagnosis, treatment, management, and prevention of a disease, thereby providing tangible benefits to the patient (31, 32). Implementing the PGx Passport in the SSN could significantly reduce the incidence of ADRs, with a significant impact on patients' health in Italy. The clinical efficacy of this tool was tested in the PREPARE study, a cluster-randomized clinical trial that evaluated the efficacy of a panel for 50 germline variants in 12 genes, (CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1, VKORC1. The study analyzed responses to all drugs for which DPWG recommendations indicated at least one drug-gene interaction. The trial involved 6,944 participants across seven European countries, including Italy, with the aim of evaluating the clinical utility of the panel in various contexts and healthcare organizations in Europe. Among these, 3,342 patients were assigned to receive genotype-guided pharmacological treatment, while 3,602 were treated with standard care. Subsequently, 99 patients (52 in the study group and 47 in the control group) withdrew consent after group assignment, while 652 participants (367 in the study group and 285 in the control group) were lost to follow-up. Among the 1,558 patients with a positive test result for a reference gene-drug pair, a clinically relevant ADR occurred in 152 (21.0%) of the 725 patients in the study group and 231 (27.7%) of the 833 patients in the control group. Considering the entire cohort, the overall incidence was 21.5% (628 out of 2,923 patients) in the study group compared to 28.6% (934 out of 3,270 patients) in the control group. In both cases, the results showed a significant reduction in the risk of clinically relevant ADRs, amounting to 30% (33). It should also be noted that these results could be even more positive if the use of the Passport were extended to the entire population, with significant benefits especially for patients on polypharmacy (34).

Despite the results of the PREPARE study, in support of reduction of ADRs the clinical impact of the preventive test for a gene panel remains a topic requiring further investigation. However, the clinical consequences of many interactions between drugs and specific pharmacogenetic variants have been extensively studied and, in some cases, are already being used to guide therapeutic decisions. Annex XII summarizes the allele-drug pairs for which the DPWG (2019) guidelines recommend therapeutic plan modifications. For each pair, the rationale for therapy adjustment is presented, with the aim of optimizing therapeutic efficacy and reducing the risk of adverse effects in relation to the patient's genetic profile.

## 3.2 Patients acceptability

The literature review identified seven studies evaluating the acceptability of pharmacogenetic testing among patients, none of them conducted in Italy highlighting a significant gap in research, particularly when considering specifically *DPYD* testing (35-41). Key findings of the included studies are reported in **Annex XIII.**

Patient acceptance of the Pharmacogenetic Passport is an essential prerequisite for the implementation of this technology in the SSN. Although PGx tests are considered to pose fewer risks of psychological harm, stigmatization, or discrimination compared to genetic tests for specific diseases (41, 42), the evidence supporting this assumption is still limited.

A discrete choice experiment by Di Dong et al. estimated a 65% uptake rate for PGx testing at a cost of SGD 400 (~$300) (35). Importantly, physician recommendations significantly enhanced acceptance, increasing uptake by 8.5 % points. Similarly, Cuffe et al. found that 97.4% of 121metastatic cancer patients undergoing chemotherapy were willing to adopt PGx testing to detect risks of severe toxicity, even when faced with a median cost of $1,000 and a turnaround time of 14 days (39). However, their study also highlighted that one in five patients lacked a basic understanding of pharmacogenetic testing, underscoring the need for effective education strategies.

Patient preferences for PGx testing appear to be shaped by their health conditions and perceived need for tailored therapies. For example, O'Shea et al. observed that individuals with chronic diseases were 2.17 times more likely to express interest in PGx services compared to those without such conditions, particularly among those managing multiple morbidities (37). Similarly, McCarthy et al. revealed an inclination among patients with treatment-resistant depression to adopt PGx testing, with participants valuing its potential to optimize pharmacological treatments (36). While concerns about discrimination, familial implications, and coping with results were present, they were generally minimal and did not substantially hinder patient enthusiasm.

The role of healthcare providers are perceived as pivotal in shaping perceptions of PGx testing. According to Kaur et al., 52% of surveyed patients were aware of PGx testing, and awareness was significantly correlated with positive attitudes. Both patients and providers acknowledged the value of point-of-care PGx testing devices, with 98% of healthcare providers and 71% of patients agreeing that such tools could improve accessibility and streamline the integration of PGx testing into routine clinical practice (38). This highlights the importance of engaging healthcare providers as key advocates for pharmacogenomic technologies, as their support not only builds patient trust but also enhances the perceived credibility of these innovations.

Despite the largely positive reception of PGx testing, several barriers remain that must be addressed to ensure equitable and effective implementation. For instance, concerns over cost, insurance coverage, and potential employment discrimination were expressed by participants in a qualitative

study conducted by Ming Lee et al. (40). These challenges suggest that, beyond raising awareness and fostering trust, systemic changes in policy and healthcare infrastructure are needed to mitigate such barriers. Additionally, the evidence highlights the critical role of clear and comprehensive patient education in improving understanding and acceptance, especially among individuals with lower baseline knowledge of genomics.

In conclusion, the available evidence suggests that PGx testing has the potential for high patient acceptability, especially when its benefits in improving treatment outcomes and reducing risks are effectively communicated. While awareness and understanding remain critical factors, addressing concerns related to cost, insurance coverage, and potential discrimination is vital for successful implementation. Broadening educational efforts for both patients and healthcare providers, along with the development of accessible and user-friendly PGx tools, can further enhance the integration of pharmacogenomic technologies into routine clinical practice.

## 3.3 Organizational feasibility and barriers

Through our literature review, we identified 6 studies analyzing challenges in the implementation of pharmacogenetics technologies, two conducted in Italy (43-48) (**Annex XIV**).

The results underscored significant gaps in pharmacogenetic knowledge among healthcare professionals across various specializations, as well as disparities in the availability and implementation of testing services. For instance, a survey conducted by Pisanu et al. (43) revealed that while a large proportion of residents (93%) and physicians (79%) acknowledged the utility of pharmacogenetic tests, only a small fraction (16% of physicians and 7% of residents) felt confident in selecting and interpreting these tests based on their training. This lack of confidence is echoed in broader findings across Europe and the United States, where only 10.3% to 14.1% of healthcare providers reported adequate readiness for interpreting PGx results, despite an overall high acceptance of PGx testing's clinical relevance (45).

Data from Preys et al. (44) provided further insights, showing that education programs could play a crucial role in addressing these gaps. Their survey highlighted a significant increase in confidence among PCPs and specialists in ordering PGx tests post-education (67.6% and 55.8%, respectively; $p < 0.001$). Additionally, PCPs were more likely to perceive PGx testing as useful compared to specialists, both before and after education interventions, emphasizing the role of targeted training programs in enhancing adoption rates.

Practical barriers to implementation were also identified. Lau-Min et al. (47) reported that mistrust in evidence and a general lack of knowledge among clinicians impeded the uptake of PGx testing. This lack of knowledge affected not only their initial decision to perform testing but also their ability to effectively counsel patients on the associated risks, benefits, and alternatives. Similarly, Gurvere et al. (48) found that while 64% of healthcare providers were familiar with PGx, low levels of testing

in clinical practice were attributed to limited access and inadequate training on test interpretation. Both patients and providers emphasized the potential of point-of-care testing devices to simplify access and integration into routine care, with 98% of healthcare providers and 71% of patients supporting their use.

Furthermore, it is important to note that another critical challenge in implementing the PGx Passport could be developing new infrastructures to facilitate test execution. Regarding this aspect, it is also important to consider territorial disparities in access to services. AGENAS conducted a survey during 2021-2022 involving 132 centers (99 public and 33 accredited private facilities), which provided information on activities using NGS platforms for the SSN, for a total of 350 active laboratories in Italy (49). The survey revealed Lombardy had the highest number of facilities (n=28), followed by Sicily (n=15) and Lazio (n=13). Overall, there were 67 facilities providing these services in the North, 24 in the Center, 23 in the South, and 17 in the Islands, of which only 2 are in Sardinia (n=44).

However, lessons from ten years of *DPYD* pharmacogenetic testing in Italy, as reported by Bignucolo et al. (46), demonstrated the transformative potential of integrating PGx into routine care. The transition from post-toxicity testing to pre-treatment approaches, supported by regulatory guidelines and nationwide reimbursement, has significantly improved clinical practice for fluoropyrimidine prescriptions, serving as a model for broader PGx Passport implementation.

In conclusion, the introduction of the PGx Passport into the SSN demands a multifaceted approach that addresses educational, infrastructural, and organizational gaps. Education and training programs, complemented by CDSS and equitable resource distribution, are essential to prepare healthcare professionals for integrating PGx testing into clinical workflows. By addressing these barriers, the PGx Passport could become a cornerstone of personalized medicine in Italy, bridging current disparities and enhancing healthcare outcomes for patients.

## 3.4 Economic impact

While reducing ADRs provides an obvious clinical advantage, it can also result in potentially significant economic savings. ADRs generate significant costs, both direct and indirect. A systematic review of studies conducted in Western countries estimated that the costs of preventable ADRs range from €2,851 to €9,015 in hospital settings and from €174 to €8,515 in outpatient settings (50). A European report, *"Costs of unsafe care and cost-effectiveness of patient safety programmes"*, estimated that the overall costs of ADRs range between €2.8 billion and €84.6 billion, depending on national contexts (51).

Our literature review included three systematic reviews of economic evaluations of PGx panels (52-54), one PGx evaluation on the use of a multigene panel in decision-making (55), and two economic

evaluations of PGx panels conducted in Italy (56-57). The list of studies included in our review and their main findings are provided in **Annex XV**.

Although comprehensive cost-effectiveness estimates for using the PGx Passport are not currently available, evidence on the preventive genotyping of specific gene-drug pairs included in the panel has been widely studied. A comprehensive review of 47 economic evaluations (52) highlighted strong evidence supporting the cost-effectiveness of genetic tests, including *HLA-B*57:01* for abacavir and *CYP2C19* for clopidogrel. However, inconclusive evidence was reported for other biomarkers such as *TPMT* and *CYP2C9*, demonstrating variability in outcomes depending on the specific drug-gene pair analyzed. Another systematic review focusing on pharmacogenomic-guided therapies (53) identified 27 economic analyses. This review revealed that most studies found pharmacogenomic-guided administration of active ingredients to be cost-effective or even cost-saving. However, the cost-effectiveness varied across different indications and depended on multiple factors, including the prevalence of biomarkers, test costs, threshold values, ADR rates, and therapy response rates. The study also noted that the perspective of the economic evaluation, whether societal, healthcare system, or payer, significantly influenced the results, highlighting the complexity of conducting these analyses. In addition, Morris et al. in 2022 systematically analyzed 108 studies evaluating 39 drugs and found that 71% of PGx tests were either cost-effective or cost-saving. The review highlighted the cost-effectiveness of pharmacogenomic testing for specific drugs like clopidogrel, warfarin, and antidepressants, while also underscoring the limited data available for preemptive and multigene panel testing. These reviews collectively underscore the economic value of pharmacogenomic testing but also highlight the need for more comprehensive evaluations to address variability across drugs, indications, and healthcare systems.

We also collect a cost-effectiveness analysis of a multigene panel including *CYP2C19*, *DPYD*, *TPMT*, and *UGT1A1* conducted in the context of the U-PGX project (55). This model estimated that implementing pharmacogenomic-guided prescribing for patients initiating one of seven drugs would reduce gene-drug-related mortality by 10.6%, preventing 419 deaths annually. While the intervention required an initial cost of €21.4 million, the estimated cost per prevented death was €51,000. These findings underscore the clinical value of multigene panels in preventing ADRs and improving patient safety.

Specific to the Italian context, two economic evaluations provided critical localized insights. One study assessed the cost-utility of PGx testing for *CYP2C19* and *CYP2D6* in patients with major depressive disorder (56). The ICERs were €60,000 and €47,000 per QALY, respectively, with probabilistic sensitivity analyses showing cost-effectiveness in approximately 60% of simulations under a €75,000 willingness-to-pay threshold. Another Italian study, also conducted as part of the U-PGx PREPARE project, evaluated PGx-guided treatment in CRC patients (57). This study demonstrated that PGx-guided treatment reduced total costs to €380 compared to €565 in the control arm while increasing mean survival by 0.25 life-years. While QALY improvements were not

statistically significant, subgroup analyses showed that PGx-guided treatment was a dominant strategy for actionable patients, with a 92% probability of cost-effectiveness.

The findings from these reviews and economic analyses collectively demonstrate the significant potential of pharmacogenomic testing to reduce healthcare costs and improve patient outcomes. Although variability in cost-effectiveness remains challenging due to differences in study perspectives and methodological approaches, the evidence supports the broader adoption of pharmacogenomic testing as a sustainable healthcare strategy. For Italy, where localized studies have already demonstrated promising results, integrating these strategies into routine clinical care could enhance efficiency and sustainability.

