Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Fluoropyrimidines (for example, 5-fluorouracil and capecitabine) are medications used to treat different types of cancer. An enzyme in the body called dihydropyrimidine dehydrogenase (or DPD) is needed to break down fluoropyrimidines. A deficiency in this enzyme, which may be caused by a variation in a gene called *DPYD*, increases the risk of some patients developing severe toxicity if they are treated with fluoropyrimidines. A test called *DPYD* genotyping can identify variants in the *DPYD* gene. Therefore, this test may be able to identify people who are at a higher risk of developing severe toxicity, allowing their treatment plan to be modified before treatment begins, for example by reducing the fluoropyrimidine dose or choosing an alternative treatment.

This health technology assessment looked at how valid, clinically useful, and cost-effective *DPYD* genotyping is in people who have planned cancer treatment with fluoropyrimidines. It also looked at how effective a reduced fluoropyrimidine dose is in lowering the risk of severe toxicity, the budget impact of publicly funding *DPYD* genotyping, and the experiences, preferences, and values of people who have planned cancer treatment with fluoropyrimidines.

What Did This Health Technology Assessment Find?

Carriers of a *DPYD* variant who were treated with a standard fluoropyrimidine dose had a higher risk of severe toxicity than non-carriers. The results of *DPYD* genotyping led physicians to change people's fluoropyrimidine treatment plans. We are not certain if reducing the treatment dose in carriers of a *DPYD* variant leads to a risk of severe toxicity that is similar to that of people without a *DPYD* variant. We are also uncertain if reducing the treatment dose in carriers of a *DPYD* variant leads to a lower risk of severe toxicity than in carriers who are treated with a standard dose.

For people with planned fluoropyrimidine treatment, *DPYD* genotyping is likely cost-effective compared to usual care (no testing). Publicly funding *DPYD* genotyping in Ontario may be cost-saving, with an estimated saving of $714,963 over the next 5 years, provided that the costs of implementation, service delivery, and program coordination do not exceed this amount.

People treated with fluoropyrimidines described the impact of cancer and treatment adverse effects on their quality of life and mental health. Barriers to *DPYD* testing included lack of awareness and limited access.

Published August 2021 Volume 21, Number 14

Acknowledgments

This report was developed by a multidisciplinary team from Ontario Health. The clinical epidemiologist was Vania Costa, the medical librarian was Corinne Holubowich, the health economists were Chunmei Li and Lindsey Falk, the health economics associate was Selena Hussain, the secondary health economist was Shawn Xie, and the patient and public partnership analyst was Jigna Mistry.

The medical editors were Tim Maguire and Jeanne McKane. Others involved in the development and production of this report were Jamie Turnbull, Claude Soulodre, Susan Harrison, Saleemeh Abdolzahraei, Elisabeth Smitko, Sarah McDowell, Vivian Ng, David Wells, Andrée Mitchell, Charles de Mestral, and Nancy Sikich.

We would like to thank the following people for lending their expertise to the development of this report:

- Richard Kim, London Health Sciences Centre
- John Bartlett, Ontario Institute for Cancer Research
- Lei Fu, Sunnybrook Health Sciences Centre
- Shinya Ito, Hospital for Sick Children, Toronto
- John Lenehan, London Health Sciences Centre
- Geoffrey Liu, Princess Margaret Cancer Centre
- Jason Yu, Royal Victoria Regional Health Centre
- Leta Forbes, Ontario Health Clinical Institutes and Quality Programs
- Aaron Pollett, Ontario Health Clinical Institutes and Quality Programs
- Brandon Meyers, Juravinski Cancer Centre
- Harriet Feilotter, Kingston Health Sciences Centre
- Michael Raphael, Sunnybrook Health Sciences Centre
- Tracy Stockley, University Health Network
- Wendy Ungar, SickKids Research Institute

We also thank our lived experience participants who generously gave their time to share their stories with us for this report.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

Citation
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

Abstract

Background

Fluoropyrimidine drugs (such as 5-fluorouracil and capecitabine) are used to treat different types of cancer. However, these drugs may cause severe toxicity in about 10% to 40% of patients. A deficiency in the dihydropyrimidine dehydrogenase (DPD) enzyme, encoded by the *DPYD* gene, increases the risk of severe toxicity. *DPYD* genotyping aims to identify variants that lead to DPD deficiency and may help to identify people who are at higher risk of developing severe toxicity, allowing their treatment to be modified before it begins. Recommendations for fluoropyrimidine treatment modification are available for four *DPYD* variants, which are the focus of this review: *DPYD**2A, *DPYD**13, c.2846A>T, and c.1236G>A. We conducted a health technology assessment of *DPYD* genotyping for patients who have planned cancer treatment with fluoropyrimidines, which included an evaluation of clinical validity, clinical utility, the effectiveness of treatment with a reduced fluoropyrimidine dose, cost-effectiveness, the budget impact of publicly funding *DPYD* genotyping, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included systematic review and primary study using the Risk of Bias in Systematic Reviews (ROBIS) tool and the Newcastle-Ottawa Scale, respectively, and we assessed the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature review and conducted cost-effectiveness and cost–utility analyses with a half-year time horizon from a public payer perspective. We also analyzed the budget impact of publicly funding pre-treatment *DPYD* genotyping in patients with planned fluoropyrimidine treatment in Ontario. To contextualize the potential value of *DPYD* testing, we spoke with people who had planned cancer treatment with fluoropyrimidines.

Results

We included 29 observational studies in the clinical evidence review, 25 of which compared the risk of severe toxicity in carriers of a *DPYD* variant treated with a standard fluoropyrimidine dose with the risk in wild-type patients (i.e., non-carriers of the variants under assessment). Heterozygous carriers of a *DPYD* variant treated with a standard fluoropyrimidine dose may have a higher risk of severe toxicity, dose reduction, treatment discontinuation, and hospitalization compared to wild-type patients (GRADE: Low). Six studies evaluated the risk of severe toxicity in *DPYD* carriers treated with a genotype-guided reduced fluoropyrimidine dose versus the risk in wild-type patients; one study also included a second comparator group of *DPYD* carriers treated with a standard dose. The evidence was uncertain, because the results of most of these studies were imprecise (GRADE: Very low). The length of hospital stay was shorter in *DPYD* carriers treated with a reduced dose than in *DPYD* carriers treated with a standard dose, but the evidence was uncertain (GRADE: Very low). One study assessed the effectiveness of a genotype-guided reduced fluoropyrimidine dose in *DPYD**2A carriers versus wild-type patients, but the results were imprecise (GRADE: Very low).

We found two cost-minimization analyses that compared the costs of the *DPYD* genotyping strategy with usual care (no testing) in the economic literature review. Both studies found that *DPYD* genotyping was cost-saving compared to usual care. Our primary economic evaluation, a cost-utility analysis, found that *DPYD* genotyping might be slightly more effective (incremental quality-adjusted life years of 0.0011) and less costly than usual care (a savings of $144.88 per patient), with some uncertainty. The probability of *DPYD* genotyping being cost-effective compared to usual care was 91% and 96% at the commonly

used willingness-to-pay values of $50,000 and $100,000 per quality-adjusted life-year gained, respectively. Assuming a slow uptake, we estimated that publicly funding pre-treatment *DPYD* genotyping in Ontario would lead to a savings of $714,963 over the next 5 years.

The participants we spoke to had been diagnosed with cancer and treated with fluoropyrimidines. They reported on the negative side effects of their treatment, which affected their day-to-day activities, employment, and mental health. Participants viewed *DPYD* testing as a beneficial addition to their treatment journey; they noted the importance of having all available information possible so they could make informed decisions to avoid adverse reactions. Barriers to *DPYD* testing include lack of awareness of the test and the fact that the test is being offered in only one hospital in Ontario.

Conclusions

Studies found that carriers of a *DPYD* variant who were treated with a standard fluoropyrimidine dose may have a higher risk of severe toxicity than wild-type patients treated with a standard dose. *DPYD* genotyping led to fluoropyrimidine treatment modifications. It is uncertain whether genotype-guided dose reduction in heterozygous *DPYD* carriers resulted in a risk of severe toxicity comparable to that of wild-type patients. It is also uncertain if the reduced dose resulted in a lower risk of severe toxicity compared to *DPYD* carriers treated with a standard dose. It is also uncertain whether the treatment effectiveness of a reduced dose in carriers was comparable to the effectiveness of a standard dose in wild-type patients.

For patients with planned cancer treatment with fluoropyrimidines, *DPYD* genotyping is likely cost-effective compared to usual care. We estimate that publicly funding *DPYD* genotyping in Ontario may be cost-saving, with an estimated total of $714,963 over the next 5 years, provided that the implementation, service delivery, and program coordination costs do not exceed this amount.

For people treated with fluoropyrimidines, cancer and treatment side effects had a substantial negative effect on their quality of life and mental health. Most saw the value of *DPYD* testing as a way of reducing the risk of serious adverse events. Barriers to receipt of *DPYD* genotyping included lack of awareness and limited access to *DPYD* testing.

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Objective

This health technology assessment evaluates the clinical validity, clinical utility, and cost-effectiveness of *DPYD* genotyping in patients who have planned cancer treatment with fluoropyrimidines. It also evaluates the effectiveness of a genotype-guided reduced dose in carriers of certain *DPYD* variants compared to patients treated with a standard dose; the budget impact of publicly funding *DPYD* genotyping; and the experiences, preferences, and values of people with cancers that can be treated with fluoropyrimidines.

Background

Fluoropyrimidines and Fluoropyrimidine-Associated Toxicity

Fluoropyrimidines are drugs frequently used to treat several different types of cancer, including colorectal, breast, head and neck, pancreatic, and gastric cancers.[1,2] This group of drugs includes 5-fluorouracil (5-FU), capecitabine, and tegafur.[3,4] Capecitabine and tegafur are prodrugs of 5-FU—that is, once absorbed, they are metabolized (converted) to 5-FU.[4,5] Fluoropyrimidines can be used alone or as the core component in several combination treatment regimens[1,3,6]; they can also be combined with radiotherapy.[7] 5-FU and capecitabine are used for cancer treatment in Ontario, but tegafur is not; it has not been approved by Health Canada.

5-FU has a narrow therapeutic window: that is, the difference between the minimum efficacious dose and the maximum tolerable dose is small.[8] Although fluoropyrimidines are important for treating several types of cancer,[6] 10% to 40% of the patients who receive them may experience severe toxicity,[8] which can be fatal in up to 1% of patients.[4,9,10] Fluoropyrimidine-associated adverse events can occur as early as the first cycle of chemotherapy[4] and include hematologic (leukopenia, neutropenia, anemia, thrombocytopenia), gastrointestinal (mucositis, diarrhea, nausea, and vomiting), and dermatologic (hand–foot syndrome) reactions.[1,11,12] These adverse events can lead to hospitalization, dose reduction, treatment delay, and treatment discontinuation.[11-13]

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) define the levels of toxicity using a scale of 1 to 5 [14]: grade 1, mild; grade 2, moderate; grade 3, severe but not immediately life-threatening; grade 4, an event with life-threatening consequences; grade 5, a fatal adverse event.[14]

Factors that can influence the risk of fluoropyrimidine-associated toxicity include the patient's age, sex, renal function, and performance status; the type and stage of cancer; and the type, mode, and duration of administration of the fluoropyrimidine.[5,10,15,16] The type of cancer treatment regimen can also play a role, because fluoropyrimidines are often used in combination with other anticancer drugs that are associated with toxicity (e.g., platinum-based drugs or irinotecan).[10,16] Genetic factors that affect people's ability to metabolize fluoropyrimidines may also affect the development of toxicity.[5,15]

The antitumour activity of 5-FU includes inhibition of DNA synthesis and repair, resulting in cell death, and incorporation into DNA and RNA, causing damage. To exert that activity, 5-FU requires intracellular conversion into cytotoxic metabolites (i.e., the body's cells convert it into active molecules that kill cancer cells).[1] Approximately 80% of the dose is catabolized into inactive metabolites (i.e., broken down into simpler molecules that do not kill cancer cells) before being eliminated, and the rest is eliminated unchanged in the urine.[1,3,16]

The dihydropyrimidine dehydrogenase (DPD) enzyme is the first and rate-limiting enzyme in the catabolic pathway[1,3]; it converts 5-FU into inactive metabolites in the liver.[2,17] If DPD activity is lower than normal, less 5-FU is converted to the inactive metabolite, and more of the active metabolite accumulates,[2] increasing a person's risk of toxicity.[1,3] Deficiency in DPD accounts for 20% to 60% of the toxicity patients experience.[10,18]

The goal of testing for DPD deficiency is to reduce the risk of severe toxicity by allowing the fluoropyrimidine dose to be adjusted or an alternative treatment to be recommended, depending on the level of deficiency.[2,10] In patients with partial DPD deficiency, the aim of a lower fluoropyrimidine dose is to maintain plasma levels of 5-FU and its metabolites at the intended therapeutic level[2] (similar to patients with normal DPD activity); decrease the risk of severe toxicity; and maintain treatment efficacy.[2,10] To avoid underdosing, the fluoropyrimidine dose can be increased in subsequent treatment cycles if the patient experiences no toxicity or clinically tolerable toxicity.[8]

Uridine triacetate is an oral antidote used after an overdose of 5-FU or capecitabine (even if asymptomatic),[19] or in cases of early-onset, severe, or life-threatening toxicity,[10,20] to reduce the risk of death.[19] Uridine competes with toxic 5-FU metabolites for incorporation into RNA, reducing cellular damage.[20] It has not been approved by Health Canada, but it is available through the Health Canada Special Access Program.[20] Because its use is limited to the 96 hours after the end of 5-FU administration[10,20] and mostly in emergency situations of overdose, we did not consider uridine triacetate as an alternative to *DPYD* genotyping, and it will not be included as a comparator in this review.

Clinical Need and Target Population

DPYD *Genotype and DPD Deficiency*

The *DPYD* gene is located on chromosome 1p22 and encompasses 23 exons. The *DPYD* gene encodes the enzyme DPD.[2]

In human cells, each gene found on an autosomal (non-sex) chromosome has two alleles—one inherited from each parent. Variations in the DNA sequence of a gene can be heterozygous (present in only one of the two alleles), homozygous (the identical variant is present in both alleles), or double or compound heterozygous (different variants present in each of the two alleles).

Normal DPD activity is thought to be associated with the wild-type allele—that is, the non-variant form. The presence of at least one variant allele of the *DPYD* gene may result in a structural change in the DPD enzyme translated from that allele and lead to reduced or absent enzyme activity.[2]

In this report, we will use the term “carrier” to refer to people who carry one or more *DPYD* gene variants that predispose to toxicity; we will use “wild-type” to refer to the form of the gene that does not predispose to toxicity.

There is wide inter- and intraindividual variation in the activity of the DPD enzyme, and the effect of each *DPYD* variant on DPD enzyme activity varies.[8] Several *DPYD* variants have been studied, but an association with DPD deficiency has been observed for four variants in particular[2]:

- 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]

Of these four variants, *DPYD**2A and *DPYD**13 have the strongest effect on DPD activity, resulting in 50% (*DPYD**2A) and 60% to 68% (*DPYD**13) reductions in enzyme activity in heterozygous carriers.[8,10] In homozygous carriers, 100%[6] (*DPYD**2A) and 75% (*DPYD**13) reductions[2,10] have been shown. Heterozygous carriers of the c.2846A>T and c.1236G>A variants display 20% to 30% (c.2846A>T) and 20% to 35% (c.1236G>A) reductions in enzyme activity, respectively.[8,10] In homozygous carriers, 50% (c.2846A>T) and 20% to 70% (c.1236G>A)reductions have been observed.[2,10]

Partial DPD deficiency affects 5% to 7% of the Caucasian population,[4,21] and 0.01% to 0.2% are estimated to have complete DPD deficiency.[4] Approximately 5% to 8% of people with African ancestry have partial DPD deficiency.[4,21] In Caucasians, the c.1236G>A variant is the most common of the four, affecting 2.6% to 6.3% of the population;[2] the estimated prevalence of c.2846A>T, *DPYD**2A, and *DPYD**13 in Caucasians is 1.1%, 0.7%, and 0.1%, respectively.[2] The estimated prevalence of homozygous *DPYD**2A carriers is 0.1% in Caucasians.[6] In people of African ancestry, the *DPYD**2A and the c.2846A>T variants have an estimated prevalence of 0.1%,[2] but another less extensively studied *DPYD* variant, c.557A>G (Y186C), is more prevalent in this population, at 3% to 5%.[8,22]

Alternative or Complementary Tests

The DPD enzyme converts endogenous uracil into dihydrouracil.[6] Its activity can be measured directly in peripheral blood mononuclear cells[8] and indirectly by measuring plasma uracil concentrations or the dihydrouracil:uracil (UH2:U) ratio.[6,8] These phenotype tests can be used as an alternative or a complement to *DPYD* genotyping.[8] Their limitations include lack of availability[8]; difficulty implementing them as routine tests[23]; issues with the interpretation of results; unclear validation for predictive use[6]; the fact that thresholds for dose adjustment may not be established[24]; and lack of standardization for some tests.[2]

Systemic 5-FU levels can be measured with therapeutic drug monitoring (pharmacokinetics), a technique that can also be used to ensure that 5-FU levels are within the therapeutic range and reduce the risk of adverse effects.[6,8]

Health Technology Under Review

DPYD genotyping is an assay that identifies specific germline variants in the *DPYD* gene. It aims to predict the level of DPD enzyme activity based on the expected effect of each variant on DPD function. Genotyping methods are faster and easier, and they may be less expensive than phenotype tests.[2]

According to a 2017 review from the Institut National de d'Excellence en Santé et en Services Sociaux (INESSS),[25] the analytical validity of *DPYD* genotyping was accurate in two studies that compared results from a real-time polymerase chain reaction (PCR) assay with those from DNA sequencing. In one of the studies (which included 165 people), the results from a *DPYD**2A real-time PCR test were identical to those from DNA sequencing.[25] In the second study (in which 568 people were tested for eight *DPYD*

variants using real-time PCR), DNA sequencing validation confirmed that there was 100% agreement between the two tests.[25]

Guidance on DPYD *Genotyping From Regulatory Agencies*

Canadian 5-FU and capecitabine monographs state that patients with DPD deficiency are at risk of severe life-threatening toxicity when treated with these drugs. The use of 5-FU and capecitabine is contraindicated in patients with known complete absence of DPD activity, and they should be used with extreme caution in patients with partial DPD deficiency.[26-29]

Some Canadian fluoropyrimidine product monographs state that testing for DPD deficiency should be considered prior to treatment, based on local availability and current guidelines.[26,28,29]

In April 2020, the European Medicines Agency (EMA)[16,24] recommended that testing for DPD deficiency be done before starting cancer treatment with 5-fluorouracil, capecitabine, or tegafur using phenotype or genotype tests. According to the EMA, the level of the available evidence does not allow for conclusive recommendations on the most suitable of the two test types.[16] The EMA states that fluoropyrimidines are contraindicated in patients with complete DPD deficiency[24]; in patients with partial deficiency, a reduced starting dose should be considered.[24] The EMA also states that therapeutic drug monitoring may improve clinical outcomes in patients who receive a continuous infusion of 5-FU.[24]

Guidelines for Treatment Based on DPYD *Genotyping*

We identified three pharmacogenetic guidelines on *DPYD* genotyping.[4,8,30] The Dutch Pharmacogenetics Working Group (DPWG),[4] the Clinical Pharmacogenetics Implementation Consortium (CPIC),[8] and the Swiss Group of Pharmacogenomics and Personalised Therapy[30] have proposed that treatment modifications for 5-FU and capecitabine be implemented before the start of treatment to reduce the risk of severe, potentially fatal toxicity in carriers of four *DPYD* variants (Table 1). The *DPYD* variants included in the guidelines are those for which sufficient evidence on an association with severe toxicity is available (*DPYD**2A, *DPYD**13, c.2846A>T, and c.1236G>A).[4] The recommendations are based on the association between the *DPYD* genotype and DPD enzyme activity, therapeutic drug monitoring (5-FU pharmacokinetics), and severe fluoropyrimidine-associated toxicity.[4,8] Based on the magnitude of their deleterious effect on DPD function, *DPYD**2A and *DPYD**13 are considered no-function variants and c.2846A>T and c.1236G>A are considered decreased-function variants.[4,8,30]

Predicted DPD activity can be expressed as the *DPYD* gene activity score, which ranges from 0 (no DPD enzyme activity) to 2 (normal DPD enzyme activity).[4] Both the DPWG[4] and the CPIC[8] state that carriers of one no-function or reduced-function variant and one normal-function variant have a gene activity score of 1 to 1.5, and those with two normal-function variants have a gene activity score of 2. The CPIC states that carriers of two no-function variants or one no-function and one reduced-function variant have a gene activity score of 0 to 0.5, and carriers of two reduced-function variants have a gene activity score of 1 to 1.5.[8] The CPIC considers patients with a gene activity score of 1 to 1.5 to be intermediate metabolizers, and those with a gene activity score of 0 to 0.5 to be poor metabolizers.[8] The DPWG also considers carriers of two no-function variants to have a gene activity score of 0.[4] However, in the presence of two reduced-function variants or one reduced-function and one no-function variant, the DPWG recommends assessment of DPD activity (phenotype testing) to guide treatment decisions, because enzyme activity cannot be predicted correctly with genotyping.[4]

All three guidelines note that further dose reduction may be required after the start of treatment, based on the development of toxicity.[4,8,30]

Some patients who carry reduced-function or no-function variants may tolerate normal doses of fluoropyrimidines.[8] To avoid underdosing and maintain drug effectiveness, the CPIC recommends that patients with genotype-guided dose reductions who experience no or clinically tolerable toxicity in the first two chemotherapy cycles or who have subtherapeutic plasma 5-FU concentrations should have their dose increased in subsequent cycles.[8] The CPIC also recommends follow-up 5-FU pharmacokinetic testing to avoid underdosing.[8]

The DPWG guideline noted that variants with a possible effect on DPD activity may be identified in the future, and that evidence for some variants is insufficient at present.[4] For the *DPYD* variant c.557A>G (Y186C), which is more prevalent in people of African ancestry, one study showed an association with reduced DPD activity, but its association with toxicity was weak.[8] Because the addition of other variants may affect the ability of *DPYD* genotyping to predict DPD enzyme activity, guidelines may be updated if new evidence becomes available.[4]

Table 1: Pharmacogenetic Guidelines for Fluorouracil and Capecitabine Regimens

Genotype[a]	Starting Dose Recommendation		
	CPIC[8,21]	DPWG[4]	SPT[30]
Carrier of normal-function variants	Use label-recommended dosage and administration	No changes to standard dose	NR
Heterozygous carrier of 1 reduced-function or 1 no-function variant	50% of full standard dose[b] Dose increase based on clinical judgment and ideally TDM[c]	50% of standard dose Further dose titration may be done, guided by toxicity	50% of standard dose Dose titration based on TDM should be favoured over toxicity-based titration[d]
Heterozygous or homozygous carrier of 2 reduced-function variants	50% of full standard dose[b] Dose increase based on clinical judgment and ideally TDM[c]	Determined by DPD activity level (phenotype)[e]	25% of standard dose (75% reduction) Dose titration based on TDM should be favoured over toxicity-based titration[d]
Carrier of 1 reduced-function and 1 no-function variant	Avoid fluoropyrimidine-based regimens If no fluoropyrimidine-free regimen is suitable, 5-FU should be administered at a strongly reduced dose[f] with early TDM[g]	Determined by DPD activity level (phenotype)[e]	No fluoropyrimidine chemotherapy recommended
Carrier of 2 no-function variants	Avoid 5-FU or 5-FU prodrug-based regimens	Avoid systemic and cutaneous administration of 5-FU or capecitabine; tegafur is not an alternative If these drugs cannot be avoided, DPD activity may be measured to adjust the dose	No fluoropyrimidine chemotherapy recommended

Abbreviations: 5-FU, 5-fluorouracil; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPD, dihydropyrimidine dehydrogenase; DPWG, Dutch Pharmacogenetics Working Group; NR, not reported; SPT, Swiss Group of Pharmacogenomics and Personalised Therapy; TDM, therapeutic drug monitoring.

