PROPHET

a PeRsOnalized Prevention roadmap for the future HEalThcare

Task N° 3.2. Identification and validation of the best framework to appraise and adopt personalized preventive approaches (The PROPHET Framework)

THL, INSA (co-lead), DEB, UCSC, KU Leuven, UGENT

Astrid Vicente - Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisbon, Portugal

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Task N° 3.2. Identification and validation of the best framework to appraise and adopt personalized preventive approaches (The PROPHET Framework)

- The aim of this task is to **develop a Health Impact Assessment (HIA) framework for personalized prevention** policies based on genomic information, and understand how this tool can be used to better inform decision makers as a crucial element of the PROPHET Framework for appraisal personalized preventive approaches (D3.5).

- M10-M24 (June 2023 – to August 2024, 14 months)

HIA Process

Phases	Steps	Questions	Actions
Policy and program development for prospective assessments	Screening	Is HIA timely and adds value to the decison making process? Who should carry out the HIA? How to carry out the screening?	Contact stakeholders and decision-makers Identify necessary resources
	Scoping	What is the geographical boundary of HIA? What skills are necessary in the HIA team? What are the priority issues?	Define roles and rules (ToR) Define HIA protocol Review existing information (country level) expert opinion
Stakeholder participation	Assessment	Does the policy have the potencial to affect determinants that impact health outcomes? Which health determinants will be assessed? Would health inequities be impacted? Is the impact to health likely to be significant in terms of number of individuals impacted, the magnitude and/or immediacy of impacts? Are methods, expertise and evidence available to assess the health impacts of the policy?	Document and secondary data review Data modeling Surveys, interviews, focus groups
Policy implementation	Reporting		Identify evidence-based recommendations Comunicate and disseminate HIA findings
	Monitoring	What needs to be monitored after the proposal is implemented to check the estimates of HIA? Are there any particular aspects that require careful consideration in case of early intervention? Did the policy decision change in a way that was consistent with the recommendations of HIA?	Monitor actual impacts on health, based on the recommendations, to enhance existing evidence

Sources: Adapted from Pyper, R., Cave, B., Purdy, J. and McAvoy, H. (2021) and WHO (https://www.who.int/tools/health-impact-assessments)

Personalised Prevention Health Impact Assesssment (HIA) – examples of policies

Policy	Basis	Genetic test	Level of preventic	Observations/Recommendations
Testing DPD for control of Adverse Drug Reactions to fluorouracil	A significant proportion of the general population has a deficiency of dihydropyrimidine dehydrogenase (DPD), which is needed to break down fluorouracil (capecitabine, tegafuor, flucytosine); toxic accumulation of these drugs in blood leads increases the risk of severe and lifethreatening side effects such as neutropenia, neurotoxicity, severe diarrhoea and stomatitis.	Dihydropyrimidine dehydrogenase gene (*DPYD*): four decreased function DPYD variants are of primary relevance due to their population frequency and established impact on enzyme function and toxicity risk	Terciary	EMA recommendation: Phenotype and/or genotype testing is therefore recommended before starting treatment with fluoropyrimidines; CPIC guidelines; Dutch Pharmacogenetic Working Group (DPWG); Cost-effectiveness analysis conducted
Etiological diagnosis of Familial Hypercholesterolemia (FH) and cascade screening	FH is under diagnosed, increasing risk for early heart attacks, stents, bypass surgery, and premature death.	Sequencing *LDLR,* APOB and *PSCK9*	Secondary	The Family Heart Foundation recommends FH genetic testing of patients with definite or probable FH, and for their at-risk relatives
Screening of severe familial forms of breast cancer	Having a variant BRCA gene greatly increases a woman's chance of developing breast cancer and ovarian cancer. They also increase a man's chance of developing male breast cancer and prostate cancer.	Sequencing of *BRCA1* and *BRCA2*	Secondary? Primary	Population screening?
Diagnosis of Maturity Onset Diabetes of the Young (MODY)	Accurate diagnosis of MODY allows for more effective therapeutic management and treatment strategies that are distinct from those used for type 1 and type 2 diabetes	Phased sequencing of 14 genes (GCK, HNF1A, HNF4A, HNF1B, INS, NEURO1, PDX1, PAX4, ABCC8, KCNJ11, KLF11, CEL, BLK, and APPL1)	Secondary	MODY diagnostic guidelines: genetic testing should be performed on individuals diagnosed with diabetes at a young age (25 years), as well as those with a familial history of diabetes, evidence of endogenous insulin secretion, detectable levels of c-peptide, and negative antibody results