# 4. Recommendations

The pharmacogenetic passport represents a critical innovation in personalized prevention and in general medicine, offering the potential to enhance the safety and efficacy of drug therapies by tailoring treatments based on an individual's genetic makeup. Its implementation in Italy, particularly in high-risk populations, promises substantial benefits, including the reduction of ADRs, improved therapeutic outcomes, and cost savings for the healthcare system. However, the successful integration of this technology requires addressing significant organizational, clinical, and ethical challenges while leveraging Italy's existing healthcare infrastructure. The following paragraphs outline a series of recommended actions to promote the adoption of the Pharmacogenetic Passport in Italy and assess potential barriers and ethical considerations, based on the evidence assessment previously detailed and the insights gathered from the expert members of the Steering Committee.

## 4.1 Strategies for Implementation

To implement the pharmacogenetic passport effectively and sustainably in Italy, a phased approach targeting specific populations and healthcare settings is recommended.

1. **Target Populations and Settings:** High-priority groups for initial implementation include elderly patients in polypharmacy, oncology patients undergoing complex treatment regimens, and pediatric populations requiring long-term therapies. These populations are at a heightened risk of ADRs and are more likely to benefit from pharmacogenetic insights. Elderly patients, who often face the complexities of multiple medications and comorbidities, the pharmacogenetic passport can provide critical guidance on drug interactions and appropriate dosing, could be the target of an initial implementation. Similarly, in oncology, where treatments such as fluoropyrimidines are associated with severe toxicities in *DPYD*-deficient patients, the integration of pharmacogenomic data can significantly improve safety and outcomes. The pediatric population, particularly those undergoing chemotherapy or long-term treatments, represents another critical group where early genetic insights could optimize therapy and prevent complications later in life. In addition, the implementation should occur across various healthcare settings, including general practitioners' offices, hospitals, and residential care facilities. General practitioners, given their trusted relationships with patients, are well-suited to initiate and oversee the use of the pharmacogenetic passport. In hospitals, particularly during admissions for complex cases, pharmacogenomic testing should be part of the diagnostic and treatment planning process.
2. **Integration into Healthcare Infrastructure:** The integration of pharmacogenomic data into Italy's healthcare infrastructure will require investments in digital health technologies. EHRs should be adapted to incorporate genetic data securely, and CDSS must be implemented to provide actionable recommendations for prescribers. Ensuring the interoperability of these systems across

regions and healthcare providers will be essential for seamless implementation. Accredited laboratories with standardized protocols must be established to perform genetic testing. Experts have emphasized the need for national accreditation and quality assurance systems, ensuring consistency and reliability in test results. Moreover, a centralized approach to data management and analysis will streamline operations and facilitate the sharing of pharmacogenetic insights across the healthcare system.

## 4.2 Actions to Promote Adoption

Promoting the adoption of the pharmacogenetic passport will require coordinated efforts involving education, policy development, and economic incentives.

1. **Education and Training**: Healthcare professionals should be equipped with the knowledge and skills to interpret pharmacogenomic data and integrate it into clinical practice. Comprehensive training programs should focus on understanding the complexities of pharmacogenomic testing, including its limitations and ethical implications. Training should also cover communication strategies for discussing genetic findings with patients, ensuring informed decision-making. Public education campaigns will be crucial in building trust and acceptance among patients. Clear, accessible information on the benefits of the pharmacogenetic passport and its role in personalized medicine can help overcome resistance and misinformation. Specific attention should be given to vulnerable populations, such as those with low health literacy, to ensure equitable understanding and adoption.
2. **Policy Development**: The establishment of national guidelines for the pharmacogenetic passport is a priority. These guidelines should address the selection of genetic panels, testing protocols, data integration, and clinical application. They should be developed through a multidisciplinary collaboration involving pharmacogenomics experts, clinicians from various specialties, regulatory agencies, and patient representatives. Financial reimbursement policies will also play a critical role in promoting adoption. The inclusion of pharmacogenetic testing and related consultations in the Livelli Esseziali di Assistenza (National Essential Level of Care) will provide a clear framework for funding and reducing economic barriers. Pilot programs targeting specific populations and regions can demonstrate the feasibility and benefits of the pharmacogenetic passport, generating evidence to support broader implementation. Incentives for early adopters, such as funding for necessary infrastructure and training, can accelerate the uptake of this innovation.

## 4.3 Main Challenges and Barriers

**1. Organizational Challenges**: The lack of standardization across laboratories and healthcare facilities remains a significant barrier. Currently, testing protocols, accreditation standards, and data management practices vary widely, creating inconsistencies and inefficiencies. To address this, a

national regulatory framework is needed to standardize laboratory practices and ensure uniformity in the generation and interpretation of genetic data.

2. **Economic Barrier**: While the literature supports the cost-effectiveness of pharmacogenomic testing, the initial investment required for infrastructure, training, and integration into clinical workflows may deter adoption. Economic evaluations must account for not only the cost of testing but also the resources needed for data integration, personnel training, and ongoing maintenance of digital platforms.

3. **Clinical Barriers**: Clinicians have expressed concerns about the complexity of interpreting pharmacogenomic data, particularly when genetic findings do not align neatly with clinical outcomes. Highlighting the importance of combining genetic data with other clinical parameters, such as renal and hepatic function, to provide a comprehensive assessment. Additionally, clear protocols for managing ambiguous or inconclusive results must be established to build confidence among healthcare providers.

## 4.4 Ethical and Equity Considerations

The implementation of the pharmacogenetic passport raises important ethical and equity concerns. Ensuring equitable access to pharmacogenomic testing across different regions and socioeconomic groups is paramount. Vulnerable populations, including those with limited access to healthcare or low health literacy, may face barriers to benefiting from this innovation. Data privacy and security are critical issues that must be addressed to gain public trust. Robust safeguards must be implemented to protect genetic data from misuse, and clear policies should be established regarding data ownership and sharing. Furthermore, the potential for stigmatization, particularly in pediatric populations, must be carefully managed through appropriate counseling and education.

## 4.5 Conclusion

The pharmacogenetic passport represents a transformative tool for advancing personalized medicine in Italy. By identifying high-risk populations, integrating genetic data into clinical workflows, and addressing organizational and economic barriers, this innovation can improve patient outcomes and reduce healthcare costs. However, its successful implementation will require a multifaceted and coordinated effort.

Firstly, it is essential to strengthen and standardize laboratory infrastructure to ensure the reliability and consistency of genetic testing across the country. This includes establishing clear guidelines, uniform quality control measures, and enhanced technological capabilities in laboratories. Additionally, there is a pressing need for comprehensive education and training programs targeted at healthcare professionals. Such programs should aim to increase awareness of the benefits of pharmacogenetics, enhance their ability to interpret genetic data, and integrate this knowledge effectively into clinical practice.

Moreover, a strong policy framework is required to support the integration of the pharmacogenetic passport into routine care. This includes creating incentives for adoption, addressing ethical and privacy concerns, and ensuring equitable access across different regions and populations. Public awareness campaigns could also play a pivotal role in fostering acceptance and understanding among patients, helping to overcome potential resistance.

While challenges remain, the insights from literature and expert discussions provide a clear and actionable roadmap for implementing the pharmacogenetic passport in Italy. This initiative has the potential to transform healthcare delivery, promoting equity, efficiency, and improved outcomes for patients. By prioritizing collaboration among stakeholders, Italy can pave the way for a more innovative and effective healthcare system that sets an example for other nations.

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# Section IV: Conclusions and Recommendations for the PROPHET Framework

Genomic testing policies, like other omics-based technologies, are generally regulated at national levels, and different countries have different financial and infrastructural systems to implement such technologies. This scenario could lead to inconsistent diagnostic and treatment strategies, and therefore inequitable health outcomes across the EU (1).

Current assessments and evaluations, supporting the adoption of genomic-based technologies (and other preventive strategies based on biomarkers) fail to integrate some dimensions like acceptability and equity. The underrepresentation of such dimensions could lead to the implementation of policies introducing personalised preventive interventions that are not aligned with patient values or that exacerbate existing health disparities (2). The failure to adequately evaluate these dimensions may hinder the equitable and effective integration of genomic medicine into healthcare systems (2).

To address this gap, the PROPHET Framework propose a multidimensional, comprehensive approach to assess and evaluate personalised prevention interventions, with a focus on equity. The sequential use of HTA, HIA and Monitoring aims to integrate both clinical utility and equity dimensions while combining qualitative and quantitative data. Each phase builds upon the knowledge gained in the previous one. By leveraging the inputs of experts, end-users, and other relevant stakeholders, the PROPHET framework facilitates a collaborative assessment of personalised prevention interventions, considering their potential impacts across key dimensions (e.g. clinical utility, acceptability and equity) for a sustainable implementation. This process enables the identification of actions to address disparities or mitigate potential negative effects, prospectively.

The PROPHET Framework was developed through an in-depth analysis of a case study based on genomic technologies (*DPYD* genotyping) carried out in three different European countries: Portugal, Italy and Finland. In addition, The PROPHET framework has been validated through other two case studies conducted in Italy: the first focusing on the evaluation of cascade screening for BRCA-related hereditary breast and ovarian cancers, and the second assessing the impact of implementing a population-based prevention strategy using a pharmacogenetic passport to personalize drug therapies. These case studies were carefully selected to test the PROPHET framework across diverse scenarios. The first case examines a prevention approach rooted in a test with long-established clinical utility, partially implemented in Italy from several years, but hampered by territorial inequalities and significant organizational barriers. In contrast, the second case

addresses a technology with emerging evidence of clinical utility that has yet to be implemented beyond research contexts, where evidence of potential impacts across multiple dimensions remains limited. The experience gained from the *DPYD* case studies and for the other two validation cases have yielded critical insights into the evaluation of personalized prevention policies.

One of the primary considerations emerging from the case studies is the critical need for comprehensive evaluations, even in scenarios where the clinical utility of a technology or intervention is strongly supported and widely recognized. While the scientific evidence backing certain approaches, such as *BRCA* cascade screening, is robust, these evaluations must go beyond clinical outcomes to account for the broader and often complex impacts on the target population and healthcare systems. Personalized prevention strategies, despite their potential, frequently encounter systemic challenges related to accessibility, organizational inefficiencies, and equity, which can significantly affect their overall effectiveness. The HIA model, with its inherently multidisciplinary approach, has proven to be an invaluable tool for such evaluations. By systematically identifying vulnerable and underserved populations, organizational barriers, and gaps in service delivery, HIA helps to uncover critical areas that require intervention. Importantly, this model is not limited forecast the impact of new policies or to assess the impact of newly introduced policies; it is equally effective for policies that have already been partially implemented but are struggling to achieve their full potential due to persistent barriers. Through its emphasis on context-specific assessments, HIA ensures that evaluations are not generic but instead finely tuned to the unique characteristics of the healthcare systems and populations in question. This approach is essential for developing sustainable and comprehensive implementation strategies that address both the systemic and local factors affecting personalized prevention policies. Ultimately, this method facilitates not only the progressive improvement of such policies but also the creation of a more resilient and equitable healthcare system that can adapt to emerging challenges.

A significant reflection emerging from the HIA exercise is the pervasive lack of data necessary for accurately assessing the impact, effectiveness, and functioning of personalized prevention policies. This deficiency is evident not only in newer, less-established approaches but also in interventions that have been implemented for many years. For instance, even in cases where clinical utility is well-documented, the absence of reliable and comprehensive data on key processes, such as patient pathways, uptake rates, and adherence to preventive strategies, poses substantial challenges to evaluating program effectiveness. Similarly, the lack of standardized outcome data, including metrics on morbidity, mortality, and cost-effectiveness, limits the ability to measure the long-term benefits of these policies and to identify areas for improvement. The fragmentation of data collection systems across regions and institutions exacerbates this issue, often leading to inconsistencies in reporting and significant gaps in information. This issue underscores one of the key aims of the PROPHET framework: addressing these data challenges by promoting a more structured and standardized approach to policy evaluation that balances both international and

context-specific dimensions. On an international level, the framework emphasizes the need for harmonizing methodologies to assess core dimensions of validity and clinical effectiveness. By creating a shared foundation of evidence, the global healthcare community can work collaboratively to reduce redundancy and maximize the efficiency of research efforts related to personalized prevention technologies. At the same time, the PROPHET framework highlights the importance of incorporating national and regional perspectives to capture the unique organizational, cultural, and systemic factors that influence the implementation and success of policies in specific contexts. Evaluating these context-sensitive dimensions is essential to identify challenges and barriers that are unique to a given healthcare system and to recommend tailored interventions that are both practical and sustainable. Furthermore, the framework stresses the critical role of monitoring in ensuring the long-term effectiveness and equity of personalized prevention policies. Continuous evaluation of processes—such as referral rates, access to genetic testing, and timeliness of preventive interventions—provides valuable insights that can guide iterative improvements and foster accountability. By integrating these context-specific and process-oriented dimensions into the evaluation framework, PROPHET seeks to address the persistent data gaps and establish a more robust foundation for policy development and assessment.

