Evaluating Health Impacts: A Framework for Personalized Prevention Policies: A Pilot Study of Pharmacogenetics in Colorectal Cancer treatment

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Poster number: **P18.082.A**

Introduction

Personalized Medicine is revolutionizing healthcare by harnessing cutting-edge research, technology, and abundant data resources to prevent diseases, enhance diagnostics, and optimize treatment. Genetic studies provide vital insights, while Health Impact Assessment (HIA) can be a valuable tool for aiding policymakers in integrating genomic data for optimized prevention strategies, promoting equity in healthcare decision-making.

Objectives

Adapt the WHO HIA framework for personalized prevention policies: through a case study of implementing a prospective policy mandating Dihydropyrimidine dehydrogenase (DPYD) genotyping prior to Fluoropyrimidine-based (FP) chemotherapy in Colorectal cancer (CRC) patients. **Assess the effectiveness** of the adapted HIA framework for personalized prevention policies**, engage stakeholders** to refine the framework and **provide evidence-based recommendations** (From the *DPYD* case study) to enhance personalized prevention strategies.

Case study

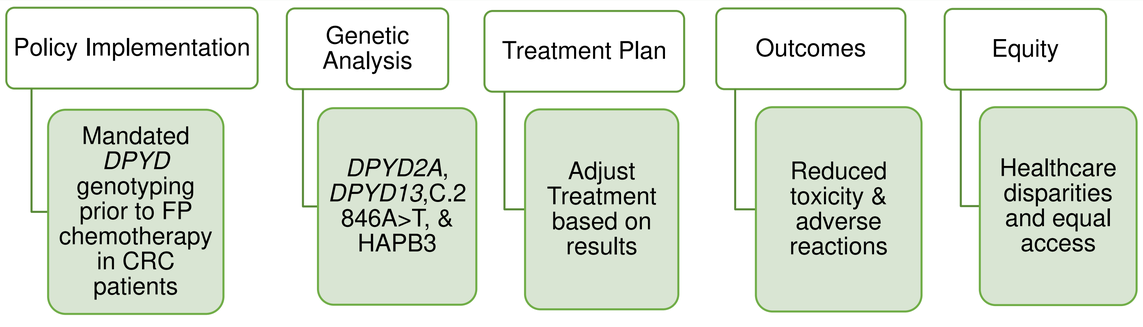


Figure1: Case study: A policy mandating pre-chemotherapy (FP-based) DPYD genotyping in CRC patients

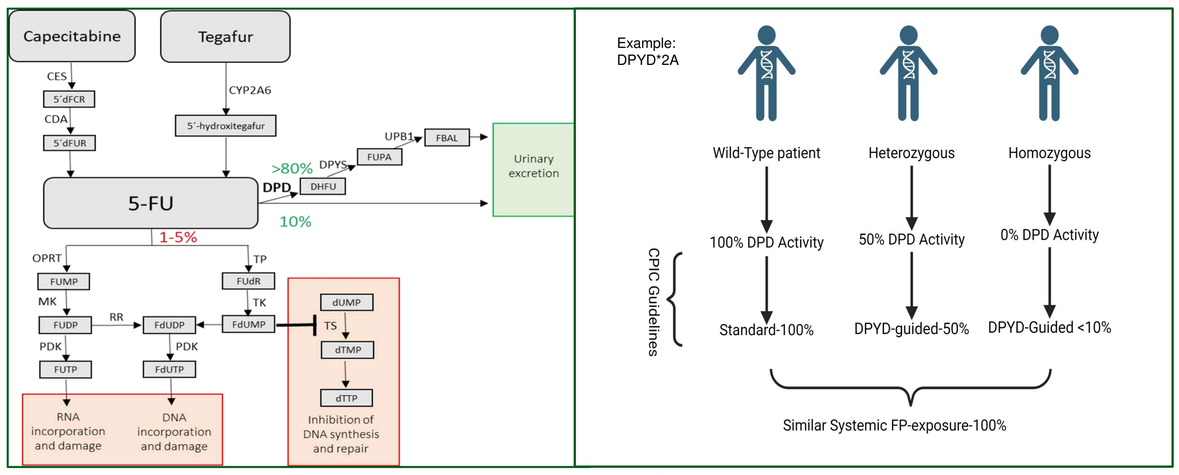


Figure 2: [2,6]***Schematic overview of the fluoropyrimidine metabolism.*** *(Adapted from Lunenburg et al, 2020; Etienne-Grimaldi et al, 2022)*

Figure 3: [5]***Adapted from: Clin Pharma and Therapeutics, Volume: 114, Issue: 4, Pages: 768-779, First published: 23 June 2023, DOI: (10.1002/cpt.2978) Created with BioRender.com***