Personalised Prevention Health Impact Assesssment (HIA) – *DPYD* testing

Testing *DPYD* gene for control of Adverse Drug Reactions (ADRs) to Fluorouracil

- The fluoropyrimidines **5-fluorouracil (5FU) and capecitabine** are widely used in the **treatment of solid tumors** including colorectal and breast cancer.
- **Reduced activity of DPD can cause severe dose-related toxicities**. There is substantial evidence **linking *DPYD* genotype with variability in DPD enzyme activity**, 5FU clearance, and 5FU toxicity;
- *DPYD* is a highly polymorphic gene, and some patients have **variants in the *DPYD* gene that lead to partial or full DPD deficiency**, which results in a **toxic build-up of 5FU** after administration at standard doses. Occurrence of ADRs can lead to a dose reduction, **treatment delay and/or therapy suspension potentially compromising the therapy efficacy**.
- **~7% of Europeans carry at least one decreased function *DPYD* variant**; prevalence of **partial and complete DPD deficiency estimated at 3%–9% and 0.01%–0.5%,** respectively;
- Between **10–40% of 5FU-treated patients develop severe and sometimes life-threatening toxicity** (neutropenia, nausea, vomiting, severe diarrhea, stomatitis, mucositis, hand-foot syndrome).
- **Prevention of fluoropyrimidines-related adverse events is of major clinical interest**.

Screening

Is HIA timely and adds value to the decison making process?
Who should carry out the HIA?
How to carry out the screening?

Contact stakeholders and decision-makers
Identify necessary resources

1. Is developing a Health Impact Assessment (HIA) framework for personalized prevention policies based on genomic information timely and adds value to decision making?

- Based on existing scientific evidence and EMA recommendations, the HIA of a policy on the use of *DPYD* testing before starting oncological treatment is timely and may add value to policy making;

Topic: Testing for DPD deficiency to prevent Adverse Drugs Reactions (ADRs) to fluorouracil (5-FU) administration in oncological patients		
Determinants that can influence physical, mental and social wellbeing	Judgement (Yes/No/Unknown)	Brief justification
Health inequalities	Yes	• Correct existing health disparities due to multiple factors including: coverage, inadequate evidence synthesis and available guidelines, and insufficient provider and patient awareness and education (White et al., 2021); • Address potential vulnerabilities: ≈3% of deaths have been reported in **frail patients** such as the **elderly**. **Ethnicity** (e.g. AfroAmerican) and **gender** (e.g. women) could be additional risk factors (EMA, 2020). • Decrease assymetric testing in clinical practice due to a lack of a standardized guidelines among health providers (inequity in access);
Healthy lifestyles	No	
Safe and cohesive communities	No	
Socioeconomic conditions	Unknown	• Need further clarification
Environmental conditions	No	
Health and social care services	Yes	• Organizational workflows within health services/providers and clinical laboratories can be expected.

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. Institute of Public Health. Dublin and Belfast.

Screening

Is HIA timely and adds value to the decison making process?
Who should carry out the HIA?
How to carry out the screening?