Another key insight derived from the case studies is the significant utility of the HIA methodology during the early stages of prevention strategy development. This was particularly evident in the pharmacogenetic passport case, where the clinical utility of the technology is emerging, but the evidence of the effectiveness and of the feasibility of the approach in the real-world remains limited. In such contexts, where quantitative assessments of the population health impact are inherently more challenging, HIA serves as a critical tool for identifying the interventions necessary to implement the policy effectively within a specific geographical or healthcare context. HIA excels at uncovering potential barriers and challenges to implementation that might otherwise go unnoticed in traditional assessments. By evaluating organizational readiness, infrastructure gaps, and the alignment of proposed interventions with local healthcare systems, HIA can provide actionable insights into the prerequisites for a successful rollout. For instance, it can identify areas requiring resource allocation, workforce training, or regulatory adjustments, enabling policymakers to address these gaps proactively rather than reactively. In addition, the multidisciplinary nature of HIA is particularly valuable in the early stages of policy development. Involving diverse stakeholders, including healthcare providers, policymakers, researchers, patient advocacy groups, and community representatives, ensures a comprehensive understanding of the policy's implications. This collaborative approach facilitates the creation of synergies among stakeholders, fostering cooperation and aligning efforts toward a common goal. Such alignment is crucial for the smooth development and eventual implementation of preventive strategies, as it reduces fragmentation and ensures that all aspects of the policy are addressed in a coordinated manner. Moreover, prospective evaluations conducted through HIA can establish a foundation for the long-term

monitoring of prevention policies. By defining clear objectives, identifying measurable indicators, and highlighting key processes to be tracked over time, HIA supports continuous evaluation and iterative improvements. This forward-looking approach not only ensures that the policy remains effective and relevant as conditions evolve but also fosters a culture of accountability and adaptability within healthcare systems. Nonetheless, it must be emphasized that the foundational principle of the PROPHET framework remains the requirement for robust evidence of clinical utility as a prerequisite for the implementation of personalized prevention policies. While the framework is designed to address the multifaceted challenges of prevention strategies—ranging from organizational barriers to regional disparities and stakeholder coordination—it fundamentally relies on the presence of strong scientific evidence demonstrating the technology's capacity to improve population health outcomes.

Based on these pilot studies we recommend:

- Assign a technical team for each phase of the PROPHET Framework, ensuring it is aligned with national agencies and their areas of expertise.
- Assess the knowledge gaps of technical teams and provide targeted training to ensure that they are equipped to handle the complexities of HTA and HIA, particularly in multidisciplinary and data-intensive contexts.
- Leverage HTA data by reusing and adapting it within the HIA context to support a broader focus on policy impacts, determinants of health, and equity-related outcomes.
- Utilize the catalogue of indicators to assess clinical utility produced by the PROPHET Consortium, as a resource to support HTA processes (8).
- Conduct HIA prospectively, with a focus on equity, to identify asymmetries and vulnerable groups that may be disproportionately affected by the policy or program under the scope and to propose actions to mitigate any gaps and negative effects identified.
- Ensure multidisciplinary teams for carrying out both HTA and HIA processes, as well as for the steering committee(s).
- Establish a structured approach for involving stakeholders at key stages of the framework's application. This includes early consultations to align priorities, mid-process reviews to address emerging barriers, and final discussions to validate recommendations and ensure feasibility.
- Deliver a concise report that integrates HTA and HIA findings, tailored for decision-makers, including the most significant findings and actionable recommendations for policy implementation and evaluation phases.
- Develop a system of periodic, rapid assessments to evaluate the ongoing effectiveness of implemented policies. This iterative process allows for real-time adjustments to address new challenges or evolving healthcare needs.

In conclusion, The PROPHET Framework aims to bridge technical, clinical, and societal dimensions, ensuring that PP interventions are effective, equitable, and sustainable in real-world settings. In the future, extending the application of this framework to other personalized prevention interventions, encompassing different levels of prevention and integrating various biomarkers, will be highly relevant as it has the potential to uncover novel insights, foster innovative strategies, and enable more comprehensive and effective outcomes in the field of personalized healthcare.

## References (Section IV)

1.Custers I. Recommendations from the 1+MG HEOR workshop. 2022 Dec 15 [cited 2024 Dec 10]; Available from: https://zenodo.org/record/7442681

2. Pezzullo A, Gris A, Scarsi N, Tona D, Porcelli M, Pumpo M, et al. A scoping review of the assessment reports of genetic or genomic tests reveals inconsistent consideration of key dimensions of clinical utility [Unpublished manuscript]. 2024;

# Annexes

## Annex I - Markov Chain Model Assumptions

| Parameter name | Parameter estimate | Range for sensitivity analysis |
|---|---|---|
| **Probability of carrying a deleterious *DPYD* gene variant** | 0.074 | **0.05, 0.08** |
| **Probability of grade 3–4 toxicity** | | |
| **- *DPYD* variant, standard-dose chemotherapy** | 0.73 | **0.65, 0.90** |
| **- *DPYD* variant, reduced-dose chemotherapy** | 0.39 | **0.34, 0.44** |
| **- *DPYD* wild-type, standard-dose chemotherapy** | 0.23 | **0.18, 0.28** |
| **- *DPYD* wild-type, reduced dose chemotherapy** | 0.23 | **0.18, 0.28** |
| **Probability of early treatment-related death** | | |
| **- *DPYD* variant, standard-dose chemotherapy** | 0.023 | **0.013, 0.039** |
| **- *DPYD* variant, reduced-dose chemotherapy** | 0.002 | **0.001, 0.005** |
| **- *DPYD* wild-type, standard-dose chemotherapy** | 0.001 | **0.001, 0.002** |
| **- *DPYD* wild-type, reduced dose chemotherapy** | 0.001 | **0.001, 0.002** |
| **- *DPYD* wild-type, reduced dose chemotherapy** | **0.001** | **0.001, 0.002** |

Source: Data from Brooks et al. (2022) and Pinheiro et al. (2023)

**Table A1**. Parameters used in Markov model, estimate and range for sensitivity analysis

| Model stage | Time from treatment | Probability of death |
|---|---|---|
| 1 | 0 to <6 months | 0.017 |
| 2 | 6 to <12 months | 0.034 |
| 3 | 12 to <18 months | 0.041 |

| | | |
|---|---|---|
| 4 | 18 to <24 months | 0.042 |
| 5 | 24 to <30 months | 0.044 |
| 6 | 30 to <36 months | 0.041 |
| 7 | 36 to <42 months | 0.04 |
| 8 | 42 to <48 months | 0.035 |
| 9 | 48 to <54 months | 0.039 |
| 10 | 54 to <60 months | 0.038 |

CRC - colorectal cancer

Source: Data from Brooks et al. (2022)

**Table A2**. Estimated probability of death after adjuvant chemotherapy for stage III CRC

# Annex II - Economic Literature Search Strategy

| | |
|---|---|
| PubMed | "DPYD"[All Fields] AND ("colorectal"[All Fields] OR "colon"[All Fields] OR "crc"[All Fields]) AND ("test*"[All Fields] OR ("genotype"[MeSH Terms] OR "genotyping"[All Fields])) AND ("economics"[MeSH Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR ("cost effectiveness analysis"[MeSH Terms] OR ("cost effectiveness"[All Fields] AND "analysis"[All Fields]) OR "cost effectiveness analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields]) OR "economic*"[All Fields] OR "ICER"[All Fields] OR "cost-utility"[All Fields]) |
| Web of Science | TS= ("DPYD") AND TS=("colorectal" OR "colon" OR “CRC”) AND TS= ("test*" OR "genotyping" OR “genotype”) AND TS= ("economic" OR “cost” OR "cost*effectiveness" OR (“cost” AND “effectiveness”) OR “cost*analysis” OR (“cost” AND “analysis”) OR “cost*effectiveness*analysis” OR (“cost” AND “effectiveness” AND “analysis”) OR "ICER" OR “cost-utility”) |
| Scopus | (TITLE-ABS-KEY(DPYD) AND TITLE-ABS-KEY (colorectal OR colon OR crc) AND TITLE-ABS-KEY (test* OR genotyping OR genotype) AND TITLE-ABS-KEY (cost OR cost*effectiveness OR (cost AND effectiveness) OR cost*effectiveness*analysis OR (cost AND effectiveness AND analysis) OR cost*analysis OR (cost AND analysis) OR icer OR economic* OR cost*utility)) |

**Table A3.** Full query for the economic impact review

## Annex III. Steering Committe Members – BRCA Case study

| | |
|---|---|
| Dr. Paolo Belli | Breast Radiology – Policlinico Gemelli |
| Dr. Alba Di Leone | Breast Surgery – Policlinico Gemelli |
| Dr. Marzia Salgarello | Plastic and Reconstructive Surgery – Policlinico Gemelli |
| Dr. Salvo Testa | MUTAGENS Foundation |
| Dr. Aldo Rosano | INAPP – National Institute for Public Policy Analysis" in English |
| Dr. Ivana Cattaneo | Executive Director Therapeutic Area Advocacy and Precision Medicine – Novartis |
| Dr. Emanuela Lucci Cordisco | Geneticist – Policlinico Gemelli |
| Dr. Alessia Tognetto | Prevention Department – ULSS 6 Veneto |

# Annex IV. Written Consultation Steering Committe - *BRCA* Case study

**Health Impact on the Population**

**Introduction**

The health impact of the policy on the population will be quantified using a comparative risk model. This model aims to calculate the health gain resulting from the full implementation of BRCA testing and subsequent preventive interventions across all regions and the eligible population, compared to the current state of implementation. To build the model, we will use estimates of the effectiveness of the test and preventive interventions collected from the literature, data on the eligible Italian population, and the current state of implementation. The missing data to date are:

- **Target Population**: We have data on the incidence of ovarian and breast cancer in Italy, but we need to establish how many of these cases are eligible for germline BRCA testing according to AIOM guidelines. With this information, we could estimate the impact of testing all eligible individuals according to current guidelines and the totality of diagnosed patients. Using estimates of mutation prevalence and family sizes (ISTAT), we will determine the number of eligible family members for testing.

- **Current State of Implementation**: To estimate the current state of implementation, the necessary data include:

  - The absolute number or percentage of patients with breast and ovarian cancer undergoing germline BRCA testing + the average number of family members tested per positive case;

  - Alternatively, the total number of germline BRCA tests conducted in Italy in a year.

Are you aware of ways to obtain these data? Or do you have suggestions on entities or individuals to contact regarding this?

**Organizational aspects**

**Access and Logistics of Multigenic (or Specific BRCA) Testing**

1. What are the general experiences regarding the test? Unfortunately, many hospital facilities still rely on monogenic tests, which are not always capable of detecting the diverse genetic alterations linked to cancers in various organs, including breast, ovary, prostate, pancreas, colorectal, and endometrium.

2. Who typically prescribes the test and/or genetic counseling?

3. What are the average waiting times for access to genetic counseling (pre-test & post-test)? What are the average waiting times to receive the test results?

**Waiting Times and Clinical Management**

1. Access to active surveillance for patients testing positive:

2. Does the partial presence of regional care pathways (PDTA) and specific exemption codes facilitate access to testing and active surveillance?

3. Should PDTAs and exemptions be standardized nationwide to ensure a homogeneous pathway?

4. Could strengthening multidisciplinary oncological groups (GOM) for hereditary-family cancers facilitate the surveillance-diagnosis-treatment pathway? If so, what interventions could improve their quality and effectiveness? Do you recommend a reference model?

5. Is access to prophylactic surgery (mastectomy and salpingo-oophorectomy) guaranteed for mutation carriers? If so, are there limitations related to these procedures under DRG 461 for BRCA 1/2 carriers (e.g., waiting lists, reimbursement, etc.)?

**Technological Support**

1. Are there computerized systems to manage mutation carriers?

2. If so, is there a single system, or are there multiple systems that do not communicate with each other?

**Patient Reactions and Implications**

1. What are the typical patient reactions to testing?

2. Is patient care activated in cases of positive results from a psychological perspective (as provided by guidelines and PDTAs)?

3. Should access to psychological support for family members be guaranteed before the test is conducted? If so, is this implemented?

4. Is psychological support access guaranteed for patients before undergoing preventive prophylaxis techniques? If so, is this implemented?

5. Is psychological support access guaranteed for patients undergoing preventive prophylaxis techniques (post-therapy accompaniment)? If so, is this implemented?

**Inequalities**

1. Do you believe there are inequalities in access to testing and subsequent preventive interventions? If so, are they driven by socio-economic or other factors?