[a]Based on *DPYD* variants *DPYD**2A, *DPYD**13, c.2846A>T, and c.1236G>A.

[b]Updated in November 2018.[21] Previous recommendation: reduce dose by 25% to 50%.[8]

[c]Increase dose in patients with no or clinically tolerable toxicity in first two cycles to maintain effectiveness; decrease dose if starting dose not tolerated to minimize toxicity.[21]

[d]"To enable TDM-based dose titration, we generally recommend treating patients carrying a *DPYD* risk variant with an infusional 5-FU regimen and avoiding the use of the oral prodrug capecitabine. Only if the use of an infusional 5-FU regimen is not possible, should a prudent titration of capecitabine doses based on monitoring of toxicity and starting with the recommended reduced dose be considered."[30]

[e]When two different genetic variants are identified in one patient, they may be located on the same allele or on different alleles.[4] Because the location of the variants results in differences in DPD function, and because genotyping methods cannot determine the allelic location of the variants, DPD function cannot be accurately predicted by genotype.[4] The DPWG recommends performing a phenotype test to assess DPD activity in this situation.[4]

[f]If available, a phenotyping test should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of < 25% of the normal starting dose is estimated, assuming additive effects of alleles.[21] No reports of the successful administration of low-dose 5-FU in *DPYD* poor metabolizers are available to date.[21]

[g]Therapeutic drug monitoring should be done at the earliest point possible to immediately discontinue therapy if the drug level is too high.[21]

Guidelines on DPYD *Genotyping From Clinical Associations*

A consensus paper from scientific medical associations in Germany, Austria, and Switzerland proposed implementation of the EMA's recommendation on DPD deficiency.[5] Before treatment with fluoropyrimidines, patients should undergo *DPYD* genotyping (*DPYD**2A, *DPYD**13, c.2846A>T, and c.1236G>A), and the genetic results should form the basis of recommendations for treatment.[5] The consensus paper noted that treatment recommendations must be tailored to the individual disease situation and alternative available treatments, and that genetic testing may be supplemented with therapeutic drug monitoring.[5] Although the group noted that the evidence base for phenotype tests was less extensive than for genotype tests, they considered pre-treatment measurement of plasma uracil or DPD activity in leukocytes to be alternatives to genotyping.[5] They also stated that recommendations based on test results should be integrated into the treatment plan without causing delays.[5]

The European Society for Medical Oncology guidelines for localized colorectal cancer note that "DPD genotyping or phenotyping is strongly recommended before initiating fluoropyrimidine-based adjuvant therapy according to regulatory bodies."[31]

The 2018 Guidelines of the Groupe de Pharmacologie Clinique Oncologique–UNICANCER on DPD Deficiency Screening recommend screening for DPD deficiency using both *DPYD* genotyping (four variants listed above) and phenotype tests (plasma uracil level) to guide decisions on dose reductions or the need for an alternative treatment.[19]

Health Technology Assessment Recommendations on DPYD *Genotyping*

In Quebec, INESSS[32] recommended that prospective genotyping for *DPYD* variants *DPYD**2A, *DPYD**13, c.2846A>T, and c.1129-5923C>G (c.1236G>A) be included in the planning of cancer treatment with fluoropyrimidines.[1,25] They noted that the association between the *DPYD* genotype and DPD activity is imperfect, but compared to phenotype testing, *DPYD* genotyping is accessible, fast, and inexpensive, and it may reduce the risk of severe toxicity in carriers.[32] According to the experts consulted by INESSS,[32] the results from *DPYD* genotyping are clinically important and could lead to a change in clinical conduct. Concerns raised by the experts included the fact that not all patients with a positive result developed severe toxicity and some patients with a negative result did, as well as the lower level of clinical evidence for the c.1236G>A variant.[32]

France's Haute Autorité de Santé (HAS) noted that the association between three *DPYD* variants (*DPYD**2A, *DPYD**13, and c.2846A>T) and severe toxicity has been demonstrated, but that the evidence was insufficient for an association between c.1236G>A and toxicity.[10] The HAS concluded that, based on three variants and despite its proven association with toxicity, *DPYD* genotyping has a low sensitivity to detect DPD deficiency (i.e., only some patients with DPD deficiency can be identified by this test).[10] As well, the variants currently identified are more common in Caucasian than non-Caucasian people.[10] The HAS recommended that DPD deficiency be tested by determining plasma uracil concentrations in patients with planned fluoropyrimidine treatment, "as it is considered to be the most likely to be able to identify at least, and as far as possible, all patients with complete DPD deficiency."[10,33] As a consequence, the plasma uracil test was standardized across French laboratories, and thresholds for deficiency and treatment decisions were developed.[10]

Equity Considerations

Health inequities are differences in the distribution of health that may be avoidable, as well as unjust and unfair.[34]

The *DPYD* variants that have been more extensively studied and for which fluoropyrimidine dose adjustment is recommended are those that are more prevalent in the Caucasian population.[10] Other *DPYD* variants with a potential effect on DPD activity that are more prevalent in other racial/ethnic groups have not been studied as extensively, so recommendations on the use of fluoropyrimidines in carriers of these variants are not available.[10]

DPYD genotyping is currently performed at one hospital in Ontario, so the test is not available to patients who are not receiving care at this hospital or who cannot be referred there.

Ethics Considerations

People with one no-function variant can be considered carriers of an inborn error of metabolism; they may wish to share this information with their offspring[8] and other close relatives in case they are also carriers. People who are homozygous for no-function *DPYD* variants have complete DPD inactivity, a clinically heterogeneous autosomal-recessive disorder of pyrimidine metabolism; clinical presentation ranges from no symptoms to severe convulsive disorders with motor and mental impairment.[8]

Regulatory Information

DPYD genotyping using laboratory-developed tests is not subject to regulatory approval.

Ontario, Canadian, and International Context

DPYD genotyping was not publicly funded in Ontario at the time of writing of this report.

At the time of writing, one hospital conducted *DPYD* genotyping in patients with planned fluoropyrimidine-based treatment. The test was being done through a research program (Richard Kim, MD, email communication, November 9, 2020). A *DPYD* genotyping assay has also been developed and validated at another hospital in Ontario (Lei Fu, PhD, email communication, February 8, 2021), but the test was not in use at the time of writing.

At the time of publication of this report, Ontario had no provincial guideline for *DPYD* genotyping before chemotherapy (Lei Fu, PhD, email communication, February 8, 2021; Richard Kim, MD, email communication, January 12, 2021; John Lenehan, MD, email communication, February 12, 2021; Geoffrey Liu, MD, email communication, January 18, 2021; Michael Raphael, MD, email communication, February 10, 2021; Jason Yu, MD, email communication, January 17, 2021). Phenotype tests for DPD activity are not routinely done in Ontario given the challenges associated with implementing them as routine tests (Richard Kim, MD, email communication, January 12, 2021; John Lenehan, MD, email communication, February 12, 2021; Geoffrey Liu, MD, email communication, January 18, 2021; Jason Yu, MD, email communication, January 17, 2021).

In Quebec, *DPYD* genotyping for all four variants (*DPYD**2A, *DPYD**13, c.2846A>T, and c.1236G>A) is publicly funded; the test is performed in three laboratories in the province.[35] We are uncertain whether other Canadian provinces are using *DPYD* genotyping and its funding status.

In 2020, the National Health Service in England, in response to an urgent policy request, recommended that all patients undergo *DPYD* genotyping (four variants mentioned above) before starting a fluoropyrimidine-based treatment.[36] They also recommended the monitoring of prescribing decisions (e.g. dose adjustments) and patient toxicity to inform future updates to the recommendation.[36]

DPYD genotyping is publicly funded in Switzerland.[37] In France, fluoropyrimidines cannot be prescribed without the results of a plasma uracil test.[38]

Expert Consultation

We engaged with experts in the specialty areas of pharmacogenetics, clinical oncology, and laboratory medicine to help inform our understanding of aspects of the health technology and our methodologies, and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42020176858), available at https://www.crd.york.ac.uk/PROSPERO.

Clinical Evidence

When planning this review, we considered the following to be out of scope:

- Phenotype tests to measure DPD activity, as such tests are not currently done in Ontario given the limitations mentioned in the Background section
- *DYPD* variants for which genotype-guided fluoropyrimidine dose recommendation guidelines were not available
- The analytical validity of *DPYD* genotyping, because studies identified by a 2017 review[25] have already demonstrated that the analytical validity of *DPYD* genotyping is accurate
- The effectiveness of alternative chemotherapy treatments in *DPYD* carriers for whom fluoropyrimidines are considered contraindicated

Research Questions

- What is the risk of severe fluoropyrimidine-associated toxicity in carriers of the *DPYD* variants under assessment (*DPYD**2A, *DPYD**13, c.2846A>T, and c.1236G>A) compared to patients with wild-type *DPYD* in those who have planned cancer treatment with fluoropyrimidines (clinical validity)?
- Does pre-treatment *DPYD* genotyping for the variants under assessment lead to changes in treatment decision-making and/or decrease the risk of severe fluoropyrimidine-associated toxicity compared to no testing or other tests for DPD deficiency in patients who have planned cancer treatment with fluoropyrimidines (clinical utility)?
- What is the effectiveness of treatment with fluoropyrimidines in patients who had their fluoropyrimidine dose adjusted before the start of treatment (because they carried at least one of the *DPYD* variants under assessment) compared to patients who did not have pre-treatment dose adjustment?

Methods

Clinical Literature Search

Because we identified relevant systematic reviews during scoping, we performed a systematic literature search for systematic reviews and health technology assessments that matched our research questions and PICOTS (population, intervention, comparator, outcomes, timing, and setting) to use them as a source of primary studies published until their literature search dates. We assessed eligible systematic reviews and health technology assessments using the Risk of Bias in Systematic Reviews (ROBIS) tool.[39] We searched for systematic reviews and health technology assessments that had a low risk of bias and matched the scope of our review; we used recency and comprehensiveness as additional inclusion criteria. We permitted the selection of more than one report in case a single report did not cover the full scope of our review.

Then, we ran a systematic literature search to identify studies published since the searches for the selected systematic reviews were performed; we used the earliest search date among the selected two systematic reviews. We included primary studies identified from the selected systematic reviews and from the systematic literature search in our review.

We performed a clinical literature search on February 20, 2020, to retrieve systematic reviews and health technology assessments published from database inception until the search date. The health technology assessments we selected searched the literature from database inception (earliest search start date) until January 2018 (earliest search end date). We then performed a clinical literature search for primary studies on February 27, 2020, to retrieve studies published from January 2018 until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED). We used the Cochrane Central Register of Controlled Trials exclusively in the search for primary studies.

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. A methodological filter was used to limit retrieval to systematic reviews, meta-analyses, and health technology assessments in our first search. The final search strategies were peer-reviewed using the PRESS Checklist.[40]

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Systematic Reviews

Inclusion Criteria

- English-language full-text publications
- Systematic reviews and health technology assessments published from database inception until February 20, 2020
- Systematic reviews and health technology assessments that included a systematic review and had a low risk of bias as assessed by the ROBIS tool[39]
- Reports whose research question and PICOTS matched or included the ones that were the focus of the present report
- Reports that provided information about their literature search methods, including databases searched, search strategy, and search start and end dates
- Reports that had prespecified eligibility criteria

Exclusion Criteria

- Nonsystematic reviews, editorials, commentaries, conference abstracts, and letters

Primary Studies

Inclusion Criteria

- English-language full-text publications
- Studies published before January 2018 that were identified from the health technology assessments selected, and from January 2018 until February 27, 2020, that were identified through the primary studies literature search
- Randomized controlled trials, prospective or retrospective comparative observational studies
- Studies that provided information about fluoropyrimidine dose adjustments before and/or after the start of treatment

Exclusion Criteria

- Animal and in vitro studies
- Editorials, commentaries, case-reports (< 10 patients included), conferences abstracts, letters

PARTICIPANTS

- Adult and pediatric patients who had planned cancer treatment with fluoropyrimidines, alone or in combination with other therapies

INTERVENTIONS

Clinical Validity

Exposure

- Included: carriers of at least one of the variants under assessment (*DPYD**2A, *DPYD**13, c.2846A>T, c.1236G>A)
- Excluded: carriers of other *DPYD* or other gene variants; those with DPD deficiency defined according to phenotype tests for DPD function (e.g., plasma uracil concentration or dihydrouracil:uracil [UH2:U] ratio)

Control

- Included: wild-type patients (noncarriers of variants under assessment) defined by *DPYD* genotyping
- Excluded: wild-type patients with an absence of DPD deficiency according to phenotype tests or other genetic tests

Clinical Utility

Intervention

- Included: *DPYD* genotyping of the variants under assessment (*DPYD**2A, *DPYD**13, c.2846A>T, c.1236G>A) before the start of treatment; or carriers of at least one of the *DPYD* variants under assessment who received a genotype-guided fluoropyrimidine dose reduction
- Excluded: treatment decisions based on testing for other *DPYD* or other gene variants; treatment decisions based on phenotype tests for DPD function (e.g., plasma uracil concentration or UH2:U ratio) or 5-FU pharmacokinetics assessment

Comparator

- Included: patients with no testing; patients with phenotype tests for DPD function (e.g., plasma uracil concentration or UH2:U ratio) before the start of treatment, or 5-FU pharmacokinetics assessment after the start of treatment; or wild-type patients or *DPYD* carriers without a genotype-guided fluoropyrimidine dose reduction
- Excluded: patients who received treatment with uridine triacetate

Fluoropyrimidine Treatment Effectiveness

Intervention

- Included: carriers of at least one of the variants under assessment, with *DPYD*-genotyping-guided fluoropyrimidine dose adjustment before the start of treatment
- Excluded: patients with no fluoropyrimidine dose adjustment before the start of treatment; patients with fluoropyrimidine dose adjustment based on criteria other than *DPYD* genotyping; patients undergoing alternative cancer treatment because of a contraindication to fluoropyrimidines

Comparator

- Included: wild-type patients or *DPYD* carriers with no fluoropyrimidine dose adjustment before the start of treatment
- Excluded: patients who had a fluoropyrimidine dose adjustment before the start of treatment

OUTCOME MEASURES

Clinical Validity

- Severe fluoropyrimidine-related toxicity, overall and by type (hematological, gastrointestinal, dermatological)
- Clinical sensitivity, specificity, and positive and negative predictive value of *DPYD* genotyping (three to four variants) for the prediction of fluoropyrimidine-associated toxicity
- Toxicity-related changes to fluoropyrimidine-based treatment (i.e., dose reduction or increase, treatment delay and discontinuation)
- Toxicity-related hospitalization
- Toxicity-related mortality

Clinical Utility

- Fluoropyrimidine dose reduction, increase, discontinuation; use of alternative treatment
- Toxicity-related changes to fluoropyrimidine-based treatment (i.e., dose reduction or increase, treatment delay and discontinuation)
- Severe fluoropyrimidine-related toxicity, overall and by type (hematological, gastrointestinal, dermatological)
- Toxicity-related hospitalization
- Toxicity-related mortality

Fluoropyrimidine Treatment Effectiveness

- Treatment response
- Disease progression
- Overall survival
- Progression-free survival

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[41] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. A single reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, time points at which the outcomes were assessed)

We contacted study authors to provide clarification as needed.

Data Presentation and Statistical Analysis

When assessing dichotomous outcomes such as severe toxicity, treatment modifications, hospitalization, and mortality, we extracted information on the number of patients from each group who experienced an event from the studies identified. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE)[14] across studies and included common toxicities with fluoropyrimidine treatment (hematological, gastrointestinal, and dermatological). Severe toxicity was defined as grade 3 or higher; specifically for hand–foot syndrome, a toxicity grade of 2 or higher was considered severe in some studies because of its clinical relevance. When possible, we reported results separately for each *DPYD* variant under assessment and by combining carriers of any one of these variants into a single group. We used risk ratios as the effect measures for these dichotomous outcomes; we calculated risk ratios and 95% confidence intervals (CIs) based on information provided in the studies. We used the exact method (R exactmeta package[42]) to calculate the confidence interval because it does not rely on approximation to normal distribution and is therefore more suitable for sparse data, as was the case with the data reported in the studies.[43] We calculated *P*-values using the Fisher exact test when risk ratios could not be calculated (e.g., in the case of zero events in one of the study groups).

The included studies also reported the clinical sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of *DPYD* genotyping for predicting severe fluoropyrimidine-related

toxicity. We used the occurrence of severe toxicity as the reference standard; sensitivity was defined as the proportion of patients identified as carriers of a *DPYD* variant among those who experienced severe toxicity. We defined specificity as the proportion of wild-type patients among those who did not experience severe toxicity. When these outcomes were not reported in the studies, we calculated them based on the information provided: number of carriers of *DPYD* variants who experienced severe toxicity (true positive); number of wild-type patients without severe toxicity (true negative); number of wild-type patients with severe toxicity (false negative); number of *DPYD* variant carriers without severe toxicity (false positive). We defined PPV as the proportion of patients who experienced toxicity among those identified as *DPYD* variant carriers and NPV as the proportion of patients who did not experience toxicity among wild-type patients. We calculated sensitivity, specificity, and the corresponding 95% confidence intervals without continuity correction (modified Wilson method) using the Mada package in R.[42]

We used the prevalence of *DPYD* variant carriers reported in the studies to calculate the pooled prevalence and 95% confidence interval for each variant individually and combined, using the exact method in R (meta package).[42]

For effectiveness outcomes, we extracted the number of patients who experienced the outcomes of interest and hazard ratios comparing *DPYD* variant carriers and wild-type patients from the study.

We had originally planned subgroup analyses (type of cancer, type of fluoropyrimidine used, route of administration, and one or more factors relevant to this topic that may predispose patients to health inequities:[34] place of residence, race/ethnicity, occupation, gender/sex, religion, education, socioeconomic status, and social capital, among others); however, the studies we identified did not provide sufficient information for us to conduct these analyses.

The study results are represented using forest plots. We judged heterogeneity by visual inspection of the forest plots. In the studies we identified, the data were sparse, so we were unable to perform tests of homogeneity (e.g., Cochran's Q test) because they rely on the large sample assumption. Instead, we based homogeneity assumptions on our knowledge of the distribution of rates of toxicity across populations. When appropriate, we performed fixed-effect meta-analyses in the absence of heterogeneity using the exact method in R (exactmeta and gplots packages).[42]

Critical Appraisal of Evidence

We assessed risk of bias using the Newcastle-Ottawa Scale (Appendix 3) for observational studies.[44] We used the ROBIS risk of bias tool[39] for systematic reviews. We used only domains 1 and 2 (study eligibility criteria and identification and selection of studies) of the ROBIS tool because we used the selected systematic reviews as a source of eligible studies (i.e., we did not use the results, synthesis, and conclusions sections of the reviews).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[45] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence. For toxicity outcomes, we assessed the quality of the evidence for overall toxicity and for the most commonly reported types of toxicity (hematological, gastrointestinal, and dermatological) because we believed these would be most relevant for decision-making.

Results

Clinical Literature Searches

SYSTEMATIC REVIEWS

The database search of the clinical literature for systematic reviews yielded 128 citations published from database inception until February 20, 2020. We identified six additional studies from other sources. In total, we identified seven studies (four systematic reviews and three health technology assessments) that met our inclusion criteria.[10,32,46-50] Figure 1 present the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search for systematic reviews.