Contact stakeholders and decision-makers
Identify necessary resources

2. Who should carry out the screening?

- **Technical team**
  - **Portugal - INSA:** Astrid Vicente, Alexandra Costa, Maria Luís Cardoso, Filipa Garvão, Cristina Costa
  - **Finland - THL:** Markus Perola, Pragathy Kannan
  - **Italy – UCSC, Sapienza University of Rome:** Angelo Pezzulo, Angelica Valz Gris, Stefania Boccia, Paolo Villari, Giuseppe Migliari, Valentina Baccolini
  - **Estonia – University of Tartu:** Andres Metspalu, Anu Reigo, Mariliis Vaht

- **Funding**
  - PROPHET

Scoping

What is the geographical boundary of HIA?
What skills are necessary in the HIA team?
What are the priority issues?

Define roles and rules (ToR)
Define HIA protocol
Review existing information (country level)
expert opinion

1. Geographical boundaries

2. Governance arrangements:

- Define the ***Stakeholders Steering Committee*** as an **advisory board** who will represent the main stakeholders, provide useful information on how the policy in study is likely to affect health, and provide a platform for intersectoral working;

- **Define Terms of Reference** (ToR) to frame governance issues and establish methods to be used in the HIA.

Scoping

What is the geographical boundary of HIA?
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Review existing information (country level) expert opinion

3. Study design:

Define the conceptual model for the HIA → Identify potential health impacts → Define priorities → Validate with Stakeholder Steering Committee

- Identify the main health outcomes/indicators and potential relations between them (pathway or workflows)
- Define groups of population;
- Define geographical boundaries;
- Revise adopted clinical guidelines for *DPYD* testing.

- Identify the expected or potential health impacts that are considered 'likely' and/or 'potentially significant' that require further analysis;

- Decide on priority issues, e.g. indicators, potential health impacts, groups of population, etc; (dependent on available information, timelines, relevance, expected effect magnitude)
- Define the HIA methods (modelling, expert consultation, other);

Scoping

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3. Study design: indicators

Dimension	Outcomes	Data sources	Sub-analysis (equity concern)
Individual (population) impact	Incidence CRC	Cancer Registries	Sex; age; region
		Literature	Race, education, employment, etc.
	DPYD test Prescription	National Registries	Sex; age; region
	Frequency of toxicity/ADRs	Regulators	Sex, age, toxicity, grade of toxicity, patient comorbidities
	Lack of response	Literature	Several socioeconomic
	Mortality CRC Incl. premature mortality from CRC (YLL)	Cancer Registries	Sex; age; region
		National Statistics (data from mortality)	Sex; age; region
		Literature	Several socioeconomic
	Lethality ADRs	Regulators	Sex, age, toxicity, grade of toxicity, patient comorbidities
		Literature	Several socioeconomic
	Premature mortality specific to ADRs on CRC (YLL)	Regulators	Deaths (stratification by gender, age and region)
		Literature	Several socioeconomic
	Disability from ADRs (YLD, DALY)	Literature	Several socioeconomic
	Patient outcomes/PROMs	Literature	If available
Societal impact (mostly economic)	Global: ICER (cost/QALY)	Literature	Review (narrative/systematic/meta-analysis) of cost-effectiveness of *DPYD* testing on CRC
	Geographic location of hospital	National Statistics	
	DPYD test reimbursement status		
Impact on healthcare services	Acceptance and/or large-scale implementation capacity	HCW survey?/ Advisory board?	
		Literature	