**Open Comments**

# Annex V. Literature Review results on impact of preventive strategies - *BRCA* Case study

| Title | First Authors (Year), Country | Type of study | Objective | Key findings |
|---|---|---|---|---|
| *Prophylactic surgery* | | | | |
| **Effectiveness of Prophylactic Surgeries in BRCA1 or BRCA2 Mutation Carriers: A Meta-analysis and Systematic Review (49)** | Xia Li et al. (2016) | Systematic review with meta-analysis | Impact of BSO and BPM on cancer risk and mortality | Prophylactic bilateral salpingo-oophorectomy and bilateral prophylactic mastectomy were both associated with a decreased breast cancer risk in BRCA1/2 mutation carriers (RR, 0.552; 95% CI, 0.448-0.682; RR, 0.114; 95% CI, 0.041-0.317, respectively). BSO was associated with significantly lower all-cause mortality in BRCA1/2 mutation carriers without breast cancer (HR, 0.349; 95% CI, 0.190-0.639) and those with breast cancer (HR, 0.432; 95% CI, 0.318-0.588) |
| **Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review (53)** | M J Bermejo-Pérez et al. (2007) | Systematic review | Impact of BSO and active surveillance on braest and ovarian cancer risk and mortality | Mastectomy and prophylactic gynaecological surgery (oophorectomy or salpingo-oophorectomy) reduced breast and gynaecological cancer incidence in carriers of BRCA mutations, by comparison to surveillance. However, all the studies presented flaws in internal and external validity, none of these preventive interventions is risk-free, and protection against breast and gynaecological cancer, as well as other cancers linked to BRCA mutations, is incomplete. No studies comparing surveillance programmes of varying intensity were found |

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| **Risk assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force (58)** | USPSTF.<br>USA<br>(2019) | Guideline | Impact of mastectomy and oophorectomy on breast and ovarian cancer risk and mortality. | No studies evaluated the effectiveness of risk assessment, genetic counseling, and genetic testing in reducing incidence and mortality of BRCA1/2-related cancer. Mastectomy was associated with 90% to 100% reduction in breast cancer incidence (6 studies; n = 2546) and 81% to 100% reduction in breast cancer mortality (1 study; n = 639); oophorectomy was associated with 69% to 100% reduction in ovarian cancer (2 studies; n = 2108); complications were common with mastectomy. |
| **Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review (50)** | Ludwig et al.<br>USA<br>(2016) | Systematic review | Impact of BSO and BPM on cancer risk and mortality | Bilateral risk-reducing mastectomy provides a 90% to 95% risk reduction in BRCA mutation carriers, although the data do not demonstrate improved mortality. The reduction in ovarian and breast cancer risks using risk-reducing bilateral salpingo-oophorectomy has translated to improvement in survival. |
| **Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in** | Marchetti et al., Italy<br>2014 | Systematic review with meta-analysis | Impact of RRSO on ovarian cancer risk and mortality | In all published studies, the RRSO consistently reduced OC risk over exclusive control. The OC risk after RRSO expressed as HR was 0.19 (95% CI: 0.13 – 0.27, p <0.00001). The all-cause mortality benefit associated with RRSO was 0.32 (95% CI: 0.27 – 0.38, p <0.00001) for all population. Among patients with or without previous breast cancer the risk reduction of RRSO was similar, with a modest benefit |

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| **BRCA 1 and BRCA 2 mutation carriers (51)** | | | | in patients without history of breast cancer: 0.29 (95% CI: 0.19 – 0.46, p <0.00001) versus 0.32 (95% CI: 0.26-0.39, p <0.00001) |
| **Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review (52)** | Xiao et al., 2018 China | Systematic review with meta-analysis | Impacto of RRSO on breast cancer risk | RRSO was associated with a significant reduction in the incidence of BC in women with BRCA1/2 mutations who had no history of BC (HR = 0.58; 95% confidence interval [CI], 0.37 to 0.78). Even in women with a history of BC, RRSO could reduce the risk of recurrence (HR = 0.50; 95% CI, 0.31 to 0.69). |
| **Prophylactic mastectomy versus surveillance for the prevention of breast cancer in women's BRCA carrier (54)** | Hanold et al. 2018 Chile | Review | Impact of mastectomy and active surveillance on breast cancer risk and mortality | Prophylactic mastectomy is associated with frequent adverse effects, but probably reduces the incidence of breast cancer RR 0.05 (0.02 to 0.1) and decreases mortality RR 0.12 (0.04 to 0.36) compared to active surveillance. |
| **AIOM (Italian Association of Medical Oncology) Linee Guida. Carcinoma Mammario in Stadio Precoce. Edizione 2023 (10)** | AIOM, Italy 2023 | Guideline | Impact prophylactic surgery on breast and ovarian cancer risk | The only approach proven to significantly reduce the risk of developing breast cancer is prophylactic surgery. It is estimated that bilateral prophylactic mastectomy, involving the removal of the breast glands, can reduce the risk of developing breast cancer by 90-100%. A meta-analysis of 10 studies conducted on BRCA-mutated |

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| | | | | patients showed an approximately 80% reduction in the risk of ovarian cancer following bilateral salpingo-oophorectomy |
| *Active Surveillance* | | | | |
| **Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis (80)** | Phi et al. 2016 | Individual patient meta-analysis | Additional contribution of mammography to screening accuracy in BRCA1/2 mutation carriers screened with MRI | In BRCA1/2 mutation carriers of all ages (BRCA1 = 1,219 and BRCA2 = 732), adding mammography to MRI did not significantly increase screening sensitivity (increased by 3.9% in BRCA1 and 12.6% in BRCA2 mutation carriers, P > 0.05). However, in women with BRCA2 mutation younger than 40 years, one-third of breast cancers were detected by mammography only. Number of screens needed for mammography to detect one breast cancer not detected by MRI was much higher for BRCA1 compared with BRCA2 mutation carriers at initial and repeat screening |
| **Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age ≥ 50 years: evidence from an individual patient data meta-analysis (81)** | Phi et al. 2014 | Individual patient meta-analysis | MRI and mammography screening accuracy | In women age ≥ 50 years, combining MRI and mammography significantly increased screening sensitivity compared with mammography alone (94.1%; 95% CI, 77.7% to 98.7% v 38.1%; 95% CI, 22.4% to 56.7%; P < .001). The combination was not significantly more sensitive than MRI alone (94.1%; 95% CI, 77.7% to 98.7% v 84.4%; 95% CI, 61.8% to 94.8%; P = .28). |

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|---|---|---|---|---|
| **Risk assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force (58)** | USPSTF.<br>USA<br>(2019) | Guideline | Impact of MRI and mammography screening | No effectiveness trials of intensive screening for breast or ovarian cancer in *BRCA1/2* mutation carriers that report cancer or mortality outcomes have been published. In 2 studies including 1364 *BRCA1/2* mutation carriers, sensitivity of screening for breast cancer was 63% to 69% for MRI, 25% to 62% for mammography, and 66% to 70% for combined modalities; specificity was 91% or higher for either modality alone or combined a study of 459 *BRCA1/2* mutation carriers, sensitivity of screening for ovarian cancer was 43% for TVUS, 71% for CA-125, and 71% for combined modalities; specificity was 99% for either modality alone or combined. |
| **Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology (57)** | NCCN.<br>USA<br>2021 | Guideline | MRI and mammography screening accuracy | Prospective studies on comparative surveillance modalities in women at high risk for familial breast cancer have consistently reported higher sensitivity of MRI screening (77%–94%) compared with mammography (33%–59%) in detecting breast cancers. False-positive rates were higher with MRI in some reports, resulting in a slightly lower or similar specificity with MRI screening (81%–98%) compared with mammography (92%–100%). |
| **AIOM (Italian Association of Medical Oncology) Linee Guida. Carcinoma Mammario in Stadio Precoce. Edizione 2023 (10)** | AIOM,<br>Italy<br>2023 | Guideline | Impact MRI screening | Annual MRI may result in a higher rate of false positives, but when combined with mammography, it achieves a sensitivity close to 100%737–741. However, the impact of breast MRI on breast cancer mortality within surveillance strategies has yet to be demonstrated. |

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|---|---|---|---|---|
| **MRI Surveillance and Breast Cancer Mortality in Women With *BRCA1* and *BRCA 2* Sequence Variations (55)** | Lubinski et al. 2024 | Cohort study | Impact of MRI annual surveillance on breast cancer mortality | After a mean follow-up of 9.2 years, 344 women (13.8%) developed breast cancer and 35 women (1.4%) died of breast cancer. The age-adjusted HRs for breast cancer mortality associated with entering an MRI surveillance program were 0.20 (95% CI, 0.10-0.43; *P* < .001) for women with *BRCA1* sequence variations and 0.87 (95% CI, 0.10-17.25; *P* = .93) for women with *BRCA2* sequence variation |

# Annex VI. Literature Review results on patients wellbeing - *BRCA Case study*

| Title | First Authors (Year), Country | Type of study | Impact | Key findings |
|---|---|---|---|---|
| **The impact of risk reducing bilateral salpingo-oophorectomy on sexual function in BRCA1/2 mutation carriers and women with Lynch syndrome: A systematic review and meta-analysis (63)** | Kershaw et al. 2021<br>UK | Systematic review with meta-analysis | Impact of RRBSO on sexual function | Fifteen of the 21 studies (71%) reported a negative impact of RRBSO on sexual function (SMD -0.63, [-0.82, -0.44], p = 0.03). There was a trend towards reduced sexual pleasure and increased discomfort but this did not reach statistical significance. There was minimal change in the frequency of sex. There was a significant increase in vaginal dryness post-RRBSO (SMD 9.25, [3.66, 14.83], p < 0.00001). There was no significant difference in sexual function between pre-menopausal and post-menopausal RRBSO. Hormone replacement therapy (HRT) did not abolish this negative impact. |
| **The psychological impact of breast and ovarian cancer preventive options in BRCA1 and BRCA2 mutation carriers (58)** | Borreani et al. 2014 | Cohort study | Psychological impact of surgical and surveillance preventive strategy | The longitudinal results indicated no clinically meaningful variations in the anxiety and depression scores in either of the two samples. Statistically significant reductions in cancer-risk perception emerged in women who chose surgery. In BRCA1/BRCA2 mutation carriers, surveillance does not influence their initial psychological condition, whereas prophylactic surgery has a significant impact in reducing the perceived risk and worry about getting sick. |

| | | | | |
|---|---|---|---|---|
| **Psychological aspects, risk and protective factors related to BRCA genetic testing: a review of the literature (59)** | Lombardi et al.<br>Italy<br>2019 | Systematic review | Impact of BRCA screening on distress, anxiety and depression. | Mutation carriers generally experience higher levels of anxiety and depression than non-carriers. Protective factors, such as pre-test education, family communication, and sibling exchanges, can reduce distress over time. Six studies reported increased anxiety and depression in mutation carriers, with elevated levels observed at 1, 3, and 6 months, returning to baseline by 6-12 months after test disclosure. Risk factors include a cancer diagnosis, sharing test results with family, being under 40, having an unoptimistic personality, and using suppression as an emotional regulation strategy. Protective factors also include pre-test education and decisions about preventive prophylaxis. |
| **How Psychophysical Stress Can Mediate the Effects of Anxiety and Depression on the Overall Quality of Life and Well-Being in Women Undergoing Hereditary Breast Cancer Screening( 60)** | Caruso et al.<br>2024<br>Italy | Survey | Mediation role of psychological distress on mental quality of life. | Path analyses revealed that psychophysical stress mediates the relationship between emotional distress and mental quality of life: higher anxiety and depression levels increase psychophysical stress, which lowers perceived mental quality of life and well-being. Depression emerged as the sole psychological predictor of physical quality of life. These findings highlight the importance of addressing anxiety and depression in genetic counseling to improve mental and overall well-being |
| **Coping Mechanisms, Psychological Distress, and Quality of Life** | Di Mattei et al.<br>Italy<br>2018 | Survey | Impact of pre-test genetic counselling on psychological distress | The results confirm that the genetic counseling procedure is not a source of psychological distress. Certain participants were identified as being more vulnerable than others; in the pre-test phase, they reported on average higher levels of distress and lower quality of life. |

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|---|---|---|---|---|
| **Prior to Cancer Genetic Counseling (61)** | | | | These participants were predominantly Ex-patients and Affected patients, who may be at risk of distress during the counseling process. |
| **Emotional impact on the results of BRCA1 and BRCA2 genetic test: an observational retrospective study (62)** | Mella et al.<br>Italy<br>2017 | Cross-sectional | Emotional state of positive woman 1 month after receiving the diagnosis | Anxiety was significantly higher than depression ($p < 0.001$), and 21.3% and 21.3% of the sample were, respectively, possible and probable cases for anxiety, whereas 13.5% and 10.1% were possible and probable cases for depression. Within the six mood states, Confusion-Bewilderment (M = 48.5) was the lowest, whereas Fatigue-Inertia (M = 52.3) was the highest. Differences were recorded within the ten assessed emotions too. Being a proband/nonproband and being or not a cancer patient were associated with many tested variables. |

# Annex VII. Literature review results on economic impact - *BRCA Case study*

| Title | First Authors (Year), Country | Type of study | Impact | Key findings |
|---|---|---|---|---|
| **Cost-Effectiveness of Targeted Genetic Testing for Breast and Ovarian Cancer: A Systematic Review (64)** | Koldehoff et al., 2021 Germany | Systematic review | Cost-effectiveness | From a payer perspective, the ICERs of (1) BRCA screening for high-risk women without cancer ranged from dominating the no test strategy to an ICER of $21 700/QALY. In studies that evaluated (2) BRCA cascade screening (ie, screening of women with cancer plus their unaffected relatives) compared with no test, the ICERs were between $6500/QALY and $50 200/QALY. Compared with BRCA alone, (3) multigene testing in women without cancer had an ICER of $51 800/QALY (one study), while for (4) multigene-cascade screening the ICERs were $15 600/QALY, $56.500/QALY, and $69 600/QALY for women in the United Kingdom, Norway, and the United States, respectively (2 studies) |
| **Cost-effectiveness and comparative effectiveness of cancer risk management strategies in BRCA1/2 mutation carriers: a systematic review (68)** | Petelin et al., 2018 Australia | Systematic review | Cost-effectiveness | Combined risk-reducing salpingo-oophorectomy and prophylactic mastectomy resulted in the greatest LE and was cost-effective in most analyses. Despite leading to increased LE and QALYs, combined mammography and breast magnetic resonance imaging (MRI) was less likely to be cost-effective than either mammography or MRI alone, particularly for women over 50 and BRCA2 carriers. Variation in patient |

