DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines: Recommendation

Final Recommendation

- Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding *DPYD* genotyping for the following variants in patients who have planned cancer treatment with fluoropyrimidines (5-fluorouracil or capecitabine):
    - c.1905+1G>A (*DPYD**2A; IVS14+1G>A; rs3918290)
    - c.1679T>G (*DPYD**13; I560S; rs55886062)
    - c.2846A>T (D949V; rs67376798)
    - c.[1236G>A; 1129-5923C>G]

Rationale for the Recommendation

The Ontario Health Technology Advisory Committee has reviewed the findings of the health technology assessment[1] and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee.

The Ontario Health Technology Advisory Committee agreed with the subcommittee's conclusion that the findings support the clinical validity and cost-effectiveness of *DPYD* genotyping for the variants listed in the recommendation. The Ontario Health Technology Advisory Committee also acknowledged the expected cost savings associated with a slightly lower rate of severe toxicity owing to *DPYD* genotyping.

In making their recommendation, the Ontario Health Technology Advisory Committee members took into account the lived experience of people diagnosed with cancer and treated with fluoropyrimidines, who valued the information *DPYD* genotyping afforded them about their risk of toxicity with fluoropyrimidine treatment.

The Ontario Health Technology Advisory Committee recognized that the *DPYD* variants listed in the recommendation are more common in White populations[2] and that *DPYD* variants that are more prevalent in other racial/ethnic groups have not been studied as extensively. The committee advises the Ministry of Health that implementation strategies for *DPYD* genotyping in Ontario should include the collection of data on race/ethnicity to inform care for all patients. Committee members also emphasized the need for equitable access to *DPYD* genotyping in Ontario as an important component of the implementation and coordination of care.

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Finally, current guidelines on fluoropyrimidine treatment modifications are available for the four *DPYD* variants listed in the recommendation. Recommendations for fluoropyrimidine treatment modifications for additional *DPYD* variants may be included in the guidelines in the future.

Decision Determinants for *DPYD* Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines

Decision Criteria	Subcriteria	Decision Determinants Considerations
Overall clinical benefit How likely is the health technology/intervention to result in high, moderate, or low overall benefit?	**Effectiveness** How effective is the health technology/intervention likely to be (taking into account any variability)?	Carriers[a] of the *DPYD* gene variants assessed may have a higher risk of severe toxicity with fluoropyrimidines than wild-type patients (GRADE: Low). It is unclear whether a reduced fluoropyrimidine dose led to a risk of toxicity and level of treatment effectiveness that was similar to that of wild-type patients, or lower risk of toxicity than that of carriers treated with a standard dose (GRADE: Very low).
	Safety How safe is the health technology/intervention likely to be?	No adverse events were reported as a result of *DPYD* genotyping.
	Burden of illness What is the likely size of the burden of illness pertaining to this health technology/ intervention?	In Ontario, 7,000–8,000 patients per year are prescribed fluoropyrimidines. The estimated prevalence of partial DPD deficiency is 5% to 7% in White populations and 5% to 8% in Black populations (prevalence is unknown in other populations). The estimated prevalence of complete DPD deficiency is 0.01% to 0.2%.
	Need How large is the need for this health technology/intervention?	*DPYD* genotyping aims to identify people with an increased risk of experiencing severe toxicity as a result of their cancer treatment with fluoropyrimidines.
Patient preferences and values How likely is adoption of the health technology/ intervention to be congruent with patient preferences and values and with ethical or legal standards?	**Patient preferences and values** Do patients have specific preferences, values, or needs related to the health condition, health technology/intervention, or life impact that are relevant to this assessment? (Note: The preferences and values of family members and informal caregivers are to be considered as appropriate.)	Patients value the information that *DPYD* tests provide. The results affect their chemotherapy decision-making. Patients value the opportunity to experience reduced uncertainty and anxiety about whether they should receive fluoropyrimidines as part of their cancer treatment.