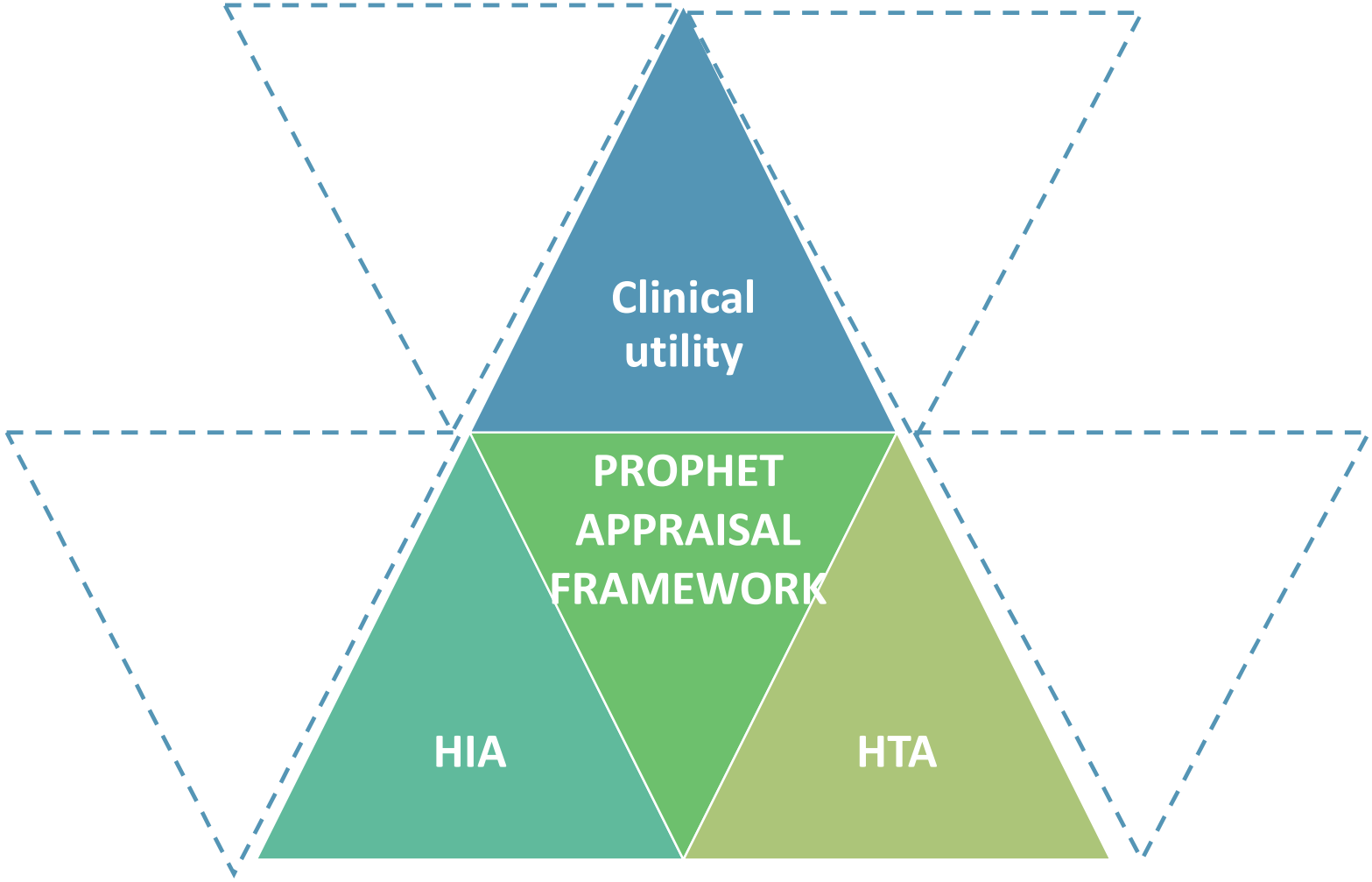
Does the policy have the potencial to affect determinants that impact health outcomes? Which health determinants will be assessed?
Would health inequities be impacted?
Is the impact to health likely to be significant in terms of number of individuals impacted, the magnitude and/or immediacy of impacts?
Are methods, expertise and evidence available to assess the health impacts of the policy?

Document and secondary data review
Data modeling
Surveys, interviews, focus groups

Identify evidence-based recommendations
Comunicate and disseminate HIA findings

Ongoing key activities

- Define and invite the Stakeholders Steering Committee composition in each of the countries;
- Develop the Terms of Reference
- Finalize the review of the evidence on clinical studies, frequency of ADR induced by 5FU/capecitabine, reduction in ADR with test; Review existing norms, guidelines, policies;
- Review the evidence for inequities across countries/across Europe – hospital profiles, test access, reimbursement, etc;
- Define the indicators/outcomes potentially impacted by a policy on DPYD testing to be assessed;
- Identify data sources in each country to homogenize information.