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| | | | | compliance to risk management interventions was incorporated in 11/34 studies with the remaining analyses assuming 100% adherence. |
| **Which BRCA genetic testing programs are ready for implementation in health care? A systematic review of economic evaluations (65)** | D'Andrea et al. 2016, Italia | Systematic review | Cost-effectiveness | Most genetic testing programs result in better health care, but usually at a higher cost, and save money only in a small minority of cases. Population-based BRCA1/2 testing is currently too expensive, costing over $1 million per QALY gained even with prophylactic surgeries for all mutation carriers.<br>Family history (FH)-based screening, which involves testing high-risk individuals and cascade testing relatives, shows promise but lacks complete economic evaluations. Key limitations include insufficient details on selecting high-risk women and the costs of cascade screening.<br>Cancer-based genetic screening, which identifies index cases among women with breast/ovarian cancer, can be cost-effective under specific conditions. More recent studies offering tests to affected women under certain age thresholds showed better cost-effectiveness when paired with prophylactic interventions for identified carriers. |
| **A cost-effectiveness analysis of an integrated clinical-radiogenomic screening program for the identification of** | Di Pilla et al. 2024 Italy | Cost-Effectiveness analysis | Cost-effectiveness | The clinical criteria/family history approach, referred to as the established clinical model, served as the baseline for comparison. The clinical-radiogenomic model, which integrates clinical criteria and a radiogenomic model with 49% sensitivity and 87% specificity, increased BRCA carrier detection by 41.8% and reduced BRCA-related cancer rates by 23.7% compared to the established clinical model, with a cost increase of €2.51 per person per year over a 62-year observation |

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| **BRCA 1/2 carriers (e-PROBE study) (66)** | | | | period. Its incremental cost-effectiveness ratio (ICER) was estimated at €3800 per year of healthy life expectancy gained. The improved clinical-radiogenomic model, which simulated enhanced performance of the radiogenomic component (80% sensitivity and 95% specificity), achieved a 68.3% increase in BRCA carrier detection and a 38.4% reduction in BRCA-related cancer rates compared to the established clinical model, with a cost increase of €0.7 per person per year. This approach demonstrated an ICER of €653 per year of healthy life expectancy gained |
| **A cost-minimization analysis of a preventive testing strategy for relatives of patients with *BRCA* mutated ovarian cancer (67)** | Di Brino et al., 2020<br>Italy | Cost-minimization analysis | Economic impact | Considering an average cost of therapy for breast and ovarian cancer major of €90,000.00 per case, the economic impact related to the preventive testing strategy are equal to –€17,814,767.25. The sensitivity analysis confirms these results in the totality of the simulations performed. Preventive genetic testing in relatives of patients affected by ovarian cancer is cost-effective and represents a sustainable cost for the National Healthcare System in Italia, also in the light of its reference values |

# Annex VIII. Literature review results on organizational impacts - *BRCA Case study*

| Title | First Authors (Year), Country | Type of study | Impact | Key findings |
|---|---|---|---|---|
| **A regional population-based hereditary breast cancer screening tool in Italy: First 5-year results (74)** | Cortesi et al., 2020<br>Italy | Retrospective observational study | Participation to the genetic counselling of woman at high risk based on family history. | 60 040 women were evaluated by the regional screening program, of which 22 289 (3.5%) were invited to the Spoke evaluation, but only 5615 accepted (25.2%). Totally, also considering women sent by GPs and specialists, 11 667 were assessed and 5554 were sent to the Hub evaluation. Finally, 2342 (42.8%) women fulfilled the criteria for genetic testing, and 544 (23.2%) resulted BRCA1/2 mutation carriers |
| **Referral of Ovarian Cancer Patients for Genetic Counselling by Oncologists: Need for Improvemen (75)** | Ricci et al. 2015<br>Italy | Retrospective observational study | Feasibility and consequences of offering genetic counselling to all ovarian cancer patients during routine oncology appointments. | Out of 104 women diagnosed with ovarian cancer undergoing an oncology visit, 94 had not had genetic counselling in the past. Twenty-nine patients (29/94, 31%) were referred to the Unit of Hereditary Cancer; of these, 14/26 (54%) were referred at the first visit and 15/68 (22%) at the follow-up visit ($p = 0.003$). Most referred women attended genetic counselling (22/29, 76%) and had BRCA genetic testing (21/22, 95%). Four BRCA1 mutations were detected (4/21, 19%). |
| **Genetic counselling legislation and practice** | McCary et al. 2024<br>EU | Review | Presence of regulations on genetic counselling | The two main document that regulate genetic consulling in italy are: Law General Authorisation No. 8/2014 for the Processing of Genetic Data (2014 and Guidelines for Medical Genetics (2004) that specifies |

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| **in cancer in EU Member States (69)** | | | | role for medical geneticists in improving genetic literacy of population. The most important change that could/will be made to improve genetic counselling identified by the italian rapresentative was the recognition of genetic counsellors as a healthcare profession. |
| **BRCA Testing for Patients Treated in Italy: A National Survey of Breast Centers Associated with Senonetwork. (70)** | Tinterri et al., 2024 Italy | Survey | Challenges in BRCA test | The majority of the analyzed BUs face challenges in BRCA testing procedures (53.2%), including obstacles for cost and reimbursement (11.9%), reporting timelines (35.7%), and pre-test counseling availability (13.8%). In the majority of BUs (78.9%), the mainstream-consent approach for genetic counseling is routinely conducted, usually led by medical oncologists (85.3%) and breast surgeons (67.9%). 70.6% of centers performed the test before surgery, 24.8% during early-stage treatment, and 4.6% at metastatic recurrence. Most BUs (87.2%) acknowledged the need for urgent testing. For urgent pre-test genetic counseling, including mainstream consent, 56.0% of centers arranged counseling within a week, 34.9% within 2–3 weeks, and 9.1% in over three weeks. In urgent cases, 55.1% reported a turnaround time of less than 21 days, 44.0% between 21–40 days, and 0.9% between 40–60 days from blood submission to test results.. |
| **Guidance Statement On BRCA1/2 Tumor Testing in Ovarian Cancer Patients (71)** | Catopolugo et al., 2024 Italy | Survey | Access and timing of BRCA test. | 70.6% of centers performed the test before surgery, 24.8% during early-stage treatment, and 4.6% at metastatic recurrence. Most BUs (87.2%) acknowledged the need for urgent testing. For urgent pre-test genetic counseling, including mainstream consent, 56.0% of centers arranged counseling within a week, 34.9% within 2–3 weeks, |

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| | | | | and 9.1% in over three weeks. In urgent cases, 55.1% reported a turnaround time of less than 21 days, 44.0% between 21–40 days, and 0.9% between 40–60 days from blood submission to test results.. |
| **Survey on knowledge, attitudes, and training needs of Italian residents on genetic tests for hereditary breast and colorectal cancer (72)** | Panic et al.<br>2014<br>Italy | Survey | Knowledge and attitudes towards genetic tests for breast and CRC of Italian residents | Approximately 70% and 20% of residents correctly answered over 80% of questions on breast and CRC tests, respectively. Knowledge of breast cancer tests was higher among those who attended cancer genetic testing courses during graduate training (OR: 1.72; 95% CI: 1.05-2.82) and lower among males (OR: 0.55; 95% CI: 0.35-0.87). For CRC, knowledge was greater among those who attended cancer genetic testing courses (OR: 2.08; 95% CI: 1.07-4.03) or postgraduate courses in epidemiology and evidence-based medicine (OR: 1.95; 95% CI: 1.03-3.69). Over 70% requested additional training on genetic tests for cancer during their specialization. |
| **Knowledge, attitudes and behavior of physicians regarding predictive genetic tests for breast and colorectal cancer (73)** | Marzuillo et al., 2013<br>Italy | Survey | Knowledge and attitudes towards genetic tests for breast and CRC of Italian Physician | A significant lack of knowledge was detected,. Less than half of the physicians agreed on the importance of efficacy and cost-effectiveness evidence in the selection of predictive genetic tests to be offered to the patients. Education had a positive influence on knowledge, attitudes and, to a lesser extent, professional use. The factor most strongly related to the physicians' use of genetic testing was patients requests for breast. A high level of interest for specific training was reported by almost all physicians surveyed. |

# Annex IX. Literature review results on impact patients' satisfaction and knowledge – *BRCA* Case study

| Title | First Authors (Year), Country | Type of study | Impact | Key findings |
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| **Satisfaction with prophylactic risk-reducing salpingo-oophorectomy in BRCA mutation carriers is very high and little dependent on the participants' characteristics at surgery: a prospective study (76)** | Grandi et al.<br>Italy<br>2021 | Cohort study | Level of satisfaction of women undergoing RRSO | Would you undergo RRSO again if it was proposed today? (0-100 visual analog scale points)" the answer was 99.4 ± 3.2 points (range 79-100). These scores were in general very high and did not change in the different groups according to pre/postmenopausal status at RRSO, cancer survivors versus healthy women at RRSO, BRCA status, hormone therapy users/nonusers after RRSO, "RRSO-caused" symptoms versus not RRSO-caused (P > 0.05). |
| **Are young women ready for BRCA testing? Comparing attitudes and comprehension of two** | Gavaruzzi et al.<br>Italy<br>2019 | Survey | Risk understand information about BRCA testing in young (18-24) versus adult (30-45) women | Younger women had a lower comprehension of important BRCA information; it was more difficult for young women to identify the risk figures of cancer, and they showed errors when answering open-ended questions. |

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| **age groups of healthy Italian women (78)** | | | | |
| **Experience with a nurse-driven genetic counseling pathway of Italian women with (77) uninformative BRCA test result[66]** | Blondeaux et al.<br>Italy<br>2023 | Survey | Experience and retention of information in women with an uninformative BRCA test result after genetic counselling | 280 women (93.6%) positively valued their experience with genetic counseling and 287 (96.0%) considered it helpful with 57.5% of them feeling reassured for themselves and their family. Information on the clinical implications of the test result was correctly retained and women acted accordingly. Overall, 252 women (87.8%) accurately reported their test result as normal/negative. Only 67 (22.4%) recognized that despite a normal BRCA test result, a low probability of a hereditary syndrome remains. Most women showed a poor ability to estimate cancer risk in BRCA mutation carriers and in the general population. |
| **Cascade testing in Italian Hereditary Breast Ovarian Cancer families: a missed opportunity for cancer prevention? (38)** | Trevisan et al.<br>Italy<br>2024 | Observational retrospective study | Level of uptake of cascade testing | The uptake of cascade testing was 22.8% (25.8%, Genoa; 19.9%, Bologna; OR=0.59:95%CI 0.43–0.82). It was strongly associated with female gender (OR=3.31, 95%CI 2.38–4.59), age≤70 years (<30years OR=3.48, 95%CI 1.85–6.56; 30–70 years OR=3.08, 95%CI 2.01–4.71), first-degree relationship with the proband (OR=16.61, 95%CI 10.50-26.28) and segregation of the PV in both the maternal (OR=2.54, 95%CI 1.72–3.75) and the paternal branch (OR=4.62, 95%CI 3.09–6.91). |
| **Intrafamilial communication of hereditary breast and ovarian cancer genetic information in Italian** | Di Pietro et al.<br>Italy<br>2020 | Survey | Factors influencing intrafamilial disclosure of genetic information, and perceived | Among those with a positive BRCA test result, 49% intended to communicate it to their offspring and 27% to their husband/partner. Spontaneous/sincere or open/profound family communication and joyful/happy familial relationships were associated with the decision to undergo genetic testing as a responsibility towards relatives. |

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| **women: towards a personalised approach (79)** | | | understanding of information received by counselees during genetic counselling | Women had a good understanding of counselling contents (mean score 9.27 in a scale 1–10). |

# Annex X. Steering Committee Members – PGx Case study

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| Erika Cecchin | Centro di riferimento Oncologico di Aviano |
| Amelia Filippeli | Università degli studi di Salerno |
| Marzia del Re | Azienda Ospedaliero Universitaria Pisana |
| Domenico Coviello | Ospedale Gaslini |
| Maurizio Simmaco | Ospedale Sant'Andrea |
| Michele Lepore | Università Cattolica del Sacro Cuore |
| Gennaro De Pascale | Università Cattolica del Sacro Cuore |
| Mario Rosario D'Andrea | Ospedale San Paolo Civitavecchia |
| Massimiliano Berretta | Università di Messina |
| Giovanna Liuzzo | Università Cattolica del Sacro Cuore |
| Gabriele Sani | Università Cattolica del Sacro Cuore |
| Fiorella Gurrieri | Campus Biomedico di Roma |

# Annex XI. Written Consultation Steering Committee – PGx Case study

**Health Impact Assessment of the Implementation of a Pharmacogenetic Passport in Italy Steering Committee Consultation**

To evaluate the potential impact of implementing the pharmacogenetic passport in Italy, our technical group is collecting data and information through scientific literature reviews and consultations with experts and stakeholders.
As members of the Steering Committee, we kindly ask you to provide your opinions on some key points regarding the implementation of this approach in Italy.