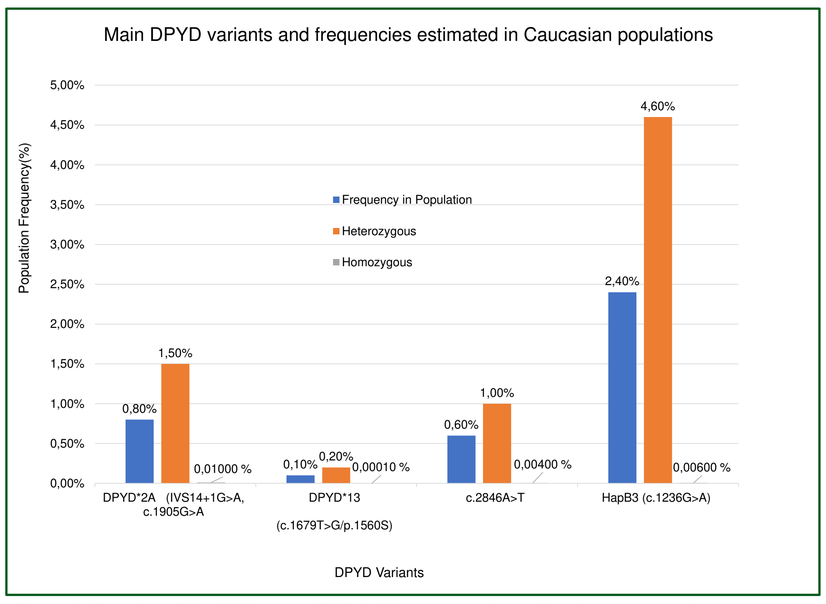


Figure 4: [3] ***Data from INCa, HAS report "DPD deficiency screening with a view to preventing some severe toxicities occurring with treatments including fluoropyrimidines', 2018)***

Methods

Figure 5: HIA in Portugal, Italy & Finland.

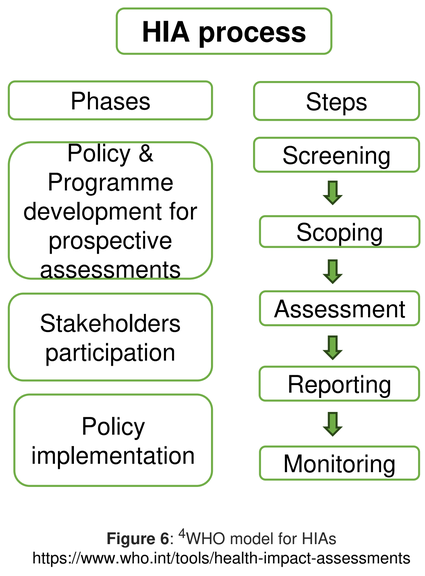


Figure 6: [4]WHO model for HIAs
https://www.who.int/tools/health-impact-assessments

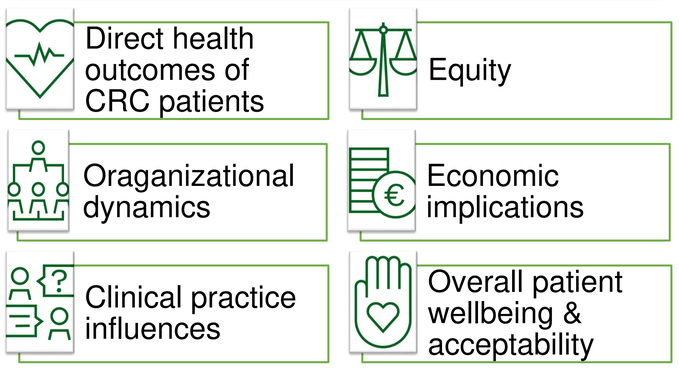
Conceptual Model: Developed for the HIA to evaluate *DPYD* genotype-guided dosing in CRC patients.
Data Collection: Literature reviews, pseudo-anonymized data from cancer and population-based registries and surveys in Finland, Italy, and Portugal.
Modeling: Developed a Markov chain model to simulate health impacts and project outcomes.
Stakeholders: National committees provided qualitative insights through interviews.
Assessment: Ongoing HIAs in three countries, focusing on health equity and contextual impacts.
Outcomes: Identifying impacts in health, organizational, economic, and equity categories.

Results & Conclusion

Key Findings from Literature

Study	Patient Population	DPYD variants	Key Findings	Cost Analysis
Deenen et al., 2016	2,038 cancer patients. Toxicity was compared with historical controls	DPYD*2A,Carriers received 50% dose reduction, followed by titration based on tolerance.85 heterozygous carriers (25-50%dose), Others: standard dose	Reduced grade ≥3 toxicity: 73% to 28%; Drug-induced death: 10% to 0%	Upfront Screening group had lower overall treatment cost: €2,772 vs. €2,817 in non-screening group. Cost savings offset screening expenses.
Henricks et al., 2018	1,103 cancer patients. Severe toxicity vs. historical full-dose DPYD carriers	DPYD*2A, c.2846A>T, DPYD*13, HapB3	Grade ≥3 toxicity: 39% (variants) vs. 23% (wild-type)	Upfront Screening incurred no additional direct medical costs and saved €51 per patient.
Fragoulakis et al., 2023	CRC patients	DPYD*2A, DPYD*13, c.2846A>T, HapB3	Marginal ADE reduction: 9.09% vs. 9.43%; Mean survival: 1.58 vs. 1.50 LYs	Average total cost per patient was €380 in PGx-guided arm vs. €565 in control arm. Major cost savings from reduced hospitalization.

Dimensions of the Conceptual model



- Established research and guidelines align with effectiveness of the *DPYD* test in mitigating adverse events among CRC patients.
- Active stakeholder engagement is an important component of the study.
- We developed a Markov simulation model to evaluate health impacts of mandating DPYD genotyping before FP-based chemotherapy in CRC patients in Portugal & Italy.
- Special subgroups, including frail elderly individuals (not suitable for chemotherapy) and ethnic minorities (Possibly underrepresented in testing programs), have been identified through the ongoing HIA.
- Initial findings emphasize the important role of HIA in assessing genomic testing in personalized prevention, prioritizing equity in policy development to ensure fairness and accessibility.

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Funding

European Commission under the Horizon Europe research & Innovation programme under Grant Agreement N°101057721