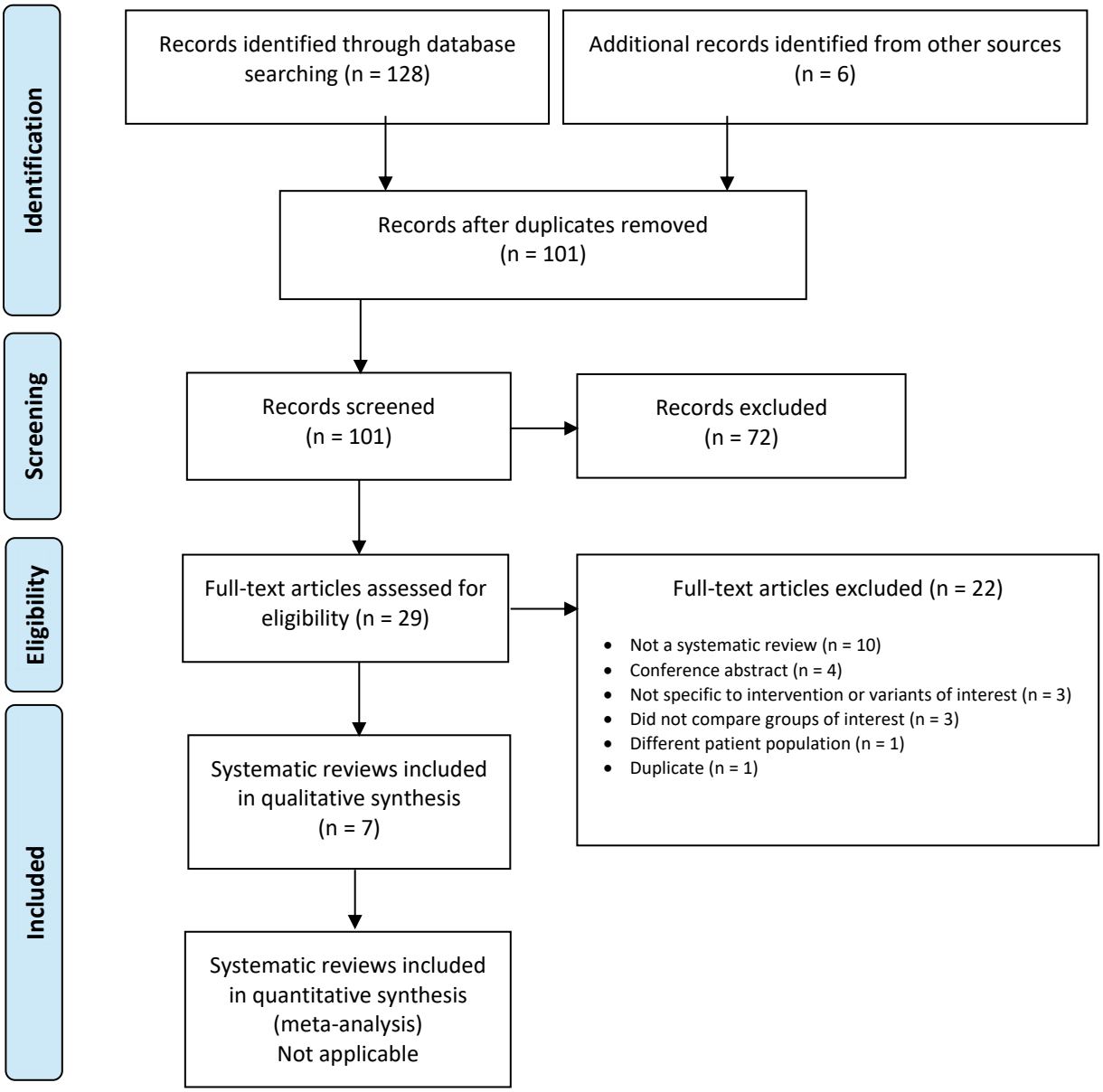

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy (Systematic Reviews)

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Moher et al.[51]

We identified four eligible systematic reviews published between 2013 and 2016 and three eligible health technology assessments published between 2016 and 2019.[10,32,46-50] All seven publications evaluated the clinical validity of *DPYD* genotyping, but only one health technology assessment included all four *DPYD* variants under assessment in the current review.[10] Two health technology assessments assessed the clinical utility of *DPYD* genotyping, including all four variants.[10,32] One also assessed treatment effectiveness among *DPYD* variant carriers who had their fluoropyrimidine dose reduced as a result of genotyping.[32]

The systematic reviews and health technology assessments we identified had a generally low risk of bias, but none covered all of the research questions and *DPYD* variants that were the object of this review. Therefore, we selected two health technology assessments[10,32] because they were recent and because together they covered all of the research questions and *DPYD* variants we assessed. Neither of the two health technology assessments planned to perform new meta-analyses.[10,32] We complemented their literature search and performed de novo analyses when appropriate.

PRIMARY STUDIES

The database search of the clinical literature for primary studies yielded 355 citations published between January 2018 and February 27, 2020. We identified 19 additional primary studies (published up to 2018) from the selected health technology assessments and one from database auto-alerts. Overall, we identified 29 studies (all observational) that met our inclusion criteria; we used 25 to answer the clinical validity research question[7,9,13,15,18,52-71]; six to answer the clinical utility research question[7,11,12,23,71,72]; and one to answer the treatment effectiveness research question.[11] (We used two studies[7,71] for both the clinical validity and clinical utility questions, and one study[11] for both the clinical utility and treatment effectiveness questions.) Figure 2 presents the PRISMA flow diagram for the clinical literature search for primary studies.

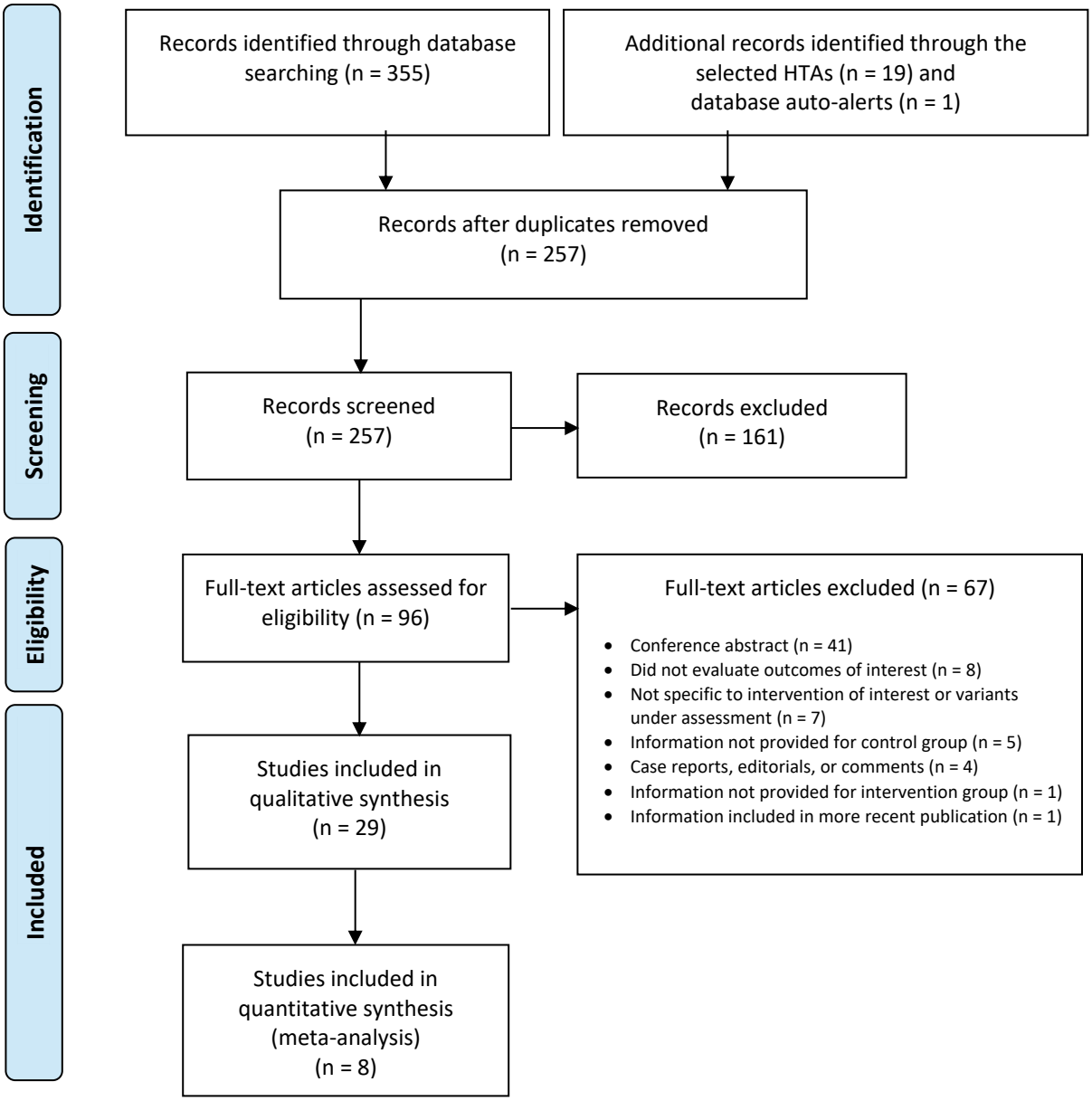

Figure 2: PRISMA Flow Diagram—Clinical Search Strategy (Primary Studies)

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[51]

Characteristics of Included Studies

CLINICAL VALIDITY

A total of 25 studies evaluated the risk of severe fluoropyrimidine-related toxicity in carriers of at least one of the *DPYD* variants under assessment and treated with a standard fluoropyrimidine dose, compared to wild-type patients.[7,9,13,15,18,52-69,71] The studies were performed in Canada, Europe, the United States, and Bangladesh. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE)[14] and included events that commonly occur with fluoropyrimidine

treatment (hematological, gastrointestinal, and dermatological). Severe toxicity was defined as grade 3 or higher, although for hand–foot syndrome, toxicity grade 2 or higher was considered severe in some studies because of its clinical relevance. We relied on the investigators' judgment regarding the association between outcomes and fluoropyrimidine treatment.

Study samples ranged in size from 73 to 2,886 patients, and the number of *DPYD* carriers ranged from 1 to 85. Overall, 4 (16%) studies identified just one carrier, and 12 (48%) identified 10 carriers or more. Participants included patients with different types of cancers (e.g., colorectal, gastrointestinal, and breast) who had planned treatment with either 5-FU or capecitabine, alone or in combination with other chemotherapy drugs. In three studies, patients also received radiotherapy.[7,62,71]

Four studies included all four *DPYD* variants under assessment,[7,56,57,61] nine studies assessed three variants,[9,15,18,53,55,58-60,62] and the remainder evaluated one or two *DPYD* variants. *DPYD**2A was the most common variant assessed (20 studies),[7,9,15,53-69] followed by c.2846A>T (16 studies),[7,9,15,18,52,53,55-62,67,70] *DPYD**13 (13 studies),[7,9,15,18,52,53,55-58,60-62] and c.1236G>A (9 studies).[7,13,18,56,57,59,61,70,71]

The timing of the evaluation of toxicity varied across studies, occurring in the first 1 to 2 cycles in 6 studies[18,56,57,61,67,68] and the first three to four cycles in three studies.[9,53,60] In the remaining studies, either the full duration of treatment was used or the period of evaluation was not reported.[7,13,15,52,54,55,58,59,62-66,69-71]

CLINICAL UTILITY

Six studies identified included carriers of one of the *DPYD* variants under assessment who received a genotype-guided reduced fluoropyrimidine dose from the start of treatment.[7,11,12,23,71,72] These studies compared the outcomes of *DPYD* carriers with those of wild-type patients who received a standard fluoropyrimidine dose. The studies were performed in Canada and Europe.

We did not include a study by Deenen et al[73] because its data were part of a larger, more recent study (Henricks et al, 2019[11]) that we did include in this report.

One study (Lunenburg et al, 2018[7]) also compared the outcomes of *DPYD* carriers treated with a genotype-guided reduced fluoropyrimidine dose with those of *DPYD* carriers treated with a standard dose. This study combined three separate databases to form the study groups.[7]

A study by Henricks et al[11] also included a comparison group of *DPYD**2A carriers treated with a standard fluoropyrimidine dose, but this group represented a historical cohort based on results reported from other studies, rather than a direct patient comparison. Given that this historical cohort did not originate from the same population base as the reduced-dose cohort, there were differences in the distribution of important patient characteristics (sex, type of cancer, fluoropyrimidine used). Because there was no adjustment for such potential confounders, we did not include this comparison group in our report.

Another study by Henricks et al[72] compared the risk ratio that they obtained in their study (for severe toxicity in *DPYD* carriers treated with a reduced dose versus wild-type patients) with the risk ratio from a previous meta-analysis that compared *DPYD* carriers treated with a standard dose versus wild-type patients. We did not include this comparison in our report because it was not a direct patient comparison.

Study samples ranged in size from 66 to 1,646 patients; 3 to 85 of those were *DPYD* carriers treated with a reduced fluoropyrimidine dose. Participants included patients with different types of cancers (e.g., colorectal, gastrointestinal, and breast) who had planned treatment with 5-FU or capecitabine, either alone or in combination with other chemotherapy drugs. In four studies, patients also received radiotherapy.[7,11,71,72]

Four studies included all four variants under assessment,[7,12,71,72] one included three variants (*DPYD**2A, c.2846A>T, and *DPYD**13),[23] and one study only included *DPYD**2A.[11] One study identified five homozygous carriers (1 carrier of *DPYD**2A, 2 carriers of c.2846A>T, two carriers of c.1236G>A) and one compound heterozygous carrier (c.2846A>T/c.1236G>A); these patients were excluded from the study and treated with individualized regimens.[72,74] The study by Wigle et al[71] identified two compound heterozygous carriers (*DPYD* variants not reported); these patients were excluded from the study, and the treating oncologists were advised to use an alternative treatment instead of fluoropyrimidines. Results refer to heterozygous carriers unless otherwise specified.

The turnaround time for *DPYD* genotyping ranged from 2 working days to 1 week, based on two studies.[23,72]

Outcomes included the frequency of treatment modification, severe toxicity, and toxicity-related hospitalization and mortality. Toxicity was graded according to the NCI-CTCAE[14] across studies and included toxicities that are common with fluoropyrimidine treatment (hematological, gastrointestinal, and dermatological). Severe toxicity was defined as grade 3 or higher, although for hand–foot syndrome, toxicity grade 2 or higher was considered severe in some studies because of its clinical relevance. Results for individual variants were provided in only one study,[72] so we reported results for all *DPYD* variants assessed in each study as a single group. Additional information is provided in Appendix 2.

FLUOROPYRIMIDINE TREATMENT EFFECTIVENESS

One study assessed the effectiveness of fluoropyrimidine treatment in 37 *DPYD*2A* carriers who received a genotype-guided reduced fluoropyrimidine dose compared to 37 wild-type patients who were treated with a standard dose and matched according to variables that were expected to affect treatment outcome.[11]

Risk of Bias in the Included Studies

CLINICAL VALIDITY

The included studies generally used appropriate methods for patient group selection (carriers and wild-type patients), exposure, and outcome ascertainment, and follow-up was adequate. However, no adjustment or matching was used when comparing the frequency of severe toxicity between study groups. Additional information is provided in Appendix 3.

CLINICAL UTILITY

The included studies generally used appropriate methods for patient group selection (carriers and wild-type patients), exposure, and outcome ascertainment, and follow-up was adequate. However, no adjustment or matching was used for the comparative groups. The study by Lunenburg et al[7] reported an imbalance in the distribution of *DPYD* variants between reduced-dose carriers and standard-dose carriers: the two variants that were expected to have a weaker effect on DPD activity were overrepresented in the latter group. This may have led to an underestimate of the frequency of severe toxicity in the standard-

dose group and consequently an underestimate in the difference between groups. Additional information is provided in Appendix 3.

FLUOROPYRIMIDINE TREATMENT EFFECTIVENESS

The included study used appropriate methods for patient group selection (carriers and wild-type), exposure, and outcome ascertainment, and follow-up was adequate. Patients were matched according to variables that were expected to affect the outcomes assessed. Additional information is provided in Appendix 3.

Clinical Validity

We assessed clinical validity by comparing the frequency of severe fluoropyrimidine-related toxicity (overall and by type) in carriers of *DPYD* variants (*DPYD**2A, *DPYD**13, c.2846A>T, c.1236G>A) treated with a standard fluoropyrimidine compared to wild-type patients. We also evaluated the frequency of treatment modifications and hospitalizations. Results are presented for the three to four *DPYD* variants as a group, and then separately for each variant.

We also calculated the clinical sensitivity, specificity, PPV, and NPV of *DPYD* genotyping to predict fluoropyrimidine-related toxicity using the occurrence of severe toxicity as the reference standard. However, the assumption that toxicity is the reference standard to calculate these parameters may not be satisfied, because DPD function is not the only factor that affects toxicity in patients treated with fluoropyrimidines; factors other than *DPYD* genotyping affect DPD function[4]; and other unknown *DPYD* variants may affect DPD function.

Given the clinical heterogeneity in terms of type of cancer, type of fluoropyrimidine, mode of administration, and combination regimens, we conducted meta-analyses of study results in only some cases.

Results refer to heterozygous carriers unless otherwise specified. Because fluoropyrimidine dosing regimens vary according to type of cancer and cancer stage, whether fluoropyrimidines are used alone or in combination, and the type of combination regimen, we have used the term “standard dose” to refer to the usual fluoropyrimidine dose in a given patient population to distinguish it from the genotype-guided reduced dose.

Although patients generally started treatment on a standard fluoropyrimidine dose, dose reductions were allowed in both *DPYD* carriers and wild-type patients according to the development of toxicity, clinical condition, and or other factors such as age.[9,13,15,54-62,64,67,68] In some studies, the reduction was based on toxicity grade of less than 3,[9,57,59,62,64,67] which may have prevented severe (grade ≥ 3) toxicity and led to an underestimate of severe toxicity. Additional information is provided in Appendix 2.

PATIENT CHARACTERISTICS

The mean age of patients in the included studies ranged from 47 to 67 years, and a large proportion were male (42% to 73%), except for two studies that included only women with breast cancer.[56,68] Based on information from nine studies;[9,13,18,53,57,58,60,67,71] 67% to 100% of patients were of Caucasian origin; another study stated that patients were mostly Caucasian (numbers not provided).[61] Additional information is provided in Appendix 4.

Colorectal cancer was the most common type of cancer, affecting all patients in 12 studies[13,15,54,55,58,59,61,62,64,66,67,69] and 35% to 85% of patients in nine studies;[7,18,52,53,57,60,63,65,71] other types of cancer included breast, gastrointestinal, esophageal, and head and neck cancers.[7,9,13,15,18,52-69] The most common fluoropyrimidine used was 5-fluorouracil: 11 studies included only patients treated with 5-FU alone or in combination regimens[13,15,54,55,58,62,64-67,69]; four included only patients treated with capecitabine alone or in combination[56,61,68,70]; and in the remaining studies, 12% to 91% of patients were prescribed 5-FU.[7,9,18,53,57,59,60,63,71] Three studies reported that none of the *DPYD* variants under assessment were present in non-Caucasian patients.[12,53,57]

Table 2 shows the prevalence of *DPYD* variant carriers identified in the included studies (Appendix 5).

Table 2: Prevalence of the *DPYD* Variants in the Included Studies

Variant	Prevalence Range, %	Pooled Prevalence, % (95% CI)
*DPYD**2A, heterozygous	0.7 to 5.0[7,9,15,53-69]	1.1 (0.9–1.4)
*DPYD**13, heterozygous	0.0 to 0.6[7,9,15,52,53,55-58,60-62]	0.2 (0.1–0.3)
c.2846A>T, heterozygous	0.6 to 2.8[7,9,15,52,53,55-62,67,70]	1.2 (1.0–1.5)
c.1236G>A, heterozygous	1.7 to 8.1[7,13,56,57,59,61,70,71]	4.0 (3.4–4.7)
Any of the 4 *DPYD* variants, heterozygous	4.5 to 7.4[7,56,57,61]	6.6 (5.6–7.7)
c.1236G>A, homozygous	0.05 to 0.2[13,57,61]	0.1 (0.03–0.3)
Compound heterozygous	*DPYD**2A/c.2846A>T: 0.03[58] to 0.4[67] *DPYD**2A/*DPYD**13: 0.2%[9] *DPYD**13/c.1236G>A: 0.2%[57]	0.09 (0.04–0.3)

Abbreviation: CI, confidence interval.

RISK OF SEVERE TOXICITY IN *DPYD* CARRIERS VERSUS WILD-TYPE PATIENTS

Carriers of Any of the 4 DPYD Variants

Overall Severe Toxicity

Of carriers of any of the *DPYD* variants under assessment who received a standard fluoropyrimidine dose, overall severe toxicity was reported in 23.5% to 100%, compared to 8.2% to 41.5% in wild-type patients, across seven studies.[7,9,57-60,62] Two studies included all four *DPYD* variants under assessment,[7,57] and five studies included three variants (*DPYD**2A, *DPYD**13, and c.2846A>T).

The results of six of the seven studies indicated a higher risk in *DPYD* carriers treated with a standard fluoropyrimidine dose compared to wild-type patients[9,57-60,62]; in the seventh study, the point estimate of the risk ratio (RR) was consistent with an increased risk in *DPYD* carriers, but the confidence interval included the possibility of a lower risk.[7] Pooling the results of these seven studies yielded a risk ratio of 2.63 (95% CI 2.15–3.96; Figure 3); we decided that the range of effect estimates observed across studies warranted meta-analysis. This analysis did not include homozygous or compound heterozygous carriers; effects for these groups were analyzed separately.