We have included a series of questions to guide the collection of your contributions. We kindly ask you to share your opinions on these topics, or if you have any materials or contacts that could help explore these aspects. Additionally, you can include free comments at the end of the document.

1. **In your opinion, on which population should the pharmacogenomic panel be conducted (e.g., the entire population, individuals undergoing polypharmacotherapy, geriatric population, pediatric population, etc.)? And in what healthcare setting (e.g., primary care physicians, hospital admissions, etc.)?**

2. **Do you think further research initiatives are necessary to implement the passport in Italy?**

3. **Regarding the development of guidelines for the use of the panel, who should lead the process, and which professionals need to be involved? From an organizational perspective, what actions are necessary to implement the panel (e.g., laboratory capacity, equipment, personnel, data integration, etc.)?**

4. **Regarding training, do you think specific training activities are necessary to effectively implement the technology? If so, who should be targeted?**

5. **What do you consider the main barriers (clinical practice, organizational, economic, etc.) to implementing the passport in Italy?**

6. **Do you believe there are particularly vulnerable populations that could be positively or negatively impacted by the implementation of the passport?**

## Annex XII - Clinical impacts of drug-gene interactions according to the Dutch Pharmacogenetics Working Group (2019) guidelines – PGX Case Study

| Allele:drug | Rational | References |
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| *HLA-B*5701*: abacavir | 48% of the HLA-B*5701-positive patients develop a severe and potentially life-threatening hypersensitivity reaction to abacavir. Abacavir is contra-indicated for HLA-B*5701-positive patients. | Swen, J J et al., 2011 |
| *VKORC1 -1639 AA*: acenocoumarol | An INR ≥ 6, resulting in an increased risk of bleeding, occurs in 8-12% of these patients during the first weeks of treatment with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to acenocoumarol. | Swen, J J et al., 2011 |
| *CYP2D6 IM*: amitriptyline | The risk of side effects is increased, because the gene variation leads to higher plasma concentrations of the active metabolite nortriptyline and to a lesser extent of amitriptyline. | Swen, J J et al., 2011 |
| *CYP2D6 PM*: amitriptyline | In theory, risk of side effects is increased, because the genetic variation results in higher plasma concentrations of the active metabolite nortriptyline and to a lesser extent of amitriptyline. | Swen, J J et al., 2011 |
| CYP2D6 UM: amitriptyline | The risk of ineffectiveness is increased and the risk of cardiotoxic side effects may be increased. The gene variation leads to increased conversion of amitriptyline and the active metabolite nortriptyline to less active and inactive metabolites. | Swen, J J et al., 2011 |
| Fact. V Leiden heterozyg: anticoncept. met oestr. | The heterozygously present genetic polymorphism “factor V Leiden” causes an increased tendency to coagulation, resulting in an increased risk of venous | Swen, J J et al., 2011 |

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| | thromboembolism. Contraceptives containing oestrogens can increase this risk even further. | |
| Fact. V Leiden homozyg: anticoncept. met oestr | The homozygously present genetic polymorphism “factor V Leiden” causes an increased tendency to coagulation, resulting in an increased risk of venous thromboembolism. Contraceptives containing oestrogens can increase this risk even further. | Swen, J J et al., 2011 |
| *CYP2D6 PM*: aripiprazol | The risk of side effects is increased. The genetic variation leads to an increase in the sum of the plasma concentrations of aripiprazole and the active metabolite. | Beunk, Lianne et al., 2024; Swen, J J et al., 2011 |
| *CYP2D6 IM*: atomoxetine | The genetic variation increases the plasma concentration of atomoxetine and can thereby reduce the dose requirement. | Nijenhuis, Marga et al., 2023; Swen, J J et al., 2011 |
| *CYP2D6 PM*: atomoxetine | The genetic variation increases the plasma concentration of atomoxetine and thereby the risk of side effects. | Nijenhuis, Marga et al., 2023; Swen, J J et al., 2012 |
| *CYP2D6 UM*: atomoxetine | The genetic variation results in an increased conversion of atomoxetine to the active metabolite 4-hydroxyatomoxetine, which has a much lower plasma concentration. As the plasma concentration of the active ingredients decreases as a result, this gene variation can result in reduced efficacy. | Nijenhuis, Marga et al., 2023; Swen, J J et al., 2013 |
| *SLCO1B1 521CC*: atorvastatine | The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy. | Brunham LR et al., 2012; Francesca Notarangelo M et al., 2012; Santos PC et al., 2012; Rodrigues AC et al., 2011; Puccetti L et al., 2010; Lee YJ et al., 2010; Voora D et al., 2009; |

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| | | Mega JL et al., 2009; He YJ et al., 2009; Pasanen MK et al., 2008; Pasanen MK et al., 2007; Hermann M et al., 2006; Thompson JF et al., 2005. |
| *SLCO1B1 521TC*: atorvastatine | The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy. | Brunham LR et al., 2012; Francesca Notarangelo M et al., 2012; Santos PC et al., 2012; Rodrigues AC et al., 2011; Puccetti L et al., 2010; Lee YJ et al., 2010; Voora D et al., 2009; Mega JL et al., 2009; He YJ et al., 2009; Pasanen MK et al., 2008; Pasanen MK et al., 2007; Hermann M et al., 2006; Thompson JF et al., 2005. |
| *NUDT15* *IM*: azathioprine/mercaptopurine | Grade ≥ 2 leukopaenia occurs in 42% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of azathioprine and mercaptopurine. | Relling, Mary V et al., 2019 |
| *NUDT15* *PM*: azathioprine/mercaptopurine | Grade ≥ 2 leukopaenia occurs in 96% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of azathioprine and mercaptopurine. | Relling, Mary V et al., 2019 |

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| *TPMT IM:* azathioprine/mercaptopurine | The genetic variation reduces the conversion of azathioprine and mercaptopurine to mainly inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression. | Swen, J J et al., 2011 |
| *TPMT PM:* azathioprine/mercaptopurine | The genetic variation reduces the conversion of azathioprine and mercaptopurine to mainly inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression. | Swen, J J et al., 2011 |
| *CYP2D6 PM:* brexpiprazol | The risk of side effects is theoretically increased, because the gene variation reduces the metabolism of brexpiprazole. | Beunk, Lianne et al., 2024; Swen, J J et al., 2011 |
| *CYP2C19 IM*: citalopram | The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset. | Brouwer, Jurriaan M J L et al., 2022 |
| *CYP2C19 PM*: citalopram | The risk of QT prolongation and therefore also the theoretical risk of torsades de pointes is increased as the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the increased risk of QT prolongation will be offset. | Brouwer, Jurriaan M J L et al., 2023 |
| *CYP2C19 UM*: clomipramine | The gene variation increases the risk of ineffectiveness for obsessive compulsive disorder and anxiety disorders by reducing the plasma concentration of clomipramine. The gene variation has little to no effect on the plasma concentration of clomipramine+desmethylclomipramine, which determines the efficacy for depression and side effects. | de Vos, A et al., 2011 |

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| *CYP2D6 IM*: clomipramine | The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of clomipramine and the active metabolite desmethylclomipramine. | Swen, J J et al., 2011 |
| *CYP2D6 PM*: clomipramine | The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of clomipramine and the active metabolite desmethylclomipramine. | Swen, J J et al., 2012 |
| *CYP2D6 UM*: clomipramine | The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of clomipramine and the active metabolite desmethylclomipramine and to increased concentrations of the potentially cardiotoxic hydroxy metabolites. | Swen, J J et al., 2013 |
| *CYP2C19 IM*: clopidogrel | The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, as the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been observed in other patients. | Swen, J J et al., 2011 |
| *CYP2C19 PM*: clopidogrel | The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, because the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been proved in other patients. | Swen, J J et al., 2012 |
| *CYP2D6 PM:* codeine | The genetic variation reduces the conversion of codeine to morphine. This can result in reduced analgesia. | Matic, Maja et al., 2022; Swen, J J et al., 2011 |

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| *CYP2D6 IM*: codeine | The genetic variation reduces the conversion of codeine to morphine. This can result in reduced analgesia. | Matic, Maja et al., 2022; Swen, J J et al., 2012 |
| *CYP2D6 UM*: codeine | The genetic variation increases the conversion of codeine to morphine. This can result in an increase in side effects. Death has occurred in children who received analgesic doses. One adult with reduced kidney function and co-medication with two CYP3A4 inhibitors became comatose after use of codeine for a cough. | Matic, Maja et al., 2022; Swen, J J et al., 2013 |
| *CYP2D6 IM*: doxepine | The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of doxepin and the active metabolite nordoxepin. | Swen, J J et al., 2011 |
| *CYP2D6 PM*: doxepine | The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of doxepin and the active metabolite nordoxepin. | Swen, J J et al., 2011 |
| *CYP2D6 UM:* doxepine | The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of doxepin and the active metabolite nordoxepin and an increase in the plasma concentrations of the potentially cardiotoxic hydroxy metabolites. | Swen, J J et al., 2011 |
| *CYP2B6 IM*: efavirenz | Genetic variations increase the efavirenz plasma concentration and therefore the risk of side effects. However, the efavirenz plasma concentration remains within the therapeutic range for the majority of patients. | Vujkovic M et al., 2017; Leger P et al., 2016; Cusato J et al., 2016; Dickinson L et al., 2016; Swart M et al., 2016; Meng X et al., 2015; Haas DW et al., 2014; Martín AS et al., 2014; Bertrand J et al., |

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| | | 2014; Sarfo FS et al., 2014; Ngaimisi E et al., 2013; Yimer G et al., 2012; Mugusi S et al., 2012; Wyen C et al., 2011; Carr DF et al., 2010; Gatanaga H et al., 2007; Haas DW et al., 2005. |
| *CYP2B6 PM*: efavirenz | Genetic variations increase the risk of side effects. The standard dose leads to an efavirenz concentration in the toxic range in the majority of patients with this genotype. | Vujkovic M et al., 2017; Leger P et al., 2016; Cusato J et al., 2016; Dickinson L et al., 2016; Swart M et al., 2016; Meng X et al., 2015; Haas DW et al., 2014; Martín AS et al., 2014; Bertrand J et al., 2014; Sarfo FS et al., 2014; Ngaimisi E et al., 2013; Yimer G et al., 2012; Mugusi S et al., 2012; Wyen C et al., 2011; Carr DF et al., 2010; Gatanaga H et al., 2007; Haas DW et al., 2005. |
| *CYP2D6 IM*: eliglustat | This gene variation reduces the conversion of eliglustat to inactive metabolites. However, in the absence of CYP2D6 and CYP3A inhibitors, this does not result in a clinically significant increased risk of side effects. | SPC's Cerdelga (Nederland en VS) |

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| *CYP2D6 PM*: eliglustat | This gene variation reduces the conversion of eliglustat to inactive metabolites. This increases the risk of side effects, such as a (small, dose-dependent) elongation of the QT interval. CYP3A inhibitors increase this risk even further. | SPC's Cerdelga (Nederland en VS) |
| *CYP2D6 UM*: eliglustat | This gene variation increases the conversion of eliglustat to inactive metabolites. As a result, a normal dose is not effective. There is not enough scientific substantiation to suggest an effective dose for all UM. | SPC's Cerdelga (Nederland en VS) |
| *CYP2C19 PM*: escitalopram | The risk of conversion to another antidepressant is increased. In addition, the risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration, the theoretically increased risk of QT prolongation and the increased risk of conversion to another antidepressant will be offset. | Brouwer, Jurriaan M J L et al., 2022; Swen, J J et al., 2013 |
| *CYP2C19 UM*: escitalopram | The risk of conversion to another antidepressant is increased as the gene variation leads to a reduction in the escitalopram plasma concentration. | Brouwer, Jurriaan M J L et al., 2022; Swen, J J et al., 2014 |
| *VKORC1 -1639 AA*: fenprocoumon | An INR ≥ 6, resulting in an increased risk of bleeding, occurs in 17% of these patients with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to phenprocoumon. | Swen, J J et al., 2011 |
| *CYP2C9 IM*: fenytoine | Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. | Swen, J J et al., 2011 |
| *CYP2C9 PM*: fenytoine | Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. | Swen, J J et al., 2012 |
| *CYP2C9*1/*3*: fenytoine | Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects | Swen, J J et al., 2011 |