Decision Criteria	Subcriteria	Decision Determinants Considerations
	Autonomy, privacy, confidentiality, and/or other relevant ethical principles as applicable Are there concerns regarding accepted ethical or legal standards related to patient autonomy, privacy, confidentiality, or other ethical principles that are relevant to this assessment? (Note: The preferences and values of the public are to be considered as appropriate.)	There may be concerns about the confidentiality of stored genetic data and who has access to the data. If the test also predicts future risk or probability of disease, such information may be relevant for family members. The nature of the informed consent sought, how it is obtained, how test results should be shared with patients, and whether genetic counselling should be part of the testing regimen are important considerations. There may be concerns about whether patient refusal of testing may affect the treatment received.
Equity and patient care How could the health technology/ intervention affect equity of access and coordination of patient care?	**Equity of access or outcomes** Are there disadvantaged populations or populations in need whose access to care or health outcomes might be improved or worsened that are relevant to this assessment?	Access to testing is presently limited to patients who can be tested at one hospital in Ontario. Current evidence is based mostly on White populations,[2] which may not reflect the entire Ontario population. Current guidelines on fluoropyrimidine treatment based on *DPYD* genotyping list variants that are more common in White populations; variants that are more common in other racial/ethnic groups have not been studied as extensively. More research on the prevalence and clinical relevance of *DPYD* variants in other racial/ethnic groups is needed to inform guidelines for care.
	Patient care Are there challenges in the coordination of care for patients or other system-level aspects of patient care (e.g., timeliness of care, care setting) that might be improved or worsened that are relevant to this assessment?	To optimize coordination of care, equitable access to *DPYD* genotyping for people who have planned cancer treatment with fluoropyrimidines will be needed.

Decision Criteria	Subcriteria	Decision Determinants Considerations
Cost-effectiveness How efficient is the health technology/ intervention likely to be?	**Economic evaluation** How efficient is the health technology/intervention likely to be?	At the commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained, *DPYD* genotyping is highly likely to be cost-effective compared to usual care (91% and 96% probability, respectively).[b] Our economic evaluation suggested that *DPYD* genotyping might be slightly more effective (better QALYs) and less costly than usual care (a savings of $144.88 per patient).
Feasibility of adoption into health system How feasible is it to adopt the health technology/ intervention into the Ontario health care system?	**Economic feasibility** How economically feasible is the health technology/intervention?	The additional cost associated with a *DPYD* genotyping test is about $167 per patient. We estimated that publicly funding *DPYD* genotyping may be cost-saving ($714,963 over the next 5 years, provided that the costs of implementation, service delivery and program coordination do not exceed this amount).
	Organizational feasibility How organizationally feasible is it to implement the health technology/intervention?	According to laboratory experts, the cost of a *DPYD* genotyping test may depend on how testing is implemented. A centralized testing model would increase throughput, which would reduce the cost per sample dramatically while maintaining a rapid turnaround time. Centralizing testing would also reduce repeat training and validation at multiple sites.

Abbreviations: DPD, dihydropyrimidine dehydrogenase; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; QALY, quality-adjusted life years.

[a]We have used the term "carrier" to refer to people who carry one or more *DPYD* gene variants that predispose to toxicity; we have used "wild-type" to refer to the form of the gene that does not predispose to toxicity.

[b]Uncertainty was classified into one of five categories based on the Ontario Decision Framework[3]: highly likely to be cost-effective (80–100% probability of being cost-effective), moderately likely to be cost-effective (60–79% probability), uncertain if cost-effective (40–59% probability), moderately likely to not be cost-effective (20–39% probability), or highly likely to not be cost-effective (0–19% probability).

References

(1) Ontario Health. *DPYD* genotyping in patients who have planned cancer treatment with fluoropyrimidines: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2021 August;21(14):1–186. Available from: https://hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/dpyd-genotyping-in-patients-who-have-planned-cancer-treatment-with-fluoropyrimidines

(2) Haute Autorité de Santé, Institut National du Cancer. Recherche de déficit en dihydropyrimidine déshydrogenase en vue de prévenir certaines toxicités sévères survenant sous traitement comportant des fluoropyrimidines (5-fluorouracile) [Internet]. 2018 [cited 2021 Feb 8]. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2018-12/recherche_dun_deficit_en_dihydropyrimidine_deshydrogenase_visant_a_prevenir_certaines_toxicites_severes_associees_aux_traite.pdf

(3) Krahn M, Miller F, Bayoumi A, Brooker AS, Wagner F, Winsor S, et al. Development of the Ontario decision framework: a values based framework for health technology assessment. Int J Technol Assess Health Care. 2018;34(3):290–9.

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