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

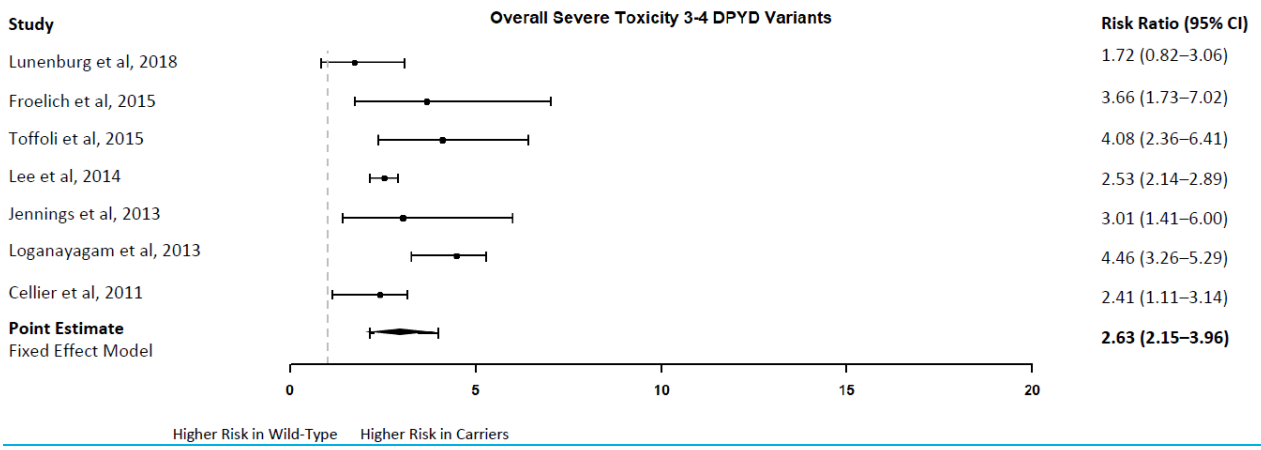

Figure 3: Carriers of Any of the Four *DPYD* Variants Versus Wild-Type Patients—Risk of Overall Severe Toxicity

Sources: Lunenburg et al,[7] Froehlich et al,[57] Toffoli et al,[9] Lee et al,[58] Jennings et al,[59] Loganayagam et al,[60] and Cellier et al.[62]

Severe Hematological Toxicity

Neutropenia was the most common hematological toxicity reported. Two (5.9%) *DPYD* carriers who received a standard fluoropyrimidine dose and 12 (1.6%) wild-type patients also treated with a standard dose had severe neutropenia (RR 3.69, 95% CI 0.53–16.97) in the study by Lunenburg et al,[7] whereas six (35.3%) *DPYD* carriers and 38 (6.5%) wild-type patients had severe neutropenia (RR 5.43, 95% CI 2.15–11.53) in the study by Toffoli et al.[9] The pooled risk ratio was 4.42 (95% CI 1.59–9.18; Figure 4); we decided that the range of effect estimates observed across studies warranted meta-analysis.

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

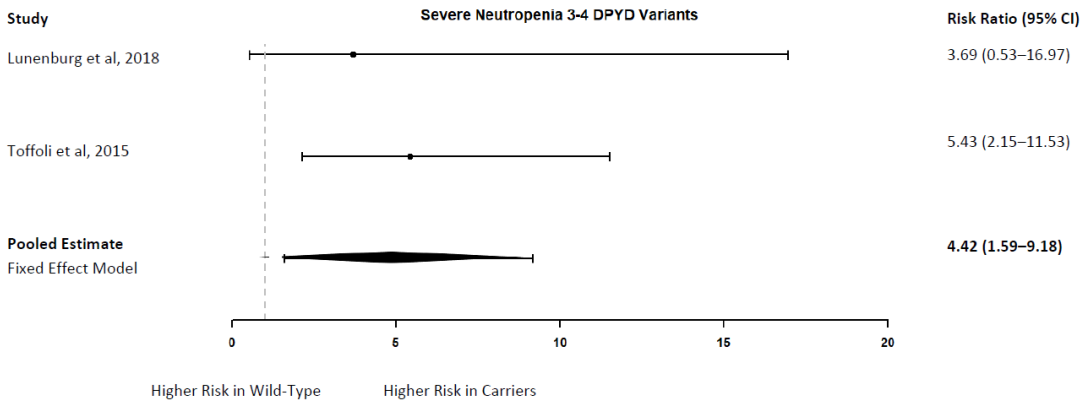

Figure 4: Carriers of Any of the Four *DPYD* Variants Versus Wild-Type Patients—Risk of Severe Neutropenia

Sources: Lunenburg et al[7] and Toffoli et al.[9]

Severe Gastrointestinal Toxicity

Diarrhea was the most common gastrointestinal toxicity reported. Six (17.6%) *DPYD* carriers who received a standard fluoropyrimidine dose and 58 (7.5%) wild-type patients also treated with a standard dose had severe diarrhea (RR 2.35, 95% CI 0.94–4.81) in the study by Lunenburg et al,[7] whereas six (35.3%) *DPYD* carriers and 34 (5.8%) wild-type patients had severe diarrhea (RR 6.09, 95% CI 2.37–12.66) in the study by Toffoli et al.[9]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

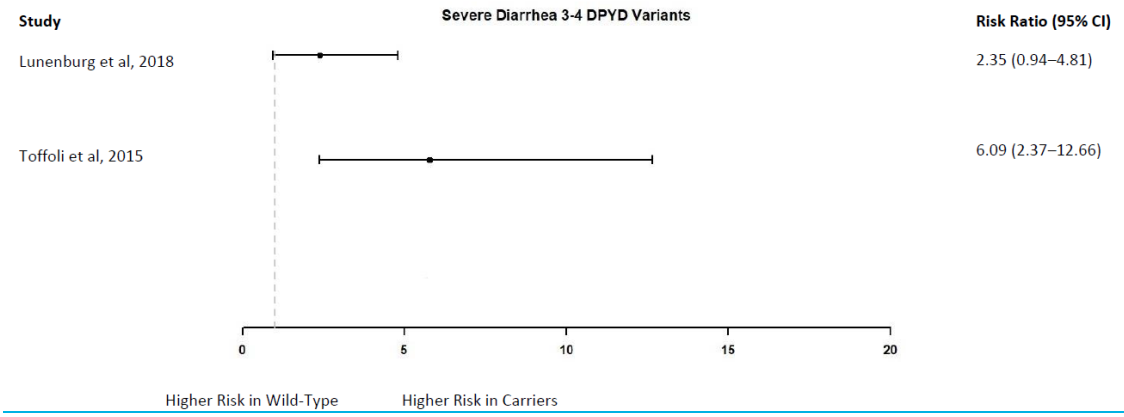

Figure 5: Carriers of Any of the Four *DPYD* Variants Versus Wild-Type Patients—Risk of Severe Diarrhea

Sources: Lunenburg et al[7] and Toffoli et al.[9]

Severe Dermatological Toxicity

Only the study by Lunenburg et al[7] reported on severe dermatological toxicity. In that study, 24 (3.1%) wild-type patients treated with a standard fluoropyrimidine dose experienced severe hand–foot syndrome, but none of the *DPYD* carriers who received a standard fluoropyrimidine dose experienced this adverse event (*P* = .62).

The GRADE quality of the evidence was very low because the evidence came from observational studies, and because of imprecision (Appendix 3).

*Carriers of the DPYD*2A Variant*

Overall Severe Toxicity

In one study,[57] none of the four *DPYD**2A carriers identified experienced severe toxicity, but in the other 16 studies,[9,15,54-56,58-65,67-69] 46.2% to 100% of *DPYD**2A carriers treated with a standard fluoropyrimidine dose experienced severe toxicity. Among wild-type patients treated with a standard fluoropyrimidine dose, 3.3% to 57.5% experienced severe toxicity, [9,15,54-60,62-65,67-69] except in one study where 85.2% of wild-type patients experienced severe toxicity.[61]

The authors of the study in which none of the *DPYD**2A carriers experienced toxicity commented that some patients had their treatment delayed or stopped as a result of grade 2 toxicity, and this may have prevented the occurrence of severe (grade ≥ 3) toxicity in these patients.[57] According to the authors, most *DPYD**2A carriers in the study experienced grade 2 toxicity and required more treatment delays and

cessation than wild-type patients, indicating a more clinically important toxicity profile in carriers that was not reflected in higher toxicity grades.[57]

The point estimates of the risk ratio from 15 of the 16 studies[9,15,54-56,58-63,65,67-69] indicated a higher risk in *DPYD**2A carriers compared to wild-type patients; however, with the exception of 8 studies,[9,54,56,58,60,65,68,69] the confidence intervals also included the possibility of a lower risk in *DPYD**2A carriers (Figure 6; Appendix 5).

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

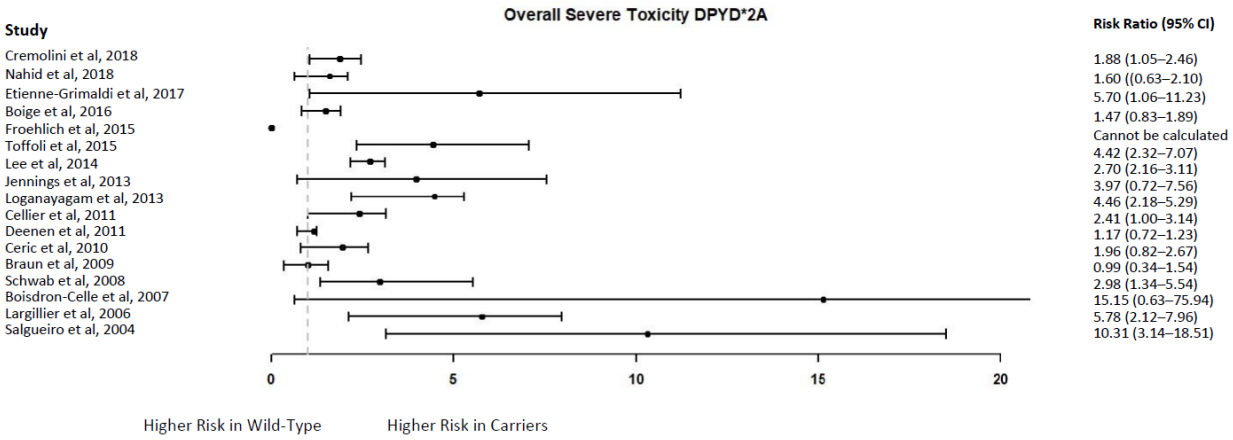

Figure 6: *DPYD**2A Carriers Versus Wild-Type Patients—Risk of Overall Severe Toxicity

Sources: Cremolini et al,[55] Nahid et al,[54] Etienne-Grimaldi et al,[56] Boige et al,[15] Froehlich et al,[57] Toffoli et al,[9] Lee et al,[58] Jennings et al,[59] Loganayagam et al,[60] Cellier et al,[62] Deenen et al,[61] Cerić et al,[63] Braun et al,[64] Schwab et al,[65] Boisdron-Celle et al,[67] Largillier et al[68], and Salgueiro et al[69]

Severe Hematological Toxicity

Neutropenia was the most common hematological toxicity reported. Severe neutropenia occurred in 33% to 100% of *DPYD**2A carriers treated with a standard fluoropyrimidine dose and 2% to 36% of wild-type patients treated with a standard dose, across nine studies (Figure 7; Appendix 5).[9,15,53-55,58,63,68,69]

The point estimates of the risk ratio indicated a higher risk in *DPYD**2A carriers compared to wild-type patients in all studies, but the confidence intervals of three studies[15,53,55] also included the possibility of a lower risk in *DPYD**2A carriers. The results for other severe hematological toxicities followed a similar pattern. Additional details are provided in Appendix 5.

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

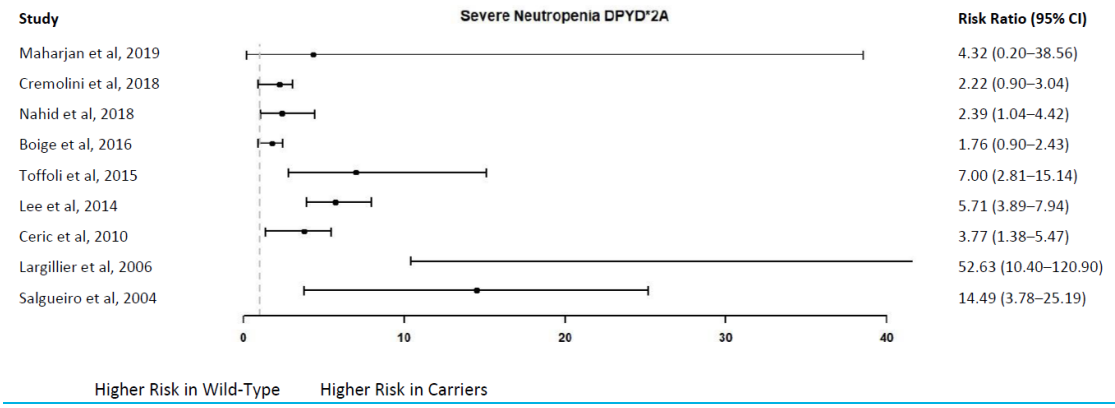

Figure 7: *DPYD**2A Carriers Versus Wild-Type Patients—Risk of Severe Neutropenia

Sources: Maharjan et al,[53] Cremolini et al,[55] Nahid et al,[54] Boige et al,[15] Toffoli et al,[9] Lee et al,[58] Cerić et al,[63] Largillier et al,[68] and Salgueiro et al.[69]

Severe Gastrointestinal Toxicity

Diarrhea was the most commonly reported gastrointestinal toxicity. Whereas two studies reported that none of the *DPYD**2A carriers treated with a standard fluoropyrimidine dose experienced severe diarrhea,[55,69] in the other nine studies[9,15,53,54,58,61,63,65,68] its frequency ranged from 12.0% to 100%. Among wild-type patients treated with a standard fluoropyrimidine dose, 1.4% to 27.5% experienced severe diarrhea.[9,15,53-55,58,61,63,65,68,69]

The point estimates of the risk ratio from nine studies indicated an increased risk in *DPYD**2A carriers compared to wild-type patients, [9,15,53,54,58,61,63,65,68] but the confidence intervals of three studies also included the possibility of a lower risk in *DPYD**2A carriers (Figure 8).[54,58,65] Similar results were reported for other types of gastrointestinal toxicity (Appendix 5).

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

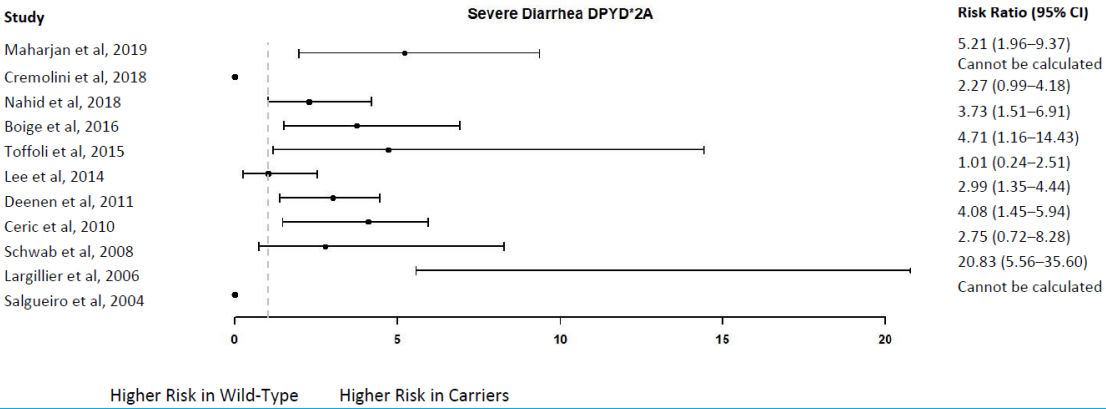

Figure 8: *DPYD**2A Carriers Versus Wild-Type Patients—Risk of Severe Diarrhea

Sources: Maharjan et al,[53] Cremolini et al,[55] Nahid et al,[54] Boige et al,[15] Toffoli et al,[9] Lee et al,[58] Deenen et al,[61] Cerić et al,[63] Schwab et al,[65] Largillier et al,[68] and Salgueiro et al.[69]

Severe Dermatological Toxicity

Severe hand–foot syndrome occurred in 3 (42.9%) *DPYD**2A carriers treated with a standard fluoropyrimidine dose and 242 (43.2%) wild-type patients treated with a standard dose in the study by Deenen et al[61] (RR 0.99, 95% CI 0.25–1.82). One carrier in the study by Largillier et al[68] developed severe hand–foot syndrome (100.0%) compared to five (4.8%) wild-type patients (RR 20.83, 95% CI 5.55–35.60). In the study by Cellier et al,[62] none of the patients, *DPYD**2A carriers or wild-type, experienced severe hand–foot syndrome.

The GRADE quality of the evidence was very low because the evidence came from observational studies, and because of imprecision (Appendix 3).

*Carriers of the DPYD*13 Variant*

Overall Severe Toxicity

Two studies that each identified a single *DPYD**13 carrier reported that neither of these carriers experienced severe toxicity[9,57]; in five other studies, the frequency ranged from 50.0% to 100.0% in *DPYD**13 carriers who received a standard fluoropyrimidine dose.[15,52,58,60,62] Among wild-type patients treated with a standard dose, 8.2% to 49.5% developed severe toxicity across the seven studies.[9,15,52,57,58,60,62]

The point estimates of the risk ratio ranged from 1.01 to 4.64 in five studies,[15,52,58,60,62] but the confidence intervals of two studies also included the possibility of a lower risk in *DPYD**13 carriers (Figure 9).[15,58,62] The risk ratio could not be calculated in the two studies in which no carriers *DPYD**13 experienced severe toxicity[9,57]; in both studies, according to the authors, the *DPYD**13 carriers either had a fluoropyrimidine dose reduction or a treatment delay as a result of a grade 2 toxicity, and this may have prevented the development of severe toxicity.[9,57]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

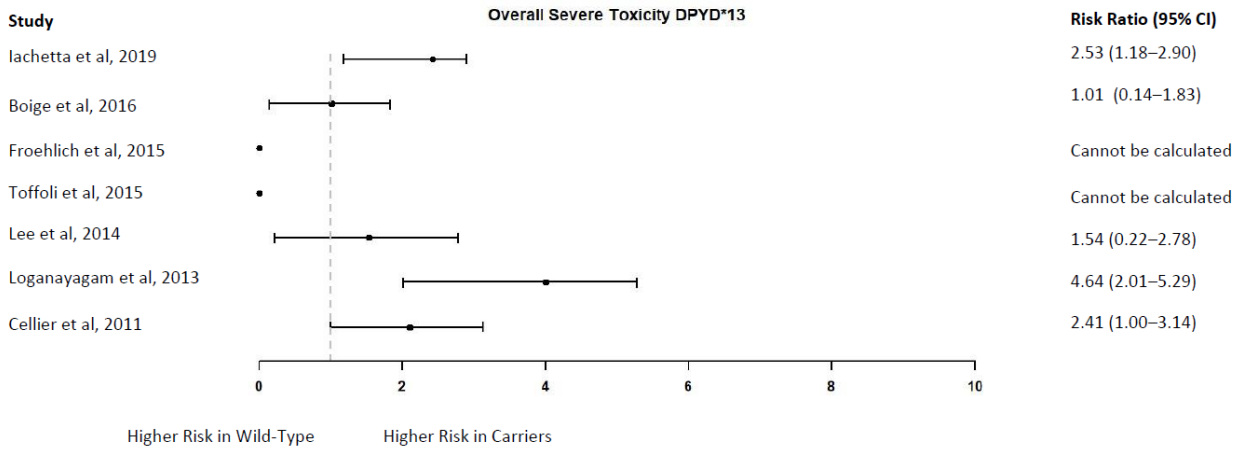

Figure 9: *DPYD**13 Carriers Versus Wild-Type Patients—Risk of Overall Severe Toxicity

Sources: Iachetta et al,[52] Boige et al,[15] Froehlich et al,[57] Toffoli et al,[9] Lee et al,[58] Loganayagam et al, [60] and Cellier et al.[62]

Severe Hematological Toxicity
In one study, one (25.0%) *DPYD**13 carrier who received a standard fluoropyrimidine dose and 561 (36.4%) wild-type patients also treated with a standard dose developed severe neutropenia (RR 0.73, 95% CI 0.02–2.10).[15] In a second study, no *DPYD**13 carriers had severe neutropenia, but 8 (1.4%) wild-type patients did (*P* = 1.00).[9]

The GRADE quality of the evidence was very low because the evidence came from observational studies, and because of imprecision (Appendix 3).

Severe Gastrointestinal Toxicity
Severe diarrhea was the most commonly reported gastrointestinal toxicity. In one study, two (50.0%) *DPYD**13 carriers treated with a standard fluoropyrimidine dose and 190 (12.3%) wild-type patients also treated with a standard dose developed severe diarrhea (RR 4.07, 95% CI 0.62–7.71).[15] One (100.0%) *DPYD**13 carrier and 18 (22.0%) wild-type patients developed severe diarrhea in a second study (RR 4.55, 95% CI 1.72–6.32).[62] In a third study, no *DPYD**13 carriers and 34 (5.8%) wild-type patients developed severe diarrhea (*P* = 1.00).[9]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

Severe Dermatological Toxicity
None of studies identified reported on this outcome.

Carriers of the c.2846A>T Variant

Overall Severe Toxicity
In one study, none of the three c.2846A>T carriers treated with a standard fluoropyrimidine dose experienced severe toxicity,[57] but in 12 studies the frequency in carriers varied between 60.0% and 100.0%.[9,15,52,55,56,58-62,67,70] Among wild-type patients treated with a standard dose, 3.3% to 50.1% experienced severe toxicity.[9,15,52,55-62,67,70]

In the study by Froehlich et al,[57] similar to what was reported for carriers of other *DPYD* variants, c.2846A>T carriers had their fluoropyrimidine treatment delayed or stopped as a result of grade 2 toxicity, and this may have prevented the development of severe (grade ≥ 3) toxicity.