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| | Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients. | |
| *CYP2C9*2/*2*: fenytoine | Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. | Swen, J J et al., 2011 |
| *CYP2C9*3/*3*: fenytoine | Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients. | Swen, J J et al., 2011 |
| *CYP2D6 IM*: flecainide | The genetic variation reduces conversion of flecainide to inactive metabolites. This may increase the risk of side effects. | Swen, J J et al., 2011 |
| *CYP2D6 PM:* flecainide | The genetic variation reduces conversion of flecainide to inactive metabolites. This increases the risk of side effects. | Swen, J J et al., 2012 |
| *CYP2D6 UM*: flecainide | The genetic variation increases conversion of flecainide to inactive metabolites. A higher dose is possibly required as a result. | Swen, J J et al., 2011 |
| *HLA-B*5701*: flucloxacilline | HLA-B*5701-positive patients have an 80-fold elevated risk of flucloxacillin-induced liver injury. However, the incidence is low (1-2 per 1000 individuals). | Daly, Ann K et al., 2009; Vera, Jaime H et al., 2013; Phillips, Elizabeth J, and Simon A Mallal., 2013 |
| *DPD AS 0*: fluorouracil cutaan | The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2011 |

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| *DPD AS 1,5:* fluorouracil/capecitabine | The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2012 |
| *DPD AS 1*: fluorouracil/capecitabine | The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2011 |
| *DPD FENO:* fluorouracil/capecitabine | The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2011 |
| *DPD AS 0:* fluorouracil/capecitabine, systemic | The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the standard dose is a more than 100-fold overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2011 |
| *CYP2D6 PM*: haloperidol | The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased plasma concentrations of haloperidol and the active metabolite. | Beunk, Lianne et al., 2024; Swen, J J et al., 2011 |
| *CYP2D6 UM*: haloperidol | The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause decreased plasma concentrations of haloperidol and the active metabolite reduced haloperidol. | Beunk, Lianne et al., 2024; Swen, J J et al., 2011 |
| *CYP2C19 IM*: imipramine | The risk of side effects is increased. The gene variation results in an increase in the plasma concentration of imipramine+desipramine. | Swen, J J et al., 2011 |
| *CYP2C19 PM*: imipramine | The risk of side effects is increased. The gene variation results in an increase in the plasma concentration of imipramine+desipramine. | Swen, J J et al., 2011 |

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| *CYP2D6 IM*: imipramine | The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of imipramine and desipramine. | Swen, J J et al., 2012 |
| *CYP2D6 PM*: imipramine | The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of imipramine and the active metabolite desipramine. | Swen, J J et al., 2012 |
| *CYP2D6 UM*: imipramine | The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of imipramine and the active metabolite desipramine and to increased plasma concentrations of the potentially cardiotoxic hydroxy metabolites. | Swen, J J et al., 2012 |
| *UGT1A1 *28/*28*: irinotecan | Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites. | Hulshof, Emma C et al., 2023; Swen, J J et al., 2011 |
| *UGT1A1 PM*: irinotecan | Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites. | Hulshof, Emma C et al., 2023; Swen, J J et al., 2011 |
| *CYP2C19 UM*: lansoprazol | The genetic variation may reduce lansoprazole plasma concentrations and therefore lansoprazole effectiveness. | Swen, J J et al., 2011 |
| *CYP2D6 IM*: metoprolol | The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia. | Swen, J J et al., 2011 |
| *CYP2D6 UM*: metoprolol | The gene variation increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target | Swen, J J et al., 2011 |

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| | dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart. | |
| *CYP2D6 IM*: nortriptyline | The risk of side effects may be increased, because the gene variation leads to an increased plasma concentration of nortriptyline. | Swen, J J et al., 2011 |
| *CYP2D6 PM*: nortriptyline | The risk of side effects may be increased, because the gene variation leads to an increased plasma concentration of nortriptyline. | Swen, J J et al., 2011 |
| *CYP2D6 UM*: nortriptyline | The risk of ineffectiveness and cardiotoxic effects may be increased. The gene variation leads to a decrease in the plasma concentration of nortriptyline and an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxynortriptyline. | Swen, J J et al., 2011 |
| *CYP2C19 UM*: omeprazol | The genetic variation may lead to a reduced omeprazole plasma concentration and therefore reduced effectiveness. | Swen, J J et al., 2011 |
| *CYP2C19 UM*: pantoprazolo | La variazione genetica può ridurre le concentrazioni plasmatiche di pantoprazolo e quindi l'efficacia del pantoprazolo. | Swen, J J et al., 2011 |
| *CYP2D6 UM*: paroxetine | Efficacy will probably be lacking. The genetic variation increases the conversion of paroxetine. | Brouwer, Jurriaan M J L et al., 2022; Swen, J J et al., 2014 |
| *CYP2D6 IM*: pimozide | Il rischio di prolungamento del QT – e quindi anche il rischio di torsade de pointes – è teoricamente aumentato, perché la variazione genetica porta a un aumento della concentrazione plasmatica di pimozide. Il rischio di una concentrazione plasmatica eccessivamente alta può essere evitato seguendo le raccomandazioni di dosaggio fornite di seguito. | Beunk, Lianne et al., 2024 |
| *CYP2D6 PM*: pimozide | The risk of QT-prolongation – and thereby also the risk of torsade de points – is theoretically increased, because the genetic variation results in an increase | Beunk, Lianne et al., 2024 |

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| | in the plasma concentration of pimozide. The risk of an excessively high plasma concentration can be negated by following the dose recommendations provided below. | |
| *CYP2D6 IM*: propafenon | Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This may increase the risk of side effects. | Swen, J J et al., 2011 |
| *CYP2D6 PM*: propafenon | Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of side effects. | Swen, J J et al., 2011 |
| *CYP2D6 UM*: propafenon | Genetic variation decreases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of reduced or no efficacy. | Swen, J J et al., 2011 |
| *CYP2C19 PM*: sertraline | The risk of side effects is increased. The gene variation leads to increased plasma concentrations of sertraline. | Brouwer, Jurriaan M J L et al., 2022; Swen, J J et al., 2014 |
| *SLCO1B1 521CC*: simvastatine | The genetic polymorphism leads to reduced simvastatin transport to the liver. This increases simvastatin plasma concentrations and therefore the risk of myopathy. | Hu M et al., 2012; Brunham LR et al., 2012; Sortica VA et al., 2012; Bailey KM et al., 2010; Voora D et al., 2009; Pasanen MK et al., 2008; SEARCH Collaborative Group et al., 2008; Pasanen MK et al., 2006; Ramsey LB et al., 2014. |

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| *SLCO1B1 521TC*: simvastatine | The genetic polymorphism leads to reduced simvastatin transport to the liver. This increases simvastatin plasma concentrations and therefore the risk of myopathy. | Hu M et al., 2012; Brunham LR et al., 2012; Sortica VA et al., 2012; Bailey KM et al., 2010; Voora D et al., 2009; Pasanen MK et al., 2008; SEARCH Collaborative Group et al., 2008; Pasanen MK et al., 2006; Ramsey LB et al., 2014. |
| *CYP3A5* heterozygote: tacrolimus | Genetic variation results in an increased conversion of tacrolimus to inactive metabolites and as a result a higher dose is required. Adjustment of the initial dose results in an increased chance of reaching a tacrolimus concentration within the target range before the start of therapeutic drug monitoring on day three. However, there is no direct evidence that this results in improved clinical results. | Swen, J J et al., 2011 |
| *CYP3A5* homozygote: tacrolimus | Genetic variation results in an increased conversion of tacrolimus to inactive metabolites and as a result a higher dose is required. Adjustment of the initial dose results in an increased chance of reaching a tacrolimus concentration within the target range before the start of therapeutic drug monitoring on day three. However, there is no direct evidence that this results in improved clinical results. | Swen, J J et al., 2011 |
| *CYP2D6 PM*: tamoxifen | This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness. | Swen, J J et al., 2011 |

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| *DPD AS 0*: tegafur | The gene variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur to inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2011 |
| *DPD AS 1,5*: tegafur | The gene variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur into inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2011 |
| *DPD AS 1:* tegafur | The gene variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur into inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2011 |
| *DPD FENO*: tegafur | The gene variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur to inactive metabolites means that the normal dose is an overdose. | Lunenburg, Carin A T C et al., 2020; Swen, J J et al., 2012 |
| *NUDT15 IM*: tioguanine | Grade ≥ 2 leukopaenia occurs in an estimated 40% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of tioguanine. | Zhu Y et al., 2018; Zhang AL et al., 2018; Yi ES et al., 2017; Kim H et al., 2017; Chao K et al., 2017; Yin D et al., 2017; Liang DC et al., 2016; Zhu X et al., 2016; Moriyama T et al., 2016; Yang JJ et al., 2015; Yang SK et al., 2014. |
| *NUDT15 PM*: tioguanine | Grade ≥ 2 leukopaenia occurs in an estimated 95% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of tioguanine. | Zhu Y et al., 2018; Zhang AL et al., 2018; Yi ES et al., 2017; Kim H et al., 2017; Chao K et al., 2017; Yin D et al., 2017; Liang DC et al., |

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| | | 2016; Zhu X et al., 2016; Moriyama T et al., 2016; Yang JJ et al., 2015; Yang SK et al., 2014. |
| *TPMT PM*: tioguanine | Genetic variation reduces conversion of thioguanine to inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression. | Swen, J J et al., 2011 |
| *CYP2D6 IM*: tramadol | The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia. | Matic, Maja et al., 2022 |
| *CYP2D6 PM*: tramadol | The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia. | Matic, Maja et al., 2022 |
| *CYP2D6 UM*: tramadol | The genetic variation increases the conversion of tramadol to a metabolite with a stronger opioid effect. This can result in an increase in potentially life-threatening side effects. | Matic, Maja et al., 2022 |
| *CYP2D6 IM*: venlafaxine | Ci sono indicazioni di un aumento del rischio di effetti collaterali e una ridotta probabilità di efficacia. La variazione genetica riduce la conversione della venlafaxina nel metabolita attivo O-desmetilvenlafaxina, mentre è stata trovata un'associazione tra alti rapporti O-desmetilvenlafaxina/venlafaxina e risposta senza effetti collaterali. | Beunk, Lianne et al., 2024; Swen, J J et al., 2011 |
| *CYP2D6 PM*: venlafaxine | There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found. | Beunk, Lianne et al., 2024; Swen, J J et al., 2012 |

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| *CYP2D6 UM*: venlafaxine | It may be difficult to adjust the dose for patients due to altered metabolism between venlafaxine and the active metabolite Odesmethylvenlafaxine. The gene variation increases the conversion of venlafaxine to O-desmethylvenlafaxine and reduces the sum of venlafaxine plus O-desmethylvenlafaxine. | Beunk, Lianne et al., 2024; Swen, J J et al., 2012 |
| *CYP2C19 IM*: voriconazol | The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects. | Swen, J J et al., 2011 |
| *CYP2C19 PM*: voriconazol | The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects. Initially, the risk of side effects is of particular interest. | Swen, J J et al., 2011 |
| *CYP2C19 UM*: voriconazol | The gene variation increases the conversion of voriconazole, which increases the risk of ineffectiveness. | Swen, J J et al., 2011 |
| *CYP2C9 IM*: warfarine | This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding. | Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; Stergiopoulos K et al., 2014; Yang J et al., 2013; Jorgensen AL et al., 2012; Lindh JD et al., 2009; Sanderson S et al., 2005. |
| *CYP2C9 PM*: warfarine | This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding. | Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; Stergiopoulos K et al., 2014; Yang |

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| | | J et al., 2013; Jorgensen AL et al., 2012; Lindh JD et al., 2009; Sanderson S et al., 2005. |
| *CYP2C9*1/*3*: warfarine | This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding. | Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; Stergiopoulos K et al., 2014; Yang J et al., 2013; Jorgensen AL et al., 2012; Lindh JD et al., 2009; Sanderson S et al., 2005. |
| *CYP2C9*2/*2*: warfarine | This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding. | Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; Stergiopoulos K et al., 2014; Yang J et al., 2013; Jorgensen AL et al., 2012; Lindh JD et al., 2009; Sanderson S et al., 2005. |
| *CYP2C9*2/*3*: warfarine | This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding. | Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; Stergiopoulos K et al., 2014; Yang J et al., 2013; Jorgensen AL et al., 2012; Lindh JD et al., 2009; Sanderson S et al., 2005. |
| *CYP2C9*3/*3*: warfarine | This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding. | Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; |

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| | | Stergiopoulos K et al., 2014; Yang J et al., 2013; Jorgensen AL et al., 2012; Lindh JD et al., 2009; Sanderson S et al., 2005. |
| *VKORC1 -1639 AA*: warfarine | The genetic variation results in increased sensitivity to warfarin. This results in an increase in the risk of excessively severe inhibition of blood clotting (INR > 4) during the first month of the treatment. | Zhang J et al., 2015; Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; Stergiopoulos K et al., 2014; Jin B et al., 2014; Yang J et al., 2013; Jorgensen AL et al., 2012; Yang L et al., 2010. |
| *CYP2D6 IM*: zuclopentixol | The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased zuclopentixol plasma concentrations. | Zhang J et al., 2015; Liao Z et al., 2015; Xu H et al., 2014; Franchini M et al., 2014; Stergiopoulos K et al., 2014; Jin B et al., 2014; Yang J et al., 2013; Jorgensen AL et al., 2012; Yang L et al., 2010. |
| *CYP2D6 UM*: zuclopentixol | The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased zuclopentixol plasma concentrations. | Beunk, Lianne et al., 2024; Swen, J J et al., 2011 |