Clinical utility
PROPHET APPRAISAL FRAMEWORK
HIA
HTA

Translation Efforts

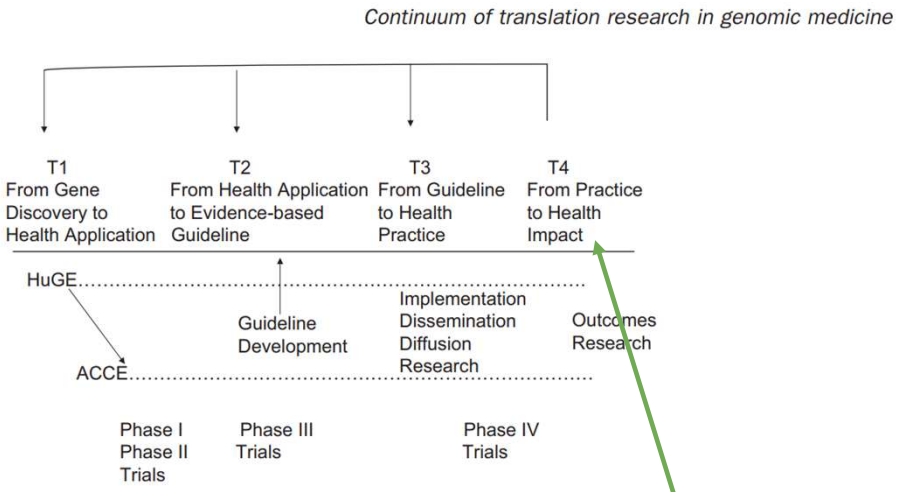
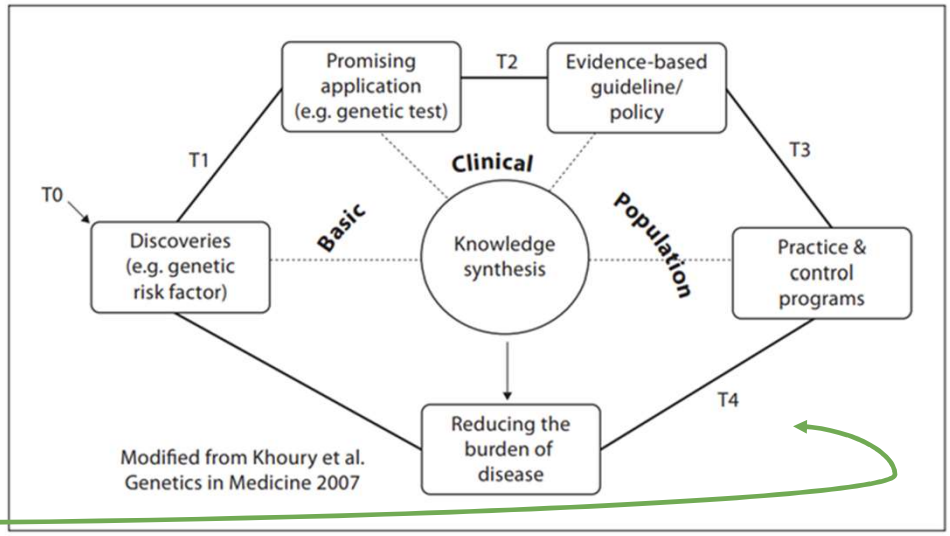


Fig. 1. The continuum of translation research in genomic medicine. HuGE, human genome epidemiology; ACCE, analytic validity, clinical validity, clinical utility, ethical, legal, and social issues. See text and Table 2 for definitions.

The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention?

Muin J. Khoury, MD, PhD, Marta Gwinn, MD, MPH, Paula W. Yoon, PhD, MPH, Nicole Dowling, PhD, Cynthia A. Moore, MD, PhD, and Linda Bradley, PhD



PROPHET Framework

Thank you!