The point estimates of the risk ratio from 12 of the 13 studies indicated a higher risk in c.2846A>T carriers versus wild-type patients,[9,15,52,55-62,67,70 but] the confidence intervals of four studies also included the possibility of no difference between groups or a lower risk in c.2846A>T carriers (Figure 10; Appendix 5).55,61,[62,70]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

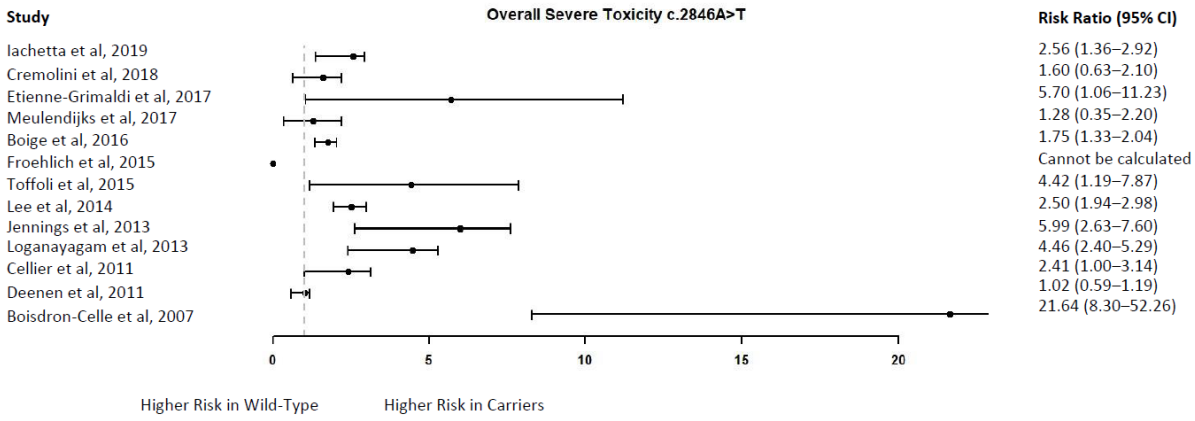

Figure 10: c.2846A>T Carriers Versus Wild-Type Patients—Risk of Overall Severe Toxicity

Sources: Iachetta et al,[52] Cremolini et al,[55] Etienne-Grimaldi et al,[56] Meulendijks et al,[70] Boige et al,[15] Froehlich et al,[57] Toffoli et al,[9] Lee et al,[58] Jennings et al,[59] Loganayagam et al,[60] Cellier et al,[61] Deenen et al,[62] and Boisdron-Celle et al.[67]

Severe Hematological Toxicity

Severe neutropenia was the most commonly reported hematological toxicity. In one of the studies, none of the two c.2846A>T carriers treated with a standard fluoropyrimidine dose developed severe neutropenia[53]; in four other studies, severe neutropenia occurred in 20.0% to 61.9% of c.2846A>T carriers.[9,15,55,58] Among the wild-type patients treated with a standard dose in the five studies, 6.5% to 36.0% experienced severe neutropenia.[9,15,53,55,58]

The point estimates of the risk ratio indicated a higher risk in carriers in four studies,[9,15,55,58] but the confidence intervals of two studies also included the possibility of a lower risk in carriers (Figure 11).[9,55] The risk ratio could not be calculated in one study, because no events occurred in c.2846A>T carriers, compared to 4 (7.7%) events in wild-type patients (P = 1.00).[53] Similar results were reported for other types of hematological toxicities. Additional information is provided in Appendix 5.

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

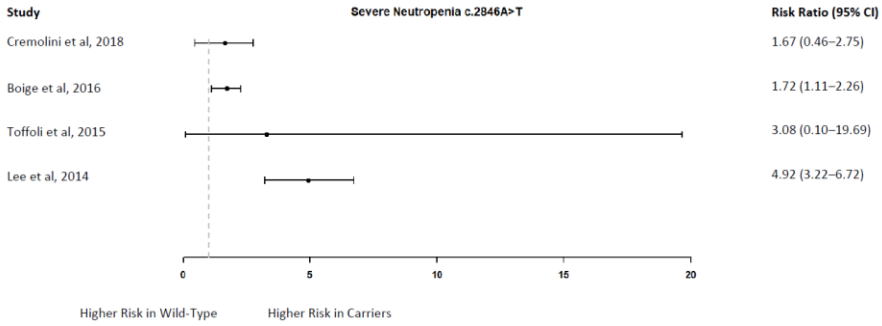

Figure 11: c.2846A>T Carriers Versus Wild-Type Patients—Risk of Severe Neutropenia

Sources: Cremolini et al,[55] Boige et al,[15] Toffoli et al,[9] and Lee et al.[58]

Severe Gastrointestinal Toxicity

Severe diarrhea was the most commonly reported gastrointestinal toxicity. It was reported in 14.3% to 100% of c.2846A>T carriers treated with a standard fluoropyrimidine dose and 5.8% to 23.9% of wild-type patients treated with a standard dose, across six studies.[9,15,53,55,58,61]

The point estimates of the risk ratio indicated a higher risk in c.2846A>T carriers in all six studies, but the confidence intervals of two studies also included the possibility of a lower risk in carriers (Figure 12).[15,55] Similar results were reported for other types of gastrointestinal toxicity. Additional information is provided in Appendix 5.

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

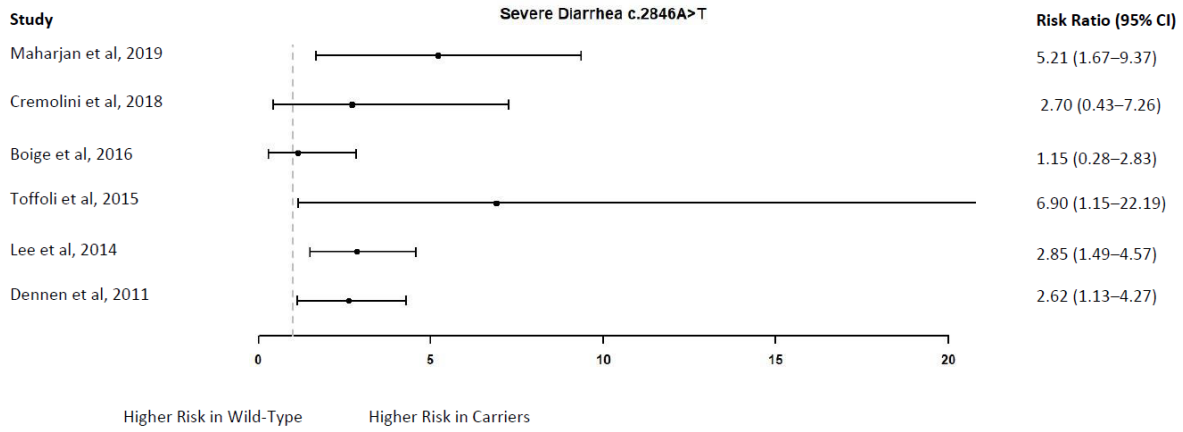

Figure 12: c.2846A>T Carriers Versus Wild-Type Patients—Risk of Severe Diarrhea

Sources: Maharjan et al,[53] Cremolini et al,[55] Boige et al,[15] Toffoli et al,[9] Lee et al,[58] and Deenen et al.[61]

Severe Dermatological Toxicity

One study reported that four (50.0%) c.2846A>T carriers treated with a standard fluoropyrimidine dose and 241 (43.1%) wild-type patients also treated with a standard dose experienced severe (grade ≥ 2) hand–foot syndrome (RR 1.16, 95% CI 0.40–1.91).[61] Additional information is provided in Appendix 5.

The GRADE quality of the evidence was very low because the evidence came from observational studies, and because of imprecision (Appendix 3).

Carriers of the c.1236G>A Variant

Overall Severe Toxicity

The frequency of overall severe toxicity varied between 30.0% and 92.9% in heterozygous c.1236G>A carriers treated with a standard fluoropyrimidine dose and 8.2% and 85.0% of wild-type patients treated with a standard dose across six studies.[13,57,59,61,70,71]

One study reported a higher risk of overall severe toxicity in carriers versus wild-type patients (RR 5.12, 95% CI 2.54–9.87).[57] However, the point estimates of the risk ratio were closer to 1 and the results were imprecise in five studies: 1.25 (0.91–1.61),[13] 1.82 (0.47–5.21),[59] 1.09 (0.91–1.19),[61] 0.83 (0.37–1.63),[70] and 1.10 (0.67–1.62).[71]

Two homozygous c.1236G>A carriers identified in two studies experienced severe toxicity (100.0%), compared to 8.5%[57]and 32.3%[13] in wild-type patients. The risk of severe toxicity in homozygous carriers was higher than in wild-type patients in both studies (RR 3.10, 95% CI 1.47–3.31;[13] RR 11.76, 95% CI 4.73–14.91[57]). One study did not report results for the one homozygous c.1236G>A carrier identified.[61]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3). Given the imprecision in the study results, the GRADE quality of the evidence was very low for heterozygous carriers (Appendix 3).

Severe Hematological Toxicity
Seventeen (22.1%) heterozygous c.1236G>A carriers treated with a standard fluoropyrimidine dose and 184 (9.8%) wild-type patients also treated with a standard dose experienced severe neutropenia in one study (RR 2.26, 95% CI 1.38–3.40).[13] The one homozygous carrier identified in this study did not experience severe neutropenia.[13]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

Severe Gastrointestinal Toxicity
Severe diarrhea was the most commonly reported gastrointestinal toxicity. In one study, 11 (14.3%) c.1236G>A heterozygous carriers treated with a standard fluoropyrimidine dose and 234 (12.5%) wild-type patients also treated with a standard dose experienced severe diarrhea (RR 1.14, 95% CI 0.61–1.92).[13] A single homozygous carrier (100.0%) experienced severe nausea and/or vomiting compared to 88 (4.7%) wild-type patients (RR 21.3, 95% CI 9.29–25.49), but not severe diarrhea.[13]

A second study reported that 14 (50.0%) carriers and 125 (23.1%) wild-type patients experienced severe diarrhea (RR 2.16, 95% CI 1.35–3.34).[61]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

Severe Dermatological Toxicity
One study reported that 26 (92.9%) heterozygous c.1236G>A carriers treated with a standard fluoropyrimidine dose and 459 (85.0%) wild-type patients also treated with a standard dose experienced severe (grade ≥3) hand–foot syndrome (RR 1.09, 95% CI 0.91–1.95).[61]

The GRADE quality of the evidence was very low because the evidence came from observational studies, and because of imprecision (Appendix 3).

Compound Heterozygous
All four compound heterozygous carriers treated with a standard fluoropyrimidine dose experienced severe toxicity; all four studies reported a higher risk compared to wild-type patients treated with a standard dose (Table 3).[9,57,58,67]

In the study by Toffoli et al,[9] the one compound heterozygous carrier experienced severe diarrhea (100.0%) compared to 34 (5.8%) wild-type patients (RR 17.2, 95% CI 6.75–22.20). The other three studies did not specify types of toxicity.[57,58,67]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

Table 3: Compound Heterozygous Carriers Versus Wild-Type Patients—Risk of Overall Severe Toxicity

Author, Year N (Carriers/Wild-Type)	Compound Heterozygous Genotype Identified	Overall Severe Toxicity, n (%)	RR (95% CI)
Froehlich et al, 2015[57] 469 (1/468)	*DPYD**13/c.1236G>A	Carrier: 1 (100.0) Wild-type: 40 (8.5)	11.76 (4.73–14.91)
Toffoli et al, 2015[9] 586 (1/585)	*DPYD**2A/*DPYD**13	Carrier: 1 (100.0) Wild-type: 84 (14.4)	6.94 (3.07–8.34)
Lee et al, 2014[58] 2,565 (1/2,564)	*DPYD**2A/c.2846A>T	Carrier: 1 (100.0) Wild-type: 834 (32.5)	3.08 (1.47–3.25)
Boisdron-Celle et al, 2007[67] 243 (1/242)	*DPYD**2A/c.2846A>T	Carrier: 1 (100.0) Wild-type: 8 (3.3)	30.30 (9.10–52.26)

Abbreviations: CI, confidence interval; RR, risk ratio.

DPYD GENOTYPING TO PREDICT SEVERE FLUOROPYRIMIDINE-RELATED TOXICITY

We used severe fluoropyrimidine-related toxicity as the reference standard to calculate the sensitivity, specificity, PPV, and NPV of *DPYD* genotyping: that is, when toxicity was observed among carriers of a *DPYD* variant, it was considered a true positive finding, and when toxicity was not reported among non-carriers it was considered a true negative.

The sensitivity of simultaneously genotyping the three to four *DPYD* variants assessed in this review ranged from 3.5% to 21.6%; the specificity ranged from 96.2% to 100.0%; the PPV ranged from 23.5% to 100.0%; and the NPV ranged from 50.5% to 91.5% (Table 4).

Table 4: *DPYD* Genotyping to Detect Severe Toxicity (3–4 Variants)—Sensitivity, Specificity, PPV, and NPV

Author, Year	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
Lunenburg et al, 2018[7]	7.1 (3.6–13.4)	96.2 (94.6–97.4)	23.5	86.4
Meulendijks et al, 2017[18]	6.0 (NR)[a]	95.0 (NR)[a]	13.0[a]	88.0[a]
Boige et al, 2016[15]	3.5 (2.5–5.1)	99.0 (98.0–99.5)	77.8	50.5
Froehlich et al, 2015[57]	21.6 (12.5–34.6)	95.3 (93.0–96.9)	34.4	91.5
Toffoli et al, 2015[9]	11.6 (0.7–19.6)	98.6 (97.2–99.3)	61.1	85.6
Lee et al, 2014[58]	5.3 (4.0–7.0)	99.4 (98.9–99.7)	82.5	67.4
Jennings et al, 2013[59]	15.9 (7.9–29.4)	96.2 (92.6–98.0)	46.7	84.5
Loganayagam et al, 2013[60]	9.6 (5.3–16.8)	100.0 (98.8–100.0)	100.0	77.6
Cellier et al, 2011[62]	8.1 (2.8–21.3)	100.0 (92.6–100.0)	100.0	58.5

Abbreviations: CI, confidence interval; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.
[a]As reported by the authors.

TOXICITY-RELATED DOSE REDUCTION, TREATMENT DELAY, AND DISCONTINUATION

In one study, six (60.0%) carriers of *DPYD**2A, *DPYD**13, or c.2864A>T required a dose reduction, compared to 98 (23.6%) wild-type patients (RR 2.54, 95% CI 1.23–4.38); four (40.0%) carriers and 27 (6.4%) wild-type patients discontinued treatment due to toxicity (RR 6.25, 95% CI 2.08–16.41).[60] Another study reported that 36.4% to 100.0% of carriers had their treatment delayed as a result of toxicity, but did not provide information for wild-type patients.[9]

Similar results were reported for individual *DPYD* variants (Appendix 5). Information was not provided for compound heterozygous or homozygous c.1236G>A carriers.

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

TOXICITY-RELATED HOSPITALIZATIONS

DPYD carriers treated with a standard fluoropyrimidine dose had a higher risk of hospitalization than wild-type patients in three studies[7,60,67]; however, the confidence interval of one study included the possibility of a lower risk in *DPYD* carriers.[7] Two other studies reported the frequency of hospitalizations in *DPYD* carriers, but not in wild-type patients.[68,69] Additional information is provided in Table 5.

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

Table 5: *DPYD* Carriers Versus Wild-Type Patients—Toxicity-Related Hospitalization

Author, Year N (Carrier/Wild-Type) *DPYD* Variants Included	Patients With Toxicity-Related Hospitalization, n (%)	RR (95% CI)	Number of Days in Hospital, Mean (Range)
Lunenburg et al, 2018[7] 805 (34/771) *DPYD**2A, *DPYD**13, c.2846A>T, c.1236G>A	Carrier: 6 (17.6) Wild-type: 60 (7.8)	2.26 (0.69—5.14)	Carrier: 23 (6–36) Wild-type: 13 (1–76)
Loganayagam et al, 2013[60] 430 (10/420) *DPYD**2A, *DPYD**13, c.2846A>T	Carrier: 10 (100.0) Wild-type: 94 (22.4)	4.46 (3.26–5.29)	Carrier: 7.1 Wild-type: 2.7
Boisdron-Celle et al, 2007[67] 243 (1/242) Compound heterozygous (*DPYD**2A/c.2846A>T)	Carrier: 1 (100.0) Wild-type: 4 (1.7)	58.82 (15.19–168.60)	Carrier: 40 Wild-type: NR
Largillier et al, 2006[68] 105 (1/104) *DPYD**2A	Carrier: 1 (100) Wild-type: NR	Could not be calculated	Carrier: 7 Wild-type: NR
Salgueiro et al, 2004[69] 73 (1/72) *DPYD**2A	Carrier: 1 (100.0) Wild-type: NR	Could not be calculated	NR

Abbreviations: CI, confidence interval; NR, not reported; RR, risk ratio.

TOXICITY-RELATED MORTALITY

The frequency of fluoropyrimidine-related mortality ranged from 0.0% to 100.0% in heterozygous *DPYD* carriers treated with a standard dose and 0.0% to 2.0% in wild-type patients (Table 6). Two studies that included *DPYD**2A carriers compared the risk between groups and found a higher risk in carriers (RR 50.00, 95% CI 6.21–74.53[63]; RR 52.63, 95% CI 10.40–120.90[68]).

One study reported a death in the only homozygous c.1236G>A carrier identified, but mortality information was not reported for wild-type patients.[57]

Among four compound heterozygous carriers treated with a standard fluoropyrimidine dose identified in four studies,[9,57,58,67] three (1 *DPYD**2A/*DPYD**13 and 2 *DPYD**2A/c.2846A>T) died as result of fluoropyrimidine-related toxicity.[9,58,67] The toxicity occurred on the first cycle in one study[9] but the timing was unclear in the other two.[58,67] Only one of these studies reported mortality in both groups: one (100%) carrier and one (0.4%) wild-type patient (RR 250.00, 95% CI 32.04–341.82).[67]

The GRADE quality of the evidence was low because the evidence came from observational studies (Appendix 3).

Table 6: Heterozygous *DPYD* Carriers Versus Wild-Type Patients—Toxicity-Related Mortality

Author, Year N (Carrier/Wild-Type)	Mortality (Any *DPYD* Variant, Heterozygous), n (%); Time of Occurrence
Wigle et al, 2021[71] 1,388 (41/1,347)	Carrier: 0 Wild-type: 10 (0.7); timing unclear
Cremolini et al, 2018[55] 438 (5/433)	Carrier: 1 (10.0); cycle 1 Wild-type: NR
Etienne-Grimaldi et al, 2017[56] 243 (6/237)	Carrier: 1 (16.7); cycle 1 Wild-type: 0
Loganayagam et al, 2013[60] 430 (10/420)	Carrier: 0 Wild-type: NR
Deenen et al, 2011[61] 604 (44/560)	Carrier: 1 (2.3); cycle 3 Wild-type: NR
Cerić et al, 2010[63] 50 (1/49)	Carrier: 1 (100.0); cycle 1 Wild-type: 1 (2.0); timing unclear
Schwab et al, 2008[65] 683 (13/670)	Carrier: 0 Wild-type: 0
Boisdron-Celle et al, 2007[67] 252 (10/242)	Carrier: 0 Wild-type: 1 (0.4); timing unclear
Largillier et al, 2006[68] 105 (1/104)	Carrier: 1 (100.0); treated until day 12 Wild-type: 2 (1.9); timing unclear

Abbreviation: NR, not reported.

Clinical Utility

Studies evaluating clinical utility should assess whether the test under evaluation (in this case, pre-treatment *DPYD* genotyping) allows treatment modifications to be implemented, resulting in improved treatment outcomes compared to not testing or to other tests (i.e.., pre-treatment DPD activity measurement). However, the studies we identified were not designed to evaluate such a comparison.

Because fluoropyrimidine dosing regimens varied (by type and stage of cancer, by whether fluoropyrimidines were used alone or in combination, and by the type of combination regimen), we have used the term “standard dose” to refer to the usual fluoropyrimidine dose in a given patient population or a given regimen to distinguish it from the genotype-guided reduced dose.

Given the clinical heterogeneity in terms of type of cancer, type of fluoropyrimidine, dose, mode of administration, and combination regimens, we did not conduct meta-analyses of study results, except in some cases.

PATIENT CHARACTERISTICS

The mean age of patients in the included studies ranged from 58 to 65 years[7,11,12,23,71,72]; 35% to 59% were male,[7,11,12,72] except for one study in women with breast cancer.[23] Based on information from four studies,[11,12,23,71] 98% to 100% of patients were of Caucasian origin. Additional information is provided in Appendix 4.

Colorectal was the most common type of cancer in most studies (53% to 77% of patients),[7,11,12,71,72] except for one study in patients with breast cancer.[23] Capecitabine was the most common fluoropyrimidine prescribed: 100% in two studies[12,23] and 52% to 90% in the remaining three.[7,11,71,72] Concomitant radiotherapy was allowed in four studies.[7,11,71,72]

The prevalence of the *DPYD* variants was as follows:

- *DPYD**2A: 0.6%–2.2%[7,12,23,71,72]
- *DPYD**13: 0.07%,[71] 0.09%,[72] and 0.1%[7] (two studies did not identify any *DPYD**13 carriers[12,23])
- c.2846A>T: 0.5%–3.0%[7,12,23,71,72]
- c.1236G>A: 3.3%–4.6%[7,12,71,72]
- 3–4 of the above variants combined: 6.0%–7.7%[7,12,71,72]

TOXICITY-RELATED DOSE REDUCTION, INCREASE, AND DISCONTINUATION

In most studies, heterozygous *DPYD**2A and *DPYD**13 carriers started fluoropyrimidine treatment with a 50% dose reduction, and heterozygous c.2846A>T and c.1236G>A carriers started treatment with a 25% dose reduction, based on institutional and international guidelines. Dose increases were permitted according to the patient's tolerance.[7,11,12,23,72] In the study by Wigle et al,[71] *DPYD**2A, *DPYD**13, and c.2864A>T carriers started fluoropyrimidine treatment with a 50% dose reduction, and heterozygous c.1236G>A carriers started treatment with a 25% to 50% dose reduction. In the studies identified, wild-type patients generally received a standard fluoropyrimidine dose, although reductions were allowed.

In one of the studies, three (3.5%) *DPYD* carriers had their fluoropyrimidine dose reduced after the start of treatment, and one (1.2%) received a full dose for two cycles and experienced fatal toxicity.[72]

Dose increases occurred in 9.1% to 54.5% of *DPYD* carriers[7,11,12,23,72] and 0.5% to 3.0% of wild-type patients who had had a previous dose reduction (Table 7).[7,72]

None of the *DPYD* variant carriers in one study required dose reduction beyond what was applied pre-treatment[23]; in other studies, 5.9% to 18.2% of carriers[7,11,12,72] and 4.4% of wild-type patients[7] required further dose reductions as a result of toxicity (Table 7).