*Source: https://api.pharmgkb.org/v1/preview/download/file/attachment/DPWG_August_2019.pdf, https://www.pharmgkb.org/guidelineAnnotations*

# Annex XIII – Literature review results on patients acceptability- PGx Case study

| Title | Authors (Year), Country | Type of study | Key findings |
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| **Measuring High-Risk Patients' Preferences for Pharmacogenetic Testing to Reduce Severe Adverse Drug Reaction: A Discrete Choice Experiment (35)** | Di Dong et al (2016), Singapore | Discrete choice experiment | Overall, the predicted take-up rate for the test is 65% at a price of SGD400. If the test was recommended by a physician or was chosen by most of the patients, the take-up rate for the test would increase by 8.5 and 1.5 percentage points, respectively. |
| **Attitudes on pharmacogenetic testing in psychiatric patients with treatment-resistant depression (36)** | McCarthy et al. (2020), USA | Survey | Testing reveals that subjects were largely positive about the use of genetic testing to guide pharmacological treatment and help plan their future. Most subjects showed only modest concerns about the impact on family, inability to cope with the results, and fear of discrimination. The severity of depression did not predict the concern expressed about negative outcomes. |
| **Public perceptions of pharmacogenomic services in Ireland - Are people with chronic disease more likely to want service availability than those without? A questionnaire study (37)** | O'Shea et al (2022) Ireland | Survey | After explaining pharmacogenomics to respondents, patients with chronic disease(s) were 2.17 times more likely ($p < 0.001$) to want pharmacogenomic services availability than those without existing conditions, adjusted for age and gender (driven by preferences of those with MMPP than those with single chronic disease). Respondents demonstrated a high level of interest and noted both the potential benefits and downsides of pharmacogenomic testing |
| **Healthcare provider and patient perspectives on the implementation of** | Kaur et al., (2018), Canada | Survey | 52% of patient respondents were aware of PGx testing, with a significant association between awareness and positive opinions toward PGx. Both healthcare providers and patients recognized the |

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| **pharmacogenetic-guided treatment in routine clinical practice (38)** | | | value of PoC PGx testing devices, with 98% of healthcare providers and 71% of patients believing PoC devices would improve the accessibility and implementation of PGx testing. |
| **Cancer patients acceptance, understanding, and willingness-to-pay for pharmacogenomic testing (39)** | Cuffe et al., (2014) | Survey | Among the 97% of 121 metastatic patients accepting chemotherapy, 97.4% wanted pharmacogenomic testing that could detect the risk of severe toxicity, accepting median incurred costs of $1000 (range $0-10,000) and turnaround time for results of 14 days (range 1-90 days). The majority of patients wanted to be involved in decision-making on pharmacogenomic testing; however, one in five patients lacked a basic understanding of pharmacogenomic testing. |
| **Assessment of patient perceptions of genomic testing to inform pharmacogenomic implementation (40)** | Ming Lee et al., (2017) USA | Qualitative study | Participants agreed that pharmacogenomics could inform prescribing and help identify problem prescriptions, but expressed concerns over insurance coverage and employment discrimination.. |

# Annex XIV – Literature Review Results on Organizational feasibility and challenges of pharmacogenetic testing – PGx Case study

| Title | Authors (Year), Country | Type of study | Key findings |
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| **Assessment of the pharmacogenomics educational environment in Southeast Europe (43)** | Pisanu et al. (2014), Italy | Survey | While a large proportion of residents and physicians acknowledged the utility of pharmacogenetic tests (93% and 79%, respectively), only a small percentage (16% of physicians and 7% of residents) felt confident in selecting and interpreting these tests based on their training. |
| **Attitudes about pharmacogenomic testing vary by healthcare specialty (44)** | Preys et al. (2023), USA | Survey | Data from 1002 physicians and 638 advance practice providers (APP) who completed the pre-education assessment and 578 physicians and 395 APPs who completed the post-education assessment were analyzed. A greater percentage of both Primary care practisioners (PCPs) and specialists reported feeling comfortable ordering PGx tests at post-education (67.6 and 55.8%, respectively; $p < 0.001$), with the increase being larger for PCPs Analyses of the perceived utility of PGx tests showed that providers in primary care were more likely to rate PGx testing as somewhat or very useful more often than providers in other specialties (89.6 vs 77.5% at pre-education, respectively; 95.1 vs 84.3% at post-education, respectively; both $p < 0.001$) |

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| **Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good (45)** | Kristi Krebs and Lili Milani (2019), Multiple Countries | Review | Surveys, which have been conducted for assessing the general situation among healthcare providers, have shown overall acceptance of the need for PGx testing. The results of different surveys show high percentages between 97.6% and 84.3% of healthcare professionals who believe in the concept of pharmacogenomics or find it relevant for clinical practice. However, when asked about the level of knowledge and readiness for interpretation of testing results, only between 10.3% and 14.1% felt adequately informed about pharmacogenomic testing. |
| **Ten-year experience with pharmacogenetic testing for *DPYD* in a national cancer center in Italy: Lessons learned on the path to implementation (46)** | Bignucolo et al. (2023) Italy | Report | *DPYD* diagnostic activity at the center has greatly evolved over the years, shifting gradually from a post-toxicity to a pre-treatment approach. Development of pharmacogenetic guidelines by national and international consortia, genotyping, and IT technology evolution have impacted *DPYD* testing uptake in the clinics. Nationwide test reimbursement together with recommendations by regulatory agencies in Europe and Italy in 2020 definitely changed the clinical practice guidelines of fluoropyrimidines prescription. |
| **Preemptive pharmacogenetic testing to guide chemotherapy dosing in patients with gastrointestinal malignancies: a qualitative study of barriers to implementation (47)** | Lau-Min et al. 2022 USA | Qualitative study: | Sixteen medical oncologists and nine oncology pharmacists interviewed cited as the main barriers of implementation a mistrust in evidence on PGx and a lack of knowledge of clinician the Clinicians cited a general lack of knowledge as a barrier that could impact not only their initial decision to perform PGx testing but also their ability to counsel patients on the risks, benefits, and alternatives to preemptive PGx-guided chemotherapy dosing |
| **Healthcare provider and patient perspectives on the implementation of pharmacogenetic-guided** | Gurvere et al., 2024 Canada | Survey | The results revealed that 64% of healthcare providers had some level of familiarity with PGx, however, PGx testing in clinical practice was low. The primary challenges identified by healthcare providers included limited access |

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| **treatment in routine clinical practice (48)** | | | to testing and lack of knowledge on PGx test interpretation. Both healthcare providers and patients recognized the value of PoC PGx testing devices, with 98% of healthcare providers and 71% of patients believing PoC devices would improve the accessibility and implementation of PGx testing. |

# Annex XV - Literature review results on Economic Impact – PGx Case study

| Title | Authors (Year), Country | Type of study | Key findings |
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| **A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions (52)** | Plumpton et al. (2016), UK | Systematic review | The study identifed 47 economic evaluation.. There was evidence supporting the cost effectiveness of testing for HLA-B*57:01 (prior to abacavir), HLA-B*15:02 and HLA-A*31:01 (prior to carbamazepine), HLA-B*58:01 (prior to allopurinol) and CYP2C19 (prior to clopidogrel treatment). Economic evidence was inconclusive with respect to TPMT (prior to 6-mercaptoputine, azathioprine and cisplatin therapy), CYP2C9 and VKORC1 (to inform genotype-guided dosing of coumarin derivatives), MTHFR (prior to methotrexate treatment) and factor V Leiden testing (prior to oral contraception). Testing for A1555G is not cost effective before prescribing aminoglycosides |
| **Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies: A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany (53)** | Plothner et al., (2016) Germany | Systematic review | This review identified 27 economic analyses exploring the cost-effectiveness of pharmacogenetic testing (PT)-guided therapies. The main findings highlighted that, in the majority of studies, PT-guided administration of an active ingredient was either cost-effective or resulted in cost savings. However, no general consensus was observed on the cost-effectiveness of test-guided therapies when applied independently of the indication for which the active ingredient was prescribed.<br>Most studies focused on the cost-effectiveness of targeted therapies in oncological settings. The cost-effectiveness of PT-guided |

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| | | | approaches was found to depend on several factors, including the prevalence of biomarkers, test costs, threshold values, the prevalence of adverse drug reactions (ADRs), and therapy response rates. Additionally, significant variability in cost-effectiveness was observed, both across different indications and within the same indication. Finally, the study perspective (e.g., societal, healthcare system, or payer) was noted to influence the results, underscoring the complexity of economic evaluations in this field.. |
| **Cost Effectiveness of Pharmacogenetic Testing for Drugs with Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines: A Systematic Review (**54) | Morris et al. (2022) USA | Systematic review | Of 108 studies evaluating 39 drugs, 77 (71%) showed pharmacogenomic (PGx) testing was cost-effective (CE) (n = 48) or cost-saving (CS) (n = 29); 21 (20%) were not cost-effective, and 10 (9%) had uncertain results. Clopidogrel was the most frequently studied drug (n = 23), with 22 studies demonstrating cost-effectiveness or cost-saving outcomes, followed by warfarin (n = 16), with 7 studies demonstrating cost-effectiveness or cost-saving results. Among 26 studies evaluating human leukocyte antigen (HLA) testing for abacavir (n = 8), allopurinol (n = 10), or carbamazepine/phenytoin (n = 8), 15 studies demonstrated cost-effectiveness or cost-saving outcomes. Similarly, nine of 11 antidepressant studies demonstrated cost-effectiveness or cost-saving results. The median Quality of Health Economic Studies (QHES) score indicated high-quality studies (median score 91; range 48-100). Overall, most studies evaluating the cost-effectiveness of pharmacogenomic testing favored its use, although limited data are available on the cost-effectiveness of preemptive and multigene testing across various disease states. |

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| **Cost-Effectiveness of Pharmacogenomics-Guided Prescribing to Prevent Gene-Drug-Related Deaths: A Decision-Analytic Model (55)** | van der Wouden, Cathelijne H et al., (2022), Netherlands | Cost-Effectiveness | For patients initiating one of seven drugs in a given year, costs for PGx-testing, interpretation, and drugs would increase by €21.4 million. Of these drug initiators, 35,762 (24.1%) would require an alternative dose or drug. PGx-guided prescribing would relatively reduce gene-drug related mortality by 10.6% (range per DGI: 8.1-14.5%) and prevent 419 (0.3% of initiators) deaths a year. Cost-effectiveness is estimated at €51,000 per prevented gene-drug-related death (range per DGI: €-752,000-€633,000). |
| **Cost-Utility Analysis of Pharmacogenetic Testing Based on CYP2C19 or CYP2D6 in Major Depressive Disorder: Assessing the Drivers of Different Cost-Effectiveness Levels from an Italian Societal Perspective (56)** | Carta et. Al, (2022) Italy | Cost-Utility | The models for CYP2C19 and CYP2D6 indicate that screening has an incremental cost-effectiveness ratio of 60,000€ and 47,000€ per quality-adjusted life year (QALY), respectively. The probabilistic sensitivity analysis shows that the treatments are cost-effective for a 75,000€ willingness to pay (WTP) threshold in 58% and 63% of the Monte Carlo replications, respectively. The post-hoc analysis highlights the factors that allow us to clearly discriminates poor cost-effectiveness from high cost-effectiveness scenarios and demonstrates that it is possible to predict with reasonable accuracy the cost-effectiveness of a genetic test and the associated therapeutic pattern. |
| **Cost-utility analysis and cross-country comparison of pharmacogenomics-guided treatment in colorectal cancer patients participating in the U-PGx PREPARE study (57)** | Fragoulakis et al., 2023 | Cost-Utility | The total cost of the study arm was estimated at €380 (~ US$416; 95%CI: 195-596) compared to €565 (~ US$655; 95%CI: 340-724) of control arm while the mean survival in study arm was estimated at 1.58 (+0.25) LYs vs 1.50 (+0.26) (Log Rank test, X2 = 4.219, df=1, p-value=0.04). No statistically significant difference was found in QALYs. ICER was estimated at €13418 (~ US$14695) per QALY, while the acceptability curve indicated that when the willingness-to-pay was |

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| | | | under €5000 (~ US$5476), the probability of PGx being cost-effective overcame 70%. The most frequent adverse drug event in both groups was neutropenia of severity grade 3 and 4, accounting for 82.6% of total events in the study arm and 65.0% in the control arm. Apart from study arm, smoking status, Body-Mass-Index and Cumulative Actionability were also significant predictors of total cost. Subgroup analysis conducted in actionable patients (7.9% of total patients) indicated that PGx-guided treatment was a dominant option over its comparator with a probability greater than 92%. In addition, a critical literature review was conducted, and these findings are in line with those reported in other European countries. |