Table 7: *DPYD* Carriers With a Genotype-Guided Reduced Fluoropyrimidine Dose Versus Wild-Type Patients—Treatment Modifications

Author, Year N (Carrier/Wild-Type)	Initial Dose Reduction	Additional Dose Reductions, n (%)	Dose Increase, n (%)
Wigle et al, 2021[71] 1,394 (47/1,347)	*Mean % of standard dose (SD)* Carriers: 52 (18.0) Wild-type: 87.4 (15.2)	NR	NR
Henricks et al, 2019[11] 1,646 (40/1,606)	*Mean % of standard dose* Carrier: 53 Wild-type: 92	Carrier: 7 (17.5) Wild-type: NR	Carrier: 11 (27.5) Wild-type: NR
Kleinjan et al, 2019[12] 185 (11/174)	NR	Carrier: 2 (18.2); 1 because of severe toxicity after dose increase Wild-type: NR	Carrier: 6 (54.5) Wild-type:
Stavraka et al, 2019[23] 63 (2/61)	*Dose reductions, n (%)* Carrier: 2 (100) Wild-type, n (%): 9 (14.8)	Carrier: 0 Wild-type: NR	Carrier: 2 (100); 1 (50) had grade 3 toxicity with increased dose and treatment was stopped Wild-type: 0
Henricks et al, 2018[72] 1,103 (85/1,018)	*Mean % of standard dose (range)* Carrier: 69 (37–97) Wild-type: 94 (49–128)	Carrier: 5 (5.9%); because of toxicity after dose increase	Carrier: 11 (12.9) Wild-type: 31 (3.0)
Lunenburg et al, 2018[7] 827 (22[a]/771/34[b])	NR	Carrier: 2 (9.1) Wild-type: 34 (4.4) Carrier[a]: 4 (11.8)	Carrier: 2 (9.1) Wild-type: 4 (0.5) Carrier[a]: NR

Abbreviation: NR, not reported; SD, standard deviation.

[a]One patient was excluded from the analyses.

[b]*DPYD* carriers who received a standard dose.

Treatment was discontinued due to toxicity in 17.5% to 50.0% of *DPYD* carriers treated with a genotype-guided reduced dose and 3.3% to 17.2% of wild-type patients.[7,11,23,71,72] The point estimates indicated a similar risk of discontinuation between groups in two studies and a higher risk in *DPYD* carriers in three other studies. However, the study results were imprecise (Figure 13, Appendix 5).

In the study by Lunenburg et al,[7] four (18.2%) *DPYD* carriers treated with a genotype-guided reduced dose and six (17.6%) treated with a standard dose discontinued treatment (RR 1.03, 95% CI 0.28–4.03).

The GRADE quality of the evidence was very low because the evidence came from observational studies, and because of imprecision (Appendix 3).

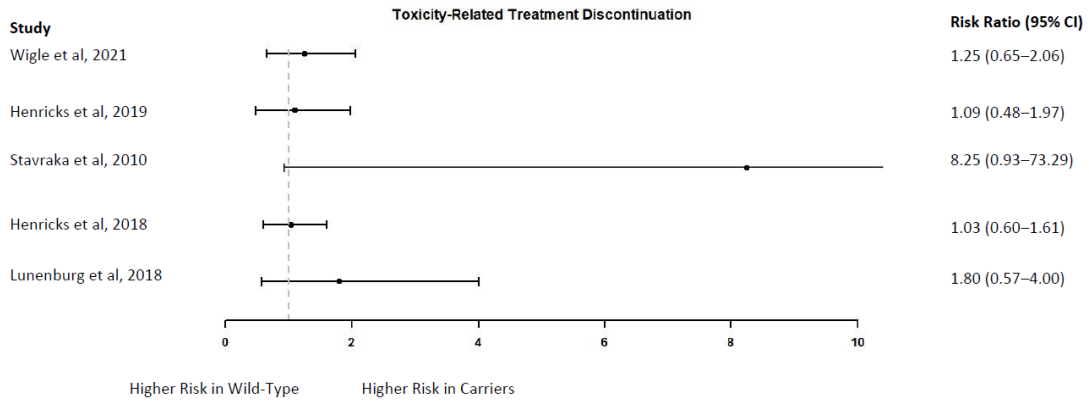

Figure 13: *DPYD* Carriers With a Genotype-Guided Reduced Fluoropyrimidine Dose Versus Wild-Type Patients—Treatment Discontinuation

Sources: Wigle et al,[71] Henricks et al (2019),[11] Stavraka et al,[23] Henricks et al (2018),[72] and Lunenburg et al.[7]

SEVERE FLUOROPYRIMIDINE-RELATED TOXICITY

Overall Severe Toxicity

Overall severe toxicity occurred in 18% to 50% of carriers with a genotype-guided reduced dose compared to 14% to 38% of wild-type patients treated with a standard dose.[7,11,12,23,71,72] The point estimates of the risk ratio indicated a lower risk of severe toxicity in *DPYD* carriers treated with a reduced dose compared to wild-type patients in three studies and a higher risk in *DPYD* carriers in three other studies. However, the confidence intervals included the possibility of both higher and lower risk in *DPYD* carriers in all but one study (Figure 14; Appendix 5).[72] The authors of that study believed that the 25% fluoropyrimidine dose reduction applied in c.2846A>T and c.1236G>A carriers was not sufficient to prevent severe toxicity.[72] A guideline that had previously recommended a 25% dose reduction in these patients has been updated to recommend a 50% dose reduction.[21]

In the study by Lunenburg et al,[7] five (22.7%) *DPYD* carriers treated with a genotype-guided reduced dose and eight (23.5%) treated with a standard dose experienced severe toxicity (RR 0.97, 95% CI 0.30–3.05).

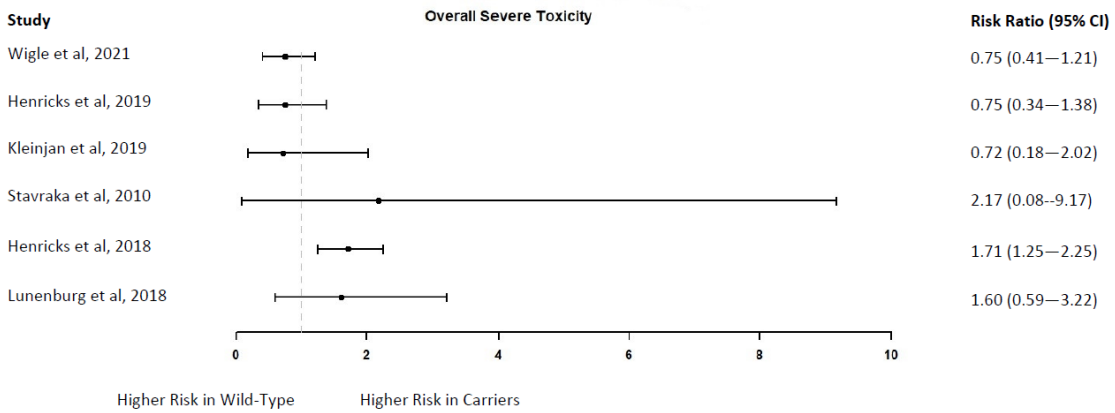

Figure 14: *DPYD* Carriers With a Genotype-Guided Reduced Fluoropyrimidine Dose Versus Wild-Type Patients—Risk of Overall Severe Toxicity

Sources: Wigle et al,[71] Henricks et al (2019),[11] Kleinjan et al,[12] Stavraka et al,[23] Henricks et al (2018),[72] and Lunenburg et al.[7]

Severe Toxicity by Type

Only the study by Henricks et al (2018)[72] reported a higher risk of both severe hematological and severe gastrointestinal toxicity in *DPYD* carriers treated with a genotype-guided reduced dose compared to wild-type patients treated with a standard dose. The results of the other studies were imprecise, and the 95% confidence intervals included the possibility of both higher and lower risk in *DPYD* carriers (Figures 15 and 16; Appendix 5).[7,11,12,23,71] For severe hand–foot syndrome, all five studies reported imprecise results, and the confidence intervals included the possibility of higher and a lower risk in *DPYD* carriers versus wild-type patients (Figure 17; Appendix 5).[7,11,12,23,71,72]

In the study by Lunenburg et al,[7] two (9.1%) *DPYD* carriers treated with a genotype-guided reduced fluoropyrimidine dose experienced severe hematological and severe gastrointestinal toxicity compared to four (11.8%) carriers who received a standard dose and experienced severe hematological toxicity and six (17.6%) carriers who received a standard dose and experienced severe gastrointestinal toxicity. The risk ratios were 0.77 (95% CI 0.12–5.72) and 0.52 (95% CI 0.08–2.28), respectively.

The GRADE quality of the evidence for the severe toxicity outcomes (*DPYD* carriers with a reduced dose vs. wild-type patients) was very low because the evidence came from observational studies, and because of imprecision (Appendix 3). As well, when comparing *DPYD* carriers who received a reduced dose with carriers who received a standard dose, the GRADE quality of the evidence was further downgraded because of risk of bias (Appendix 3).

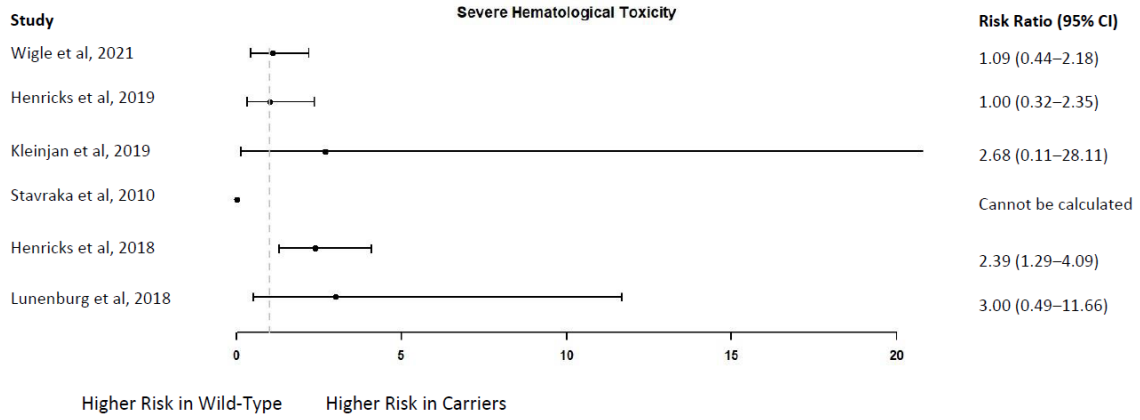

Figure 15: *DPYD* Carriers With a Genotype-Guided Reduced Fluoropyrimidine Dose Versus Wild-Type Patients—Risk of Severe Hematological Toxicity

Sources: Wigle et al,[71] Henricks et al (2019),[11] Kleinjan et al,[12] Stavraka et al,[23] Henricks et al (2018),[72] and Lunenburg et al.[7]

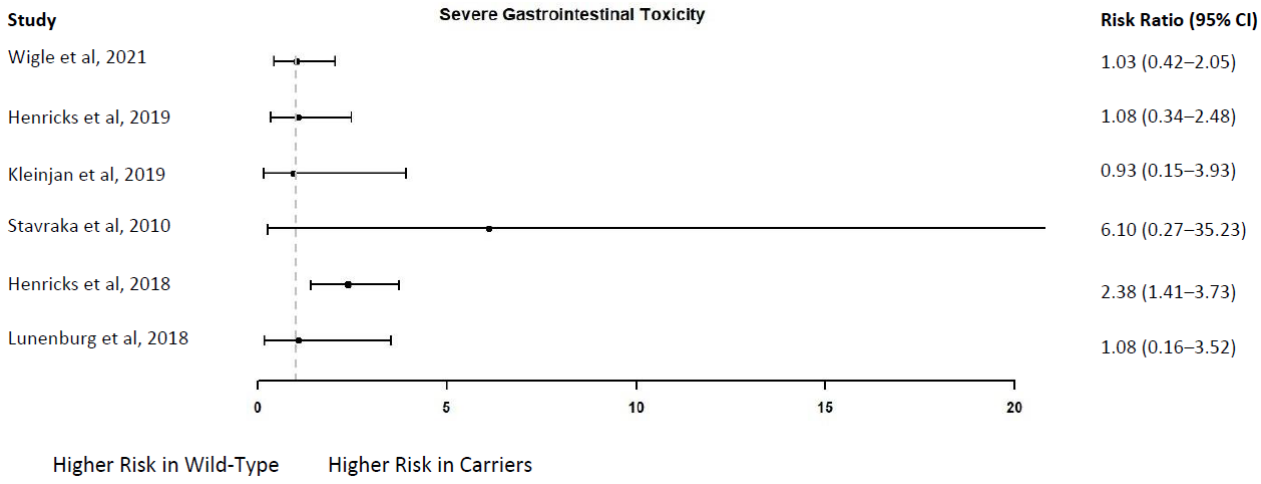

Figure 16: *DPYD* Carriers With a Genotype-Guided Reduced Fluoropyrimidine Dose Versus Wild-Type Patients—Risk of Severe Gastrointestinal Toxicity

Sources: Wigle et al,[71] Henricks et al (2019),[11] Kleinjan et al,[12] Stavraka et al,[23] Henricks et al (2018),[72] and Lunenburg et al.[7]

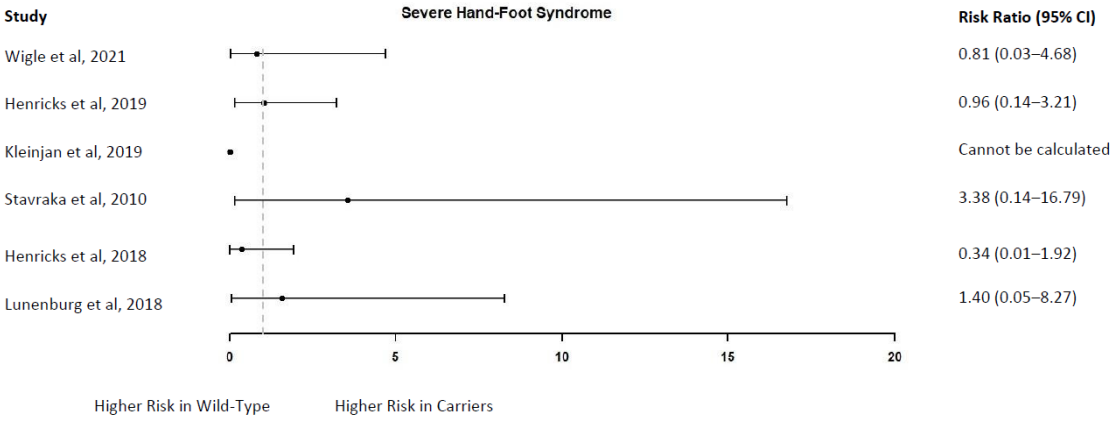

Figure 17: *DPYD* Carriers With a Genotype-Guided Reduced Fluoropyrimidine Dose Versus Wild-Type Patients—Risk of Severe Hand–Foot Syndrome

Sources: Wigle et al,[71] Henricks et al (2019),[11] Kleinjan et al,[12] Stavraka et al,[23] Henricks et al (2018),[72] and Lunenburg et al.[7]

TOXICITY-RELATED HOSPITALIZATIONS

Toxicity-related hospitalizations were reported in 15% to 50% of *DPYD* carriers who received a genotype-guided reduced fluoropyrimidine dose and in 0% to 14% of wild-type patients treated with a standard dose.[7,11,12,23,72] The point estimates of four studies indicated a higher risk of treatment-related hospitalization in carriers compared to wild-type patients, but the confidence intervals also included the possibility of lower risk in *DPYD* carriers (Figure 18).[7,11,12,72] The risk ratio could not be calculated in one study because none of the wild-type patients were hospitalized as a result of toxicity (compared to one [50.0%] carrier, $P = .03$). Additional information is provided in Appendix 5.

The median number of days in hospital ranged from 4 to 6.5 in *DPYD* carriers treated with a genotype-guided reduced dose and 5 to 13 in wild-type patients, based on three studies.[7,12,72]
Lunenburg et al[7] reported a similar risk of hospitalization between *DPYD* carriers who received a genotype-guided reduced fluoropyrimidine dose and *DPYD* carriers who received a standard dose (18.2% vs. 17.6%, respectively, RR 1.03, 95% CI 0.27—4.03). However, the length of stay in hospital was shorter in *DPYD* carriers treated with a reduced dose (mean 4 days, range 2–5) than in those treated with a standard dose (mean 23 days, range 6–36; *P* = .010).[7]

The GRADE quality of the evidence (*DPYD* carriers with a reduced dose vs. wild-type) was very low because the evidence came from observational studies, and because of imprecision (Appendix 3). As well, when comparing *DPYD* carriers who received a reduced dose with carriers who received a standard dose, the GRADE quality of the evidence was further downgraded because of risk of bias (Appendix 3).

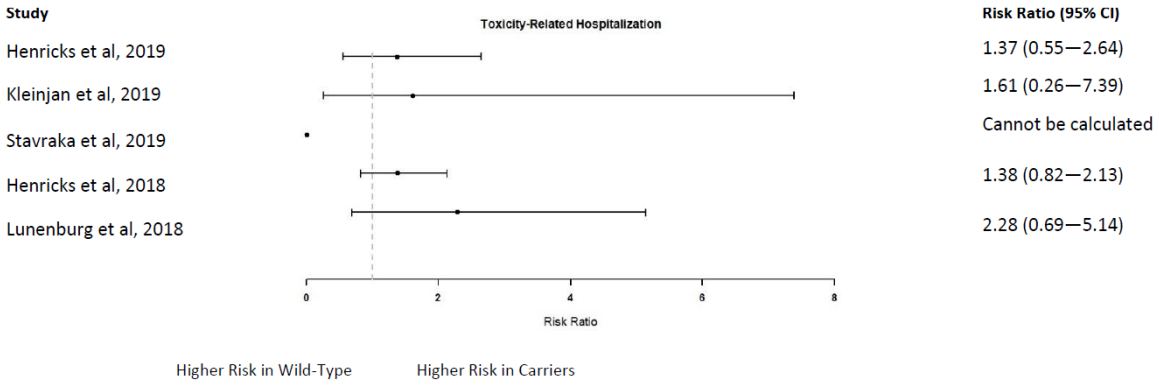

Figure 18: *DPYD* Carriers With a Genotype-Guided Reduced Fluoropyrimidine Dose Versus Wild-Type Patients—Risk of Hospitalization

Sources: Henricks et al (2019),[11] Kleinjan et al,[12] Stavraka et al,[23] Henricks et al (2018),[72] and Lunenburg et al.[7]

TOXICITY-RELATED MORTALITY
The only fluoropyrimidine-related death reported in *DPYD* carriers who were treated with a reduced dose occurred after the patient had been wrongly prescribed a standard fluoropyrimidine dose for two cycles.[72] Therefore, we could not determine what the outcome would have been if the patient had received a reduced dose. In wild-type patients, one study reported 2 (0.1%) deaths[11] a second study reported three (0.3%) deaths,[72] and a third study reported 10 (0.7%) deaths.[71] Additional information is provided in Appendix 5.

Fluoropyrimidine Treatment Effectiveness

We evaluated fluoropyrimidine treatment effectiveness in carriers of the *DPYD* variants under assessment who were treated with a genotype-guided reduced dose and compared it with treatment effectiveness in wild-type patients treated with a standard dose. Outcomes included treatment response, disease progression, overall survival, and progression-free survival.

The authors did not provide baseline characteristics specific to the matched *DPYD* carriers and wild-type patients. However, based on the full cohort, 45% of patients were male, the median age was 61 years (range 21–91), 96% were Caucasian, and approximately half had colorectal cancer.[11]

Median survival was 27 months (range 1–83) in *DPYD**2A carriers and 24 months (range 0.7–97) in wild-type patients (hazard ratio 0.82, 95% CI 0.47–1.43).[11] The median progression-free survival was 14 months (range 0.7–83) in *DPYD**2A carriers and 10 months (range 0.2–97) in wild-type patients (hazard ratio 0.83, 95% CI 0.47–1.50).[11] Results for treatment response and disease progression followed a similar direction (Appendix 5).

The GRADE quality of the evidence for both outcomes was very low because the evidence came from observational studies, and because of imprecision (Appendix 3).

Experience With DPYD Genotyping in Canada

Wigle et al[71] reported experiences with *DPYD* genotyping at an Ontario hospital between December 2013 and December 2019. Initially, testing included three variants (*DPYD**2A, *DPYD**13, and c.2864A>T), but in May 2018 a fourth variant (c.1236G>A) was added, based on its addition to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline in 2017.[71] During the study period, a total of 1,845 patients were tested before they started cancer treatment with fluoropyrimidines.[71] Among 1,394 patients who started treatment at the hospital before December 2019, nine (0.6%) *DPYD**2A carriers, one (0.07%) *DPYD**13 carrier, 19 (1.4%) c.2864A>T carriers, and 18 (1.3%) c.1236G>A carriers were identified and started treatment with a genotype-guided reduced fluoropyrimidine dose.[71] Two (0.1%) compound heterozygous carriers were identified, and the treating oncologist was advised to prescribe an alternative treatment instead of fluoropyrimidines.[71] Forty-one patients who received a standard fluoropyrimidine dose were retrospectively identified as c.1236G>A carriers when this variant was added to the panel.[71]

In Quebec, public funding is available for all four *DPYD* variants assessed in this review.[35] The province's experience with *DPYD**2A, the first variant introduced, has been published.[75] A total of 2,617 *DPYD**2A genotype tests were performed between March 2017 and August 2018.[75] The test was performed at one site, and samples were sent from hospitals across the province; test results were available in a mean of 6 days, including transportation time between institutions.[75] A total of 25 patients were identified as *DPYD**2A carriers: 24 (0.92%) heterozygous and one (0.038%) homozygous.[75] All carriers identified were Caucasian, but most patients tested were Caucasian.[75] *DPYD* genotyping allowed treatment modifications in all 14 carriers who were tested before the start of treatment: five patients received an alternative regimen, one refused treatment, and eight started treatment with a 50% to 75% fluoropyrimidine dose reduction.[75] Some of these patients had their dose increased, but in two patients who reached a full dose, the dose had to be decreased because of grade 2 toxicity.[75] According to the authors, none of the patients treated with a genotype-guided reduced fluoropyrimidine dose experienced severe (grade ≥ 3) toxicity or required treatment withdrawal because of toxicity.[75] The authors concluded that pre-treatment *DPYD* genotyping was feasible in clinical practice and could prevent severe toxicities and hospitalizations without delaying treatment initiation.[75]

Ongoing Studies

We are aware of the following ongoing studies that have potential relevance to our research questions.

One study is assessing the additional value of pre-treatment DPD phenotyping to guide dose individualization in wild-type patients. As a secondary objective, the authors are evaluating the effect of a 50% dose reduction on fluoropyrimidine-related toxicity in c.1236G>A and c.2846A>T carriers.[76] The estimated study completion date was January 2021.[76]

Another study is evaluating the effect on toxicity of a fluoropyrimidine dose reduction based on pre-treatment genotyping and phenotyping according to the French guidelines compared to a dose reduction based on the literature.[77] The expected study completion date is September 2021.[77]

Discussion

Our systematic review identified a large number of studies (n = 29), all in adult patients.[7,9,11-13,15,18,23,52-69,71,72] The prevalence of each variant (*DPYD**2A 1.1%, *DPYD**13 0.2%, c.2846A>T 1.2%, c.1236G>A 4.0%) and of all four variants combined (6.6%) was consistent with what has been reported in the literature. Few homozygous carriers were identified (0.05%–0.2%), and of those, only for variant c.1236G>A.[13,57,61] Compound heterozygous carriers constituted 0.03% to 0.4% of the patients in four studies.[9,57,58,67]

The frequency of severe toxicity varied considerably across studies, both in wild-type patients (3% to 89%) and *DPYD* variant carriers treated with a standard fluoropyrimidine dose (30% to 100%, except for two studies in which carriers had their dose reduced due to non-severe toxicity). Many factors can affect the risk of toxicity (e.g., age, sex, renal function, performance status, type, dose, and mode administration of fluoropyrimidines, combination with other cytotoxic chemotherapy drugs, and the timing of toxicity measurement).[8,10,13,15,16] The studies we identified included patients that may have differed with respect to some of these factors, reflecting the population that may receive cancer treatment with fluoropyrimidines. We were unable to conduct subgroup analyses, but the point estimates from most included studies were consistent in suggesting an increased risk of severe toxicity in carriers of the *DPYD* variants under assessment who received a standard fluoropyrimidine dose compared to wild-type patients. However, we found wide variation in the point estimates of the risk ratios across studies, and wide confidence intervals in some studies. As stated by the Clinical Pharmacogenetics Implementation Consortium (CPIC), disease and treatment regimens may affect the risk of toxicity, but the association of *DPYD* variants with fluoropyrimidine-related toxicity has been fairly consistent across regimens.[8]

Death as a result of fluoropyrimidine-related toxicity is estimated to occur in approximately 0.1% to 1.0% of patients.[4,9,10] The frequency of mortality in wild-type patients reported in five studies ranged from 0.0% to 2.0%[56,63,65,67,68,71] and seemed to be consistent with the literature. In heterozygous *DPYD* carriers treated with a standard fluoropyrimidine dose, three studies reported no deaths,[60,65,67] and five studies reported that 14.3% to 100% of carriers died as a result of toxicity.[55,56,61,63,68] In four studies, three of four compound heterozygous carriers died as a result of fluoropyrimidine-related toxicity,[9,57,58,67] and in the single study that reported mortality, the one homozygous c.1236G>A carrier died.[57]

Most studies did not directly assess the clinical utility of *DPYD* genotyping, because they were not specifically designed to compare pre-treatment *DPYD* genotyping with no testing or with other tests to measure DPD deficiency. Phenotype tests that measure DPD function have limitations such as issues with standardization, validation, and interpretation of results, because thresholds for treatment decisions have not been established.[2,6] They are also difficult to implement in routine practice and involve a longer turnaround time compared to genotyping.[23,72] At present, DPD function phenotype tests are not routinely done in Ontario, in part because of some these reasons (Richard Kim, MD, email communication, January 12, 2021; Leta Forbes, MD, email communication, January 8, 2021; John Lenehan, MD, email communication, February 12, 2021; Michael Raphael, MD, email communication, February, 10, 2021).

Strengths and Limitations

Our results were consistent with those of previous systematic reviews and built on the results of two health technology assessments, complementing the evidence base with nine additional studies. Limitations in the literature identified included the following:

- Some study results were imprecise, partly because of the low prevalence of *DPYD* variants, leading to reduced statistical power to detect differences between groups
- Some studies reported fluoropyrimidine dose reduction based on a toxicity grade lower than 3 without knowledge of *DPYD* genotyping results,[9,57,59,62,64,67] and this may have prevented severe (grade ≥ 3) toxicity from occurring, leading to an underestimate of severe toxicity
- Mostly Caucasian patients were included in the studies, and authors recommended that more research on the frequency and clinical relevance of these and other *DPYD* variants in other racial/ethnic groups be performed[72]
- Clinical utility was assessed indirectly in most studies by comparing the outcomes of *DPYD* carriers who received a genotype-guided fluoropyrimidine dose reduction with wild-type patients who received a standard dose. One study retrospectively compared *DPYD* carriers who received a genotype-guided reduced fluoropyrimidine dose with *DPYD* carriers who received a standard dose.[7] However, it was difficult to draw conclusions based on this study given the small number of carriers identified and imbalances in the distribution of *DPYD* variants between the two groups
- We were unable to perform subgroup analyses based on factors that may affect the risk of severe toxicity (e.g., age, sex, cancer type, fluoropyrimidine type and dose, and combination with other cytotoxic chemotherapy drugs) for clinical validity, clinical utility, and fluoropyrimidine treatment effectiveness

Conclusions

Clinical Validity

Studies found that heterozygous carriers of any one of the variants under assessment (*DPYD**2A, *DPYD**13, c.2846A>T, c.1236G>A) treated with a standard fluoropyrimidine dose (assessed as a single group) may have a higher risk of severe fluoropyrimidine-related toxicity than wild-type patients treated with a standard dose. This may lead to dose reduction, treatment discontinuation, and hospitalization (GRADE: Low).

- A similar trend was observed when each variant was evaluated separately, but the results of some of the studies were imprecise, especially for *DPYD**13, the variant with the lowest prevalence, and c.1236G>A (GRADE: Low to Very low, depending on the variant)
- A similar trend was observed for compound heterozygous carriers and homozygous c.1236G>A carriers (GRADE: Low)
- *DPYD* genotyping had a high clinical specificity to detect severe toxicity. However, because some of the wild-type patients also experienced severe toxicity, the clinical sensitivity of the test to detect severe toxicity was low. This may have been due to the fact that other unmeasured *DPYD* variants may also contribute to DPD deficiency, and that severe toxicity in patients treated with fluoropyrimidines may be explained by causes other than DPD deficiency

Clinical Utility

We were unable to adequately assess the clinical utility of *DPYD* genotyping because the studies identified were not specifically designed to evaluate this outcome. Six studies compared outcomes between heterozygous carriers of one of the *DPYD* variants under assessment who received a genotype-guided reduced fluoropyrimidine dose with wild-type patients who received a standard dose. One study also compared outcomes with *DPYD* carriers who received a standard dose.

- *DPYD* genotyping led to changes in clinical conduct by permitting fluoropyrimidine treatment modifications (dose modifications or avoiding fluoropyrimidines)
- Given the imprecision in study results, it is uncertain whether genotype-guided dose reduction in heterozygous *DPYD* carriers led to a risk of severe toxicity and toxicity-related hospitalization that was comparable to that of wild-type patients on a standard dose (GRADE: Very low)
- One study compared *DPYD* carriers treated with a reduced fluoropyrimidine dose and *DPYD* carriers treated with a standard dose; however, given the imprecision in study results and imbalances in the distribution of *DPYD* variants between groups, it is uncertain whether genotype-guided dose reduction in heterozygous *DPYD* carriers led to a lower risk of severe toxicity and toxicity-related hospitalization than that of carriers treated with a standard dose (GRADE: Very low). Hospital length of stay was shorter in *DPYD* carriers treated with a reduced dose than in *DPYD* carriers treated with a standard dose, but the evidence was uncertain (GRADE: Very low)
- Compound heterozygous and homozygous *DPYD* carriers were not represented in the clinical utility studies. According to some study authors and experts, *DPYD* genotyping is important for identifying these patients, because they are expected to have very low or even absent DPD activity; a full fluoropyrimidine dose could be life-threatening,[72] even with the first dose (Richard Kim, MD, email communication, January 12, 2021; John Lenehan, MD, email communication, February 12, 2021; Michael Raphael, MD, email communication, February 10, 2021)

Fluoropyrimidine Treatment Effectiveness

It is uncertain whether the treatment effectiveness of a reduced dose in *DPYD* carriers is comparable to the treatment effectiveness of a standard dose in wild-type patients (GRADE: Very low).

Challenges in assessing the evidence included the low frequency of the *DPYD* variants under assessment, which led to imprecision in the results of some studies. The current evidence is based mostly on experience in Caucasian patients, and study authors pointed out that more research on the frequency and clinical relevance of these and other *DPYD* variants in other racial/ethnic groups is necessary.[72]

Economic Evidence

Research Question

What is the cost-effectiveness or cost impact of pre-treatment *DPYD* genotyping compared to usual care (no testing) or with other tests for DPD deficiency before the start of treatment in patients who have planned cancer treatment with fluoropyrimidines?

Methods

Economic Literature Search

We performed an economic literature search on February 20, 2020, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied. In addition to the databases used for the clinical systematic review search, we also used the Ovid interface in the Cochrane Central Register of Controlled Trials.

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search section, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until February 20, 2020
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, cost–consequence analyses, cost–utility analyses, or cost analyses

Exclusion Criteria

- Narrative reviews, letters/editorials, case reports, commentaries, conference abstracts, posters, and unpublished studies

POPULATION

- Adult and pediatric patients who had planned cancer treatment with fluoropyrimidines, alone or in combination with other therapies

INTERVENTIONS

Inclusion Criterion

- *DPYD* genotyping of the variants under assessment (*DPYD**2A, *DPYD**13, c.2846A>T, c.1236G>A) before the start of treatment
- Carriers of *DPYD* variants under assessment who had their fluoropyrimidine dose reduced as a result of pre-treatment genotyping

Exclusion Criteria

- Treatment decisions based on testing for other *DPYD* or other gene variants (e.g., *TYMS, CES*)
- Treatment decisions based on either phenotypic measurement of dihydropyrimidine dehydrogenase (DPD) enzyme activity, such as plasma uracil concentration or dihydrouracil:uracil (UH2:U) ratio, or 5-fluorouracil (5-FU) pharmacokinetics assessment

COMPARATOR

Inclusion Criteria

- No *DPYD* genotyping
- Phenotypic tests for DPD deficiency (e.g., plasma uracil concentration or UH2:U ratio) before the start of treatment, or 5-FU pharmacokinetics assessment
- Wild-type patients or carriers who did not have the fluoropyrimidine dose adjusted as a result of pre-treatment genotyping

Exclusion Criterion

- Treatment with uridine triacetate (antidote for 5-FU toxicity), given its limited use

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs], number of adverse events)
- Incremental costs and incremental effectiveness
- Incremental cost-effectiveness ratios (ICER)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[41] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention, comparator)
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

If an eligible study was identified, we determined the usefulness of each study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[78] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly applicable.

Results

Economic Literature Search

The database search of the economic literature yielded 158 citations published from database inception to February 20, 2020. We identified eight additional studies from other sources, for a total of 131 after removing duplicates. We excluded a total of 100 articles based on information in the title and abstract. We then obtained the full text of 31 potentially relevant articles for further assessment. Two studies met the inclusion criteria. Figure 19 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

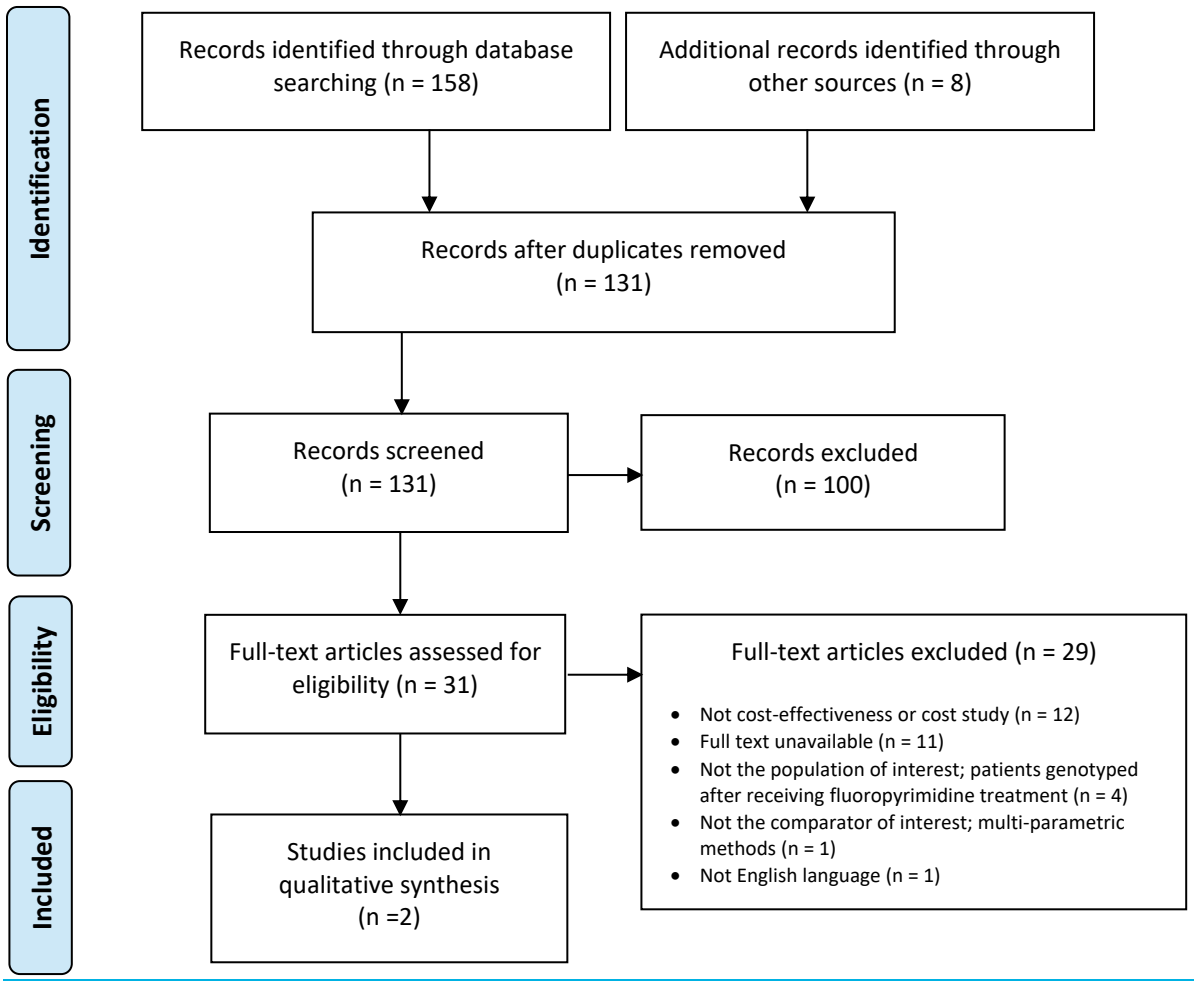

Figure 19: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[51]

Overview of Included Economic Studies

We identified two cost-minimization analyses[79,80] that met the inclusion criteria. The characteristics and results of the included studies are summarized in Table 8.

Both studies[79,80] were conducted in the Netherlands and used similar decision-tree models to compare the costs of a pre-treatment *DPYD* genotyping strategy with no genotyping. The analyses were conducted alongside two prospective observational studies.[79,81] Both studies included patients who were intended to start on a fluoropyrimidine-based chemotherapy and both studies conducted *DPYD* genotyping before treatment initiation. Deenen et al,[79] who screened patients for one variant (*DPYD**2A), identified 1.1% of patients (22 of 2,038) as heterozygous *DPYD* variant carriers. Henricks et al,[81] who screened for four variants (*DPYD**2A, c.2846A>T, c.1679T>G, and c.1236G>A), identified 7.7% of patients (85 of 1,103) as heterozygous *DPYD* variant carriers. *DPYD* variant carriers were given a dose reduction and wild-type patients received the standard dose. The outcome measured was frequency of severe (grade ≥ 3) toxicities. Because a randomized trial comparing genotyping to no testing was considered unethical, both studies obtained toxicity data on *DPYD* variant carriers treated with standard-dose fluoropyrimidines

from two different historical cohorts identified from the literature. Both analyses were conducted from a Dutch health care payer perspective and included only direct medical costs, such as costs for *DPYD* genotyping, fluoropyrimidine drug therapy, and treatment of severe toxicity. The cost of the *DPYD* genotyping test ranged from €75 per test for one variant[79] to €100 per test for four variants.[80]

Both analyses found the *DPYD* genotyping strategy to be slightly less costly than usual care (no testing), with some uncertainty. The savings were attributed to a reduction in severe fluoropyrimidine-related toxicities. Deenen et al[79] estimated the total treatment cost to be €2,772 per patient for *DPYD* genotyping and €2,817 per patient for no genotyping, resulting in an average cost savings of €44 per patient (range: −€74 to €331, in 2014 Euros). The result was most sensitive to the risk of hospitalization in *DPYD* variant carriers receiving standard dose, frequency of *DPYD* variant genotype, and genotyping cost. Henricks et al[80] had very similar results. The estimated cost of the *DPYD* genotyping strategy and the no-genotyping strategy was €2,599 and €2,650 per patient, respectively. The average incremental cost was −€52 per patient (range: −€176 to €38, in 2019 Euros), indicating savings. The average incremental rate of severe toxicity was −0.89% (range: −1.79% to 0.04%), indicating improved safety. One-way sensitivity analysis showed that the most influential parameters were the frequency of *DPYD* variant genotypes, risk of hospitalization, and genotyping costs.

Table 8: Summary of the Included Economic Studies

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Deenen et al, 2016[79] Netherlands	• Cost-minimization analysis • Decision-tree model • Health care payer perspective • Time horizon not specified	• Cancer patients intended to undergo fluoropyrimidine-based treatment (n = 2,038) • Age (mean): 61 y • Male: 45% • Prevalence of *DPYD* variant carrier: 1.1% (22/2,038)	• Pre-treatment *DPYD* genotyping for 1 variant (*DPYD**2A) • Usual care (no testing)	*Proportion of people experiencing severe toxicity (grade ≥ 3)* • Pre-treatment *DPYD* genotyping: 23.18%[a] • Usual care: 23.72%[a] • Difference: −0.54%	*Total cost per patient (in 2014 Euros)* • Pre-treatment *DPYD* genotyping: €2,772 • Usual care: €2,817 • Difference, deterministic: −€45 • Difference, probabilistic: −€44 (−€331 to €74)	Pre-treatment *DPYD* genotyping was slightly more effective and less costly
Henricks et al., 2019[80] Netherlands	• Cost-minimization analysis • Decision-tree model • Health care payer perspective • Time horizon not specified	• Cancer patients intended to undergo fluoropyrimidine-based treatment (n = 1,103) • Age (mean): 64 y • Male: 54% • Prevalence of *DPYD* variant carriers: 7.7% (85/1,103)	• Pre-treatment *DPYD* genotyping for 4 variants (*DPYD**2A, c.2846A>T, c.1679T>G, and c.1236G>A) • Usual care (no testing)	*Proportion of people experiencing severe toxicity (grade ≥ 3)* • Pre-treatment *DPYD* genotyping: 23.93%[b] • Usual care: 24.81%[b] • Difference, deterministic: −0.88% • Difference, probabilistic: −0.89% (−1.79% to 0.04%)	*Total cost per patient (in 2019 Euros)* • Pre-treatment *DPYD* genotyping: €2,599 • Usual care: €2,650 • Difference, deterministic: −€51 • Difference, probabilistic: −€52 (−€176 to €38)	Pre-treatment *DPYD* genotyping was cost-saving or cost neutral

[a]Calculated based on Appendix Table A21(prevalence of *DPYD* variant carriers and the probability of severe toxicity).

[b]Calculated based on prevalence of *DPYD* variant carriers and the probability of severe toxicity.

Applicability of the Included Studies

Appendix 7 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. Both studies were deemed partially applicable to our research question because they considered our population and intervention of interest. However, both studies were conducted from a Dutch health care payer perspective and were not directly applicable to the Canadian setting.

Discussion

Our literature review showed that the economic evidence for *DPYD* genotyping is still very limited. Only two studies met the inclusion criteria, and both were cost-minimization analyses. There is a lack of cost-effectiveness and cost–utility studies that evaluate the effect of *DPYD* genotyping on patients' survival or quality of life. The strength of the two cost-minimization analyses was that clinical and resource-use data on wild-type patients and *DPYD* variant carriers who received reduced doses were collected directly from two prospective observational studies.[79,81] Although the studies are well conducted, there were some limitations. First, ethical considerations prevented randomized clinical trials from directly comparing pre-treatment *DPYD* genotyping with no genotyping. Instead, Deenen et al[79] and Henricks et al[72] assessed the impact of *DPYD* genotyping indirectly by comparing *DPYD* variant carriers who received reduced-dose fluoropyrimidines with historical controls (*DPYD* variant carriers who received a standard dose, identified from the literature). As a result, many confounding factors might have contributed to the observed toxicity outcomes (e.g., differences in age, sex, cancer type, and treatment regimens between the comparison groups). For example, in Deenen et al,[79] historical controls were more often treated with 5-FU–based regimens than with capecitabine-based regimens, compared to the prospective patient cohort. Second, the impact of *DPYD* genotyping could have been slightly underestimated in both studies because they did not include any compound heterozygous or homozygous *DPYD* variant carriers (i.e., poor metabolizers). Although poor metabolizers are very rare, according to the literature and clinical experts, they may actually benefit the most from *DPYD* genotyping because standard-dose fluoropyrimidines could cause very severe or even life-threatening toxicities. Last, both studies were conducted in the Netherlands. Because practice patterns and unit prices may be different between the Netherlands and Canada, the study results may not be generalizable to the Ontario setting.

Excluded Studies

We also identified three cost studies and one cost–utility analysis in patients who received retrospective *DPYD* genotyping. These studies did not meet our inclusion criteria because the patients were genotyped after they had already received fluoropyrimidine treatment.[82-85] The studies were also excluded because they did not compare a pre-treatment *DPYD* genotyping strategy to a no-genotyping strategy.

Cortejoso et al[82] compared the cost of *DPYD* genotyping for three variants (*DPYD**2A, c.2846A>T, and c.1679T>G) with the cost of treating severe fluoropyrimidine-induced neutropenia in a Spanish hospital setting. Based on hospital records of 20 colorectal cancer patients who developed severe neutropenia, the average cost of treating a patient with severe neutropenia was estimated to be €3,044, and the cost of testing 1,000 patients was estimated to be €6,400. Therefore, the researchers concluded that *DPYD* genotyping would be cost-effective if 2.1 cases of neutropenia could be avoided for every 1,000 patients treated.

Another cost analysis, by Murphy et al,[83] investigated the costs of two *DPYD* testing strategies in an Irish hospital setting: reactive *DPYD* screening (testing patients for *DPYD* variants after experiencing severe

toxicity) and prospective screening. Over a period of 3 years, a total of 134 patients who received first-line fluoropyrimidine-based chemotherapy for colorectal cancer were included in the study. Thirty patients experienced severe toxicity (23%) and were subsequently tested for four *DPYD* variants (*DPYD**2A, c.2846A>T, c.1679T>G, and c.1601G>A). Of these, five (17% of those tested, 4.5% of total population) were heterozygous *DPYD* variant carriers. The total cost of toxicity-related hospitalization for these five patients was €232,061 (an average of €46,412 per case). However, the cost of conducting pre-treatment *DPYD* genotyping in all 134 patients would have been €23,718 (at €177 per test). The authors concluded that if 60% of patients identified as *DPYD* variant carriers were prevented from experiencing severe toxicity resulting in hospitalization, approximately €120,000 in costs could have been avoided over a 3-year period.

A third cost analysis was conducted by Toffoli et al[84] on 550 colorectal cancer patients who were treated with fluoropyrimidine-based chemotherapy in Italy. Patients were retrospectively genotyped for four variants (*DPYD**2A, *DPYD**13, *DPYD* c.2846A>T and *DPYD-HapB3*). Their results showed that carriers of at least one *DPYD* variant had higher toxicity management costs (€2,972; 95% CI: €2,456–€3,505) than noncarriers (€825; 95% CI: €785–€864) and a higher risk for toxicity requiring hospitalization (odds ratio, 4.14; 95% CI: 1.87–9.14).

Lastly, Fragoulakis et al[85] conducted a cost–utility analysis on patients who received fluoropyrimidine-based chemotherapy and were retrospectively genotyped for four *DPYD* variants (*DPYD**2A, *DPYD**13, *DPYD* c.2846A>T, and *DPYD-HapB3*) in Italy. They compared the costs, survival, and QALYs of two groups of patients: wild-type patients and *DPYD*-variant carriers. The results showed that wild-type patients had lower cost, slightly higher survival, and higher QALYs.

Conclusions

We found two cost-minimization analyses comparing pre-treatment *DPYD* genotyping with no genotyping in patients with planned fluoropyrimidine treatment. The studies suggested that, compared to no genotyping, pre-treatment *DPYD* genotyping may reduce severe fluoropyrimidine-related toxicity and lead to small cost savings.

Primary Economic Evaluation

We found two published cost-minimization analyses comparing pre-treatment *DPYD* genotyping with no testing in patients with planned fluoropyrimidine treatment. Although those studies addressed our research question, they were not directly applicable to the Canadian setting as both studies were conducted from a Dutch health care payer perspective. Also, they evaluated only costs and the frequency of severe toxicities and did not consider the impact of *DPYD* genotyping on patients' survival or quality of life. Owing to these limitations, we conducted a primary economic evaluation to estimate the cost-effectiveness of *DPYD* genotyping in Ontario.

Research Question

What is the cost-effectiveness of pre-treatment *DPYD* genotyping compared to usual care (no testing) in patients who have planned cancer treatment with fluoropyrimidines from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[86]

Type of Analysis

We conducted a probabilistic cost–utility analysis as it is the recommended reference case approach by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluation. The effectiveness outcome is quality-adjusted life years (QALYs), which considers both patient's survival and quality of life (e.g., 1 QALY represents 1 year of perfect health). A generic outcome measure such as QALY allows decision-makers to make comparisons across different conditions and interventions. We also conducted a cost-effectiveness analysis with outcome expressed in natural units, such as the proportion of patients with severe fluoropyrimidine-related toxicities.

Target Population

The target population was adults who had planned fluoropyrimidine-based anticancer treatment. Based on 23 clinical validity studies identified from the clinical evidence review, the mean age of patients in clinical studies ranged from 47 to 67 years. Between 42% and 68% of patients were male, except for two studies that focused on women with breast cancer. Patients often had different types of cancer, with colorectal being the most common. Among the fluoropyrimidines, 5-fluorouracil (5-FU) was used more commonly.

We also obtained data on patients treated with fluoropyrimidines in Ontario (Ontario Health; Ontario Cancer Registry, Cancer Activity Level Reporting and Ontario Drug Benefit datasets; prepared March 2020). Compared to the clinical literature, the characteristics of the Ontario patient population were very similar (Table 9). The mean age was 63.6 years, and 50.8% were female. The most common types of cancer were colorectal, breast, and upper gastrointestinal. Similarly, a majority of the patients in Ontario received 5-FU.

Table 9: Characteristics of the Ontario Population—Patients Who Received Fluoropyrimidines From 2014/2015 to 2018/2019 in Ontario (N = 38,225)

Patient Characteristics	Mean Value
Age	63.6 years
Sex	
Male	49.2%
Female	50.8%
Type of cancer	
Colorectal	40%
Breast	22%
Upper gastrointestinal	10%
Other (e.g., pancreatic, prostate, skin, lymphoid)	28%
Fluoropyrimidine prescribed	
5-Fluorouracil alone	66.8%
Capecitabine alone	25.1%
Both	8.1%

Source: Data prepared in March 2020 by Ontario Health (Cancer Care Ontario) using Ontario Cancer Registry, Cancer Activity Level Reporting and Ontario Drug Benefit datasets.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Intervention and Comparator

We compared pre-treatment *DPYD* genotyping with usual care (no testing). In the *DPYD* genotyping strategy, all patients with planned fluoropyrimidine treatment would receive an upfront *DPYD* genotyping test for the four most common and well-established risk variants (*DPYD*2A, DPYD*13, c.2846A>T, c.1236G>A*).[6,8] The result of the *DPYD* genotyping test would be used to guide treatment decisions and dosing of fluoropyrimidines. Individuals without the variants (wild-type) were classified as *DPYD* normal metabolizers, and carriers of the variants were classified as *DPYD* intermediate or poor metabolizers. We assumed that the treatment decisions and dose adjustments made would follow the 2017 Clinical Pharmacogenetics Implementation Consortium guidelines (Table 10).[8]

In the usual care strategy, no *DPYD* genotyping is conducted, and all patients receive standard-dose fluoropyrimidines. The dose may vary by patient depending on age, cancer type, disease stage, and other characteristics.[87] We did not consider strategies using other measures of dihydropyrimidine dehydrogenase (DPD) deficiency or 5-FU pharmacokinetics assessment due to their complexity and implementation challenges (Aaron Pollett, MD, email communication, September 20, 2020; Leta Forbes, MD, email communication, September 30, 2020). We also did not consider treating severe fluoropyrimidine-related toxicity with uridine triacetate (i.e., an antidote), because this treatment is available only through the Special Access Program and, based on expert opinion (Aaron Pollett, MD,

email communication, September 20, 2020; Leta Forbes, MD, email communication, September 30, 2020), is rarely used in practice, is reserved for emergency treatment, and should not be considered a surrogate for prospective genotyping of *DPYD* alleles.[32]

Table 10: Genotype Determination and Treatment Adjustments

DPYD Genotype	Gene Activity Score	Likely Phenotype	Treatment Adjustment
Wild-type or noncarrier: • 2 normal-function variants	2	Normal metabolizer; normal DPD enzyme activity with "normal" risk for fluoropyrimidine toxicity	No dose adjustments; use label-recommended dose
DPYD variant carrier: • 1 normal-function variant and 1 no-function variant • 1 normal-function variant and 1 decreased-function variant • 2 decreased-function variants	1 or 1.5	Intermediate metabolizer; reduced DPD enzyme activity and increased risk for severe or fatal toxicity when treated with fluoropyrimidine drugs	Reduced dose followed by titration of dose based on occurrence of toxicity
DPYD variant carrier: • 2 no-function variant • 1 no-function variant and 1 decreased-function variant	0 or 0.5	Poor metabolizer; complete DPD deficiency and high risk for severe or fatal toxicity when treated with fluoropyrimidine drugs	Alternative chemotherapy regimen

Abbreviation: DPD, dihydropyrimidine dehydrogenase.

Source: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline, 2017.[8]

Time Horizon and Discounting

For the reference case analysis, we used a 6-month time horizon to capture the impact of *DPYD* genotyping on short-term costs and outcomes. No discounting was applied because the time horizon was less than 1 year. We chose a short time horizon because most toxicities associated with fluoropyrimidines resolve within a few months and have relatively short-term impacts on people's health (Jason Yu, MD, Geoffrey Liu, MD, Theodore Wigle, MD, Leta Forbes, MD, personal communication, June 21 to September 25, 2020). To capture the potential QALY loss due to rare but fatal toxicities, we assumed that death due to severe fluoropyrimidine-related toxicity would usually occur after the first or second cycle of chemotherapy.

We did not model the long-term impact of *DPYD* genotyping on cancer morbidity and mortality. These cancer-related outcomes are inherently connected to chemotherapy efficacy. We assumed that chemotherapy efficacy would be similar between *DPYD* carriers who received a reduced dose and wild-type patients. We based this assumption on the fact that *DPYD* genotyping-guided dose reduction aims to maintain plasma levels of 5-FU and its metabolites at the intended therapeutic levels (hence similar treatment efficacy). The clinical review identified a matched-pair analysis that compared overall survival and progression-free survival between 37 *DPYD*2A* carriers who received a reduced fluoropyrimidine dose and 37 wild-type patients.[11] In that study, Henricks et al[11] found that, compared to wild-type

patients, a reduced dose did not negatively affect overall survival (median 27 vs. 24 months, *P* = 0.47) or progression-free survival (median 14 vs. 10 months, *P* = 0.54). It is possible that *DPYD* genotyping may produce false-positive results. Reducing the fluoropyrimidine dose in patients who do not have DPD deficiency may cause them to be underdosed. However, to avoid underdosing, clinical guidelines recommend that doses be increased in subsequent cycles in people who experience no clinically tolerable toxicity in the first two chemotherapy cycles[21] and that people should be monitored (e.g., using pharmacokinetic testing) to identify those who can tolerate higher 5-FU doses. Based on these considerations, we assumed that long-term treatment efficacy would be similar and therefore it was not modelled.

Model Structure

We developed a decision-tree model based on the treatment pathways in Ontario, clinical guidelines,[8] and published economic studies.[79,80] The model structure is depicted in Figure 20.

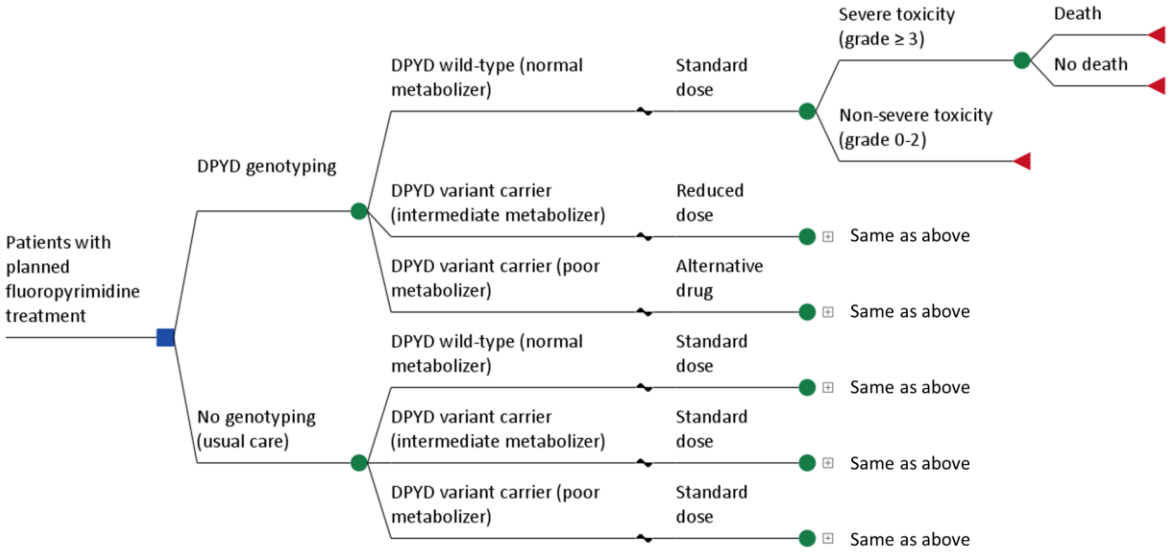

Figure 20: Decision Model Structure

The decision tree compared *DPYD* genotyping with usual care. In the usual care strategy, no *DPYD* genotyping was conducted and all patients received a standard fluoropyrimidine dose. In the *DPYD* genotyping strategy, all patients received a *DPYD* genotyping test prior to the start of fluoropyrimidine treatment. Patients were then classified into one of three groups based on their test results: *DPYD* normal metabolizers, intermediate metabolizers, and poor metabolizers. Based on the 2017 Clinical Pharmacogenetics Implementation Consortium guidelines, *DPYD* normal metabolizers would receive standard-dose fluoropyrimidines, intermediate metabolizers would receive reduced-dose fluoropyrimidines, and poor metabolizers would receive an alternative to fluoropyrimidines (Table 10).

Each group of patients might experience severe (grade ≥ 3) or non-severe (grade 0–2) toxicities at different rates of occurrence. A small proportion of severe toxicities might be fatal. We calculated the costs of *DPYD* genotyping, fluoropyrimidine chemotherapy, and toxicity-related treatment for both strategies. We also calculated the total number of severe toxicities and patient QALYs. We did not model background mortality and cancer-related mortality because they were not expected to be affected by *DPYD* genotyping.

Main Assumptions

The main assumptions for the reference case analysis were:

- Most patients would be heterozygous *DPYD* variant carriers because most patients in the included clinical studies were such carriers. Data from these studies were used to inform input parameters for *DPYD* intermediate metabolizers in the model
- There are limited clinical data on *DPYD* poor metabolizers (compound heterozygous and homozygous carriers) treated with standard-dose fluoropyrimidines. This is likely because *DPYD* poor metabolizers are rare (approximately 0.19% of patients treated with fluoropyrimidines). Because these patients are expected to have a very low or even absent DPD activity, we assumed that if they were treated with standard-dose fluoropyrimidines, all would experience severe toxicities. We based this assumption on a few cases of compound heterozygous and homozygous carriers identified from the clinical evidence review (all of whom experienced severe toxicities) and consultation with clinical experts. We also assumed that, compared to intermediate metabolizers treated with a standard dose, a higher proportion of poor metabolizers would be hospitalized and their hospital length of stay would be longer (Brandon Meyers, MD, email communication, June 16, 2020)
- Data are also lacking on *DPYD* poor metabolizers treated with an alternative regimen. We assumed that these patients could metabolize non-fluoropyrimidine drugs normally, and therefore the risks of overall severe toxicity, hospitalization, and death, as well as hospital length of stay, would be similar to those for *DPYD* wild-type patients. This assumption was validated by clinical experts as reasonable (Geoffrey Liu, MD, telephone communication, June 24, 2020)
- Treatment-related hospitalization would occur only in patients with severe toxicities
- Approximately 1% to 2% of *DPYD* tests would fail (e.g., issues with DNA extraction, reaction failure, etc.) and need to be re-run (Richard Kim, MD, email communication, February 20, 2020; Lei Fu, PhD, email communication, June 22, 2020)
- *DPYD* genotype-guided dosing and treatment adjustments would follow the 2017 Clinical Pharmacogenetics Implementation Consortium guidelines[8]

Clinical Parameters

The clinical parameters used in the model are presented in Table 11.

PREVALENCE OF *DPYD* PHENOTYPES

The prevalence of *DPYD* phenotypes (i.e., normal, intermediate, and poor metabolizers) was estimated based on the prevalence of *DPYD* genotypes. Based on the pooled prevalence of *DPYD* variant carriers from the clinical evidence review, we estimated the proportion of *DPYD* intermediate and poor metabolizers to be 6.60% and 0.19%, respectively.

PROBABILITY OF OVERALL SEVERE TOXICITY AND HOSPITALIZATION

The clinical evidence review identified 23 studies that compared *DPYD* variant carriers treated with a standard dose versus wild-type patients and five studies that compared *DPYD* variant carriers treated with a reduced dose versus wild-type patients. Among these studies, only Lunenburg et al[7] evaluated all four variants under assessment and included all three groups of patients (wild-type receiving standard

dose, *DPYD* carrier receiving standard dose, and *DPYD* carrier receiving reduced dose) in the same study. Therefore, we selected this study to inform the reference case analysis.

Lunenburg et al[7] reviewed the medical records of 828 patients who received fluoropyrimidine-based chemoradiation therapy from three cancer centres in the Netherlands and northern Italy. The study included 771 wild-type patients who received a standard dose, 34 *DPYD* variant carriers who received a standard dose, and 23 *DPYD* variant carriers who received a reduced dose (one patient was excluded from the statistical analysis because of a substantial dose increase). The probability of overall severe toxicity was 13.62% (105/771) in wild-type patients receiving standard dose, 23.53% (8/34) in *DPYD* variant carriers who received a standard dose, and 22.73% (5/22) in *DPYD* variant carriers who received a reduced dose. The probability of hospitalization was 7.8% (60/771), 17.6% (6/34), and 18.2% (4/22), respectively. Although the probabilities of treatment-related severe toxicity and hospitalization were similar in the two *DPYD* carrier groups, the mean duration of hospitalization was much shorter in the reduced-dose group ($P = 0.010$). For patients who were hospitalized, the mean hospital length of stay was 13 days in wild-type patients who received a standard dose, 23 days in *DPYD* variant carriers who received a standard dose, and 4 days in *DPYD* variant carriers who received a reduced dose. According to the study authors, there were two possible explanations for this observation. It is possible that treating physicians were responding to the potentially increased risk of toxicity in *DYPD* variant carriers by more rapidly hospitalizing patients with signs of potential toxicity. It is also possible that *DPYD* variant carriers given dose reductions recovered more quickly from toxicity episodes. All but two patients in the Lunenburg study were heterozygous carriers, so we used these data to inform input parameters for *DPYD* intermediate metabolizers in the model.

As mentioned before, the clinical evidence for *DPYD* poor metabolizers is very limited. To estimate the probability of overall toxicity and hospitalization in *DPYD* poor metabolizers, we made several assumptions. Studies included in the clinical evidence review reported only a few cases of patients who were *DPYD* poor metabolizers. There were four compound heterozygous and two homozygous *DPYD* variant carriers; all received standard-dose fluoropyrimidines, and all had severe toxicity (four were fatal). Therefore, we assumed that all *DPYD* poor metabolizers treated with a standard dose would experience severe toxicities and about two-thirds would be hospitalized. We also assumed that the hospital length of stay would be longer than for intermediate metabolizers.

PROBABILITY OF TREATMENT-RELATED DEATH

Since treatment-related mortality was not reported by Lunenburg et al,[7] we estimated the probability of death among patients with severe toxicity from other studies. Henricks et al[11] was a large observational study that conducted pre-treatment *DPYD* genotyping for four variants in a cohort of 1,103 patients with planned fluoropyrimidine treatment. Of these patients, 1,018 (92%) were wild-type and 85 (8%) were heterozygous *DPYD* variant carriers. Compound heterozygous and homozygous *DPYD* variant carriers were not included in the study. Severe toxicity was experienced by 23% (231/1,018) of the wild-type patients and 39% (33/85) of the *DPYD* variant carriers treated with a reduced dose. Three patients in the wild-type group (1.3%) died because of fluoropyrimidine-related toxicity, and no treatment-related death occurred in the *DPYD* variant carrier group (one patient died due to protocol violation). Because the lack of deaths in the carrier group may have been driven by the small sample size, we assumed that the probability of treatment-related death in *DPYD* intermediate metabolizers who received a reduced dose was the same as for wild-type patients (1.3%).

For *DPYD* intermediate metabolizers who received a standard dose, we obtained the probability of treatment-related death from Deenen et al.[79] These authors selected a group of patients (n = 48) who

were genotyped for *DPYD**2A and treated with a standard fluoropyrimidine dose. Of these 48 patients, 35 had severe toxicity and five died because of fluoropyrimidine-related toxicity. Therefore, we estimated the probability of treatment-related death among *DPYD* variant carriers who received a standard dose and experienced severe toxicity to be 14.3% (5/35).

For *DPYD* poor metabolizers, we assumed that those who received an alternative regimen would have a risk of treatment-related death similar to the wild-type patients. For those treated with a standard fluoropyrimidine dose, we used information from the studies included in the clinical evidence review, in which four of six patients with severe toxicity died (66.7%).

AVERAGE NUMBER OF TOXICITIES PER PERSON

Patients may experience more than one severe toxicity during their course of chemotherapy. This is evident from Lunenburg et al,[7] where the total number of severe toxicities (the sum of the different types of toxicity) was greater than the number of patients who experienced severe toxicities. We calculated the average number of toxicities per person for wild-type patients and *DPYD* variant carriers who received a reduced dose and a standard dose, and we used these values to adjust the costs and utilities in patients who experience severe toxicities.

Table 11: Clinical Inputs Used in the Economic Model

Model Parameter	Mean	Distribution	Reference
Prevalence of *DPYD* Phenotypes			
Intermediate metabolizer	6.60%	Beta	Clinical evidence review (pooled prevalence)
Poor metabolizer	0.19%	Beta	Clinical evidence review (pooled prevalence)
Normal metabolizer	93.21%	—	Calculated
Genotype Testing Parameters			
Test failure	1.5%	Beta[a]	Expert opinion
Probability of Overall Severe Toxicity in All Patients			
DPYD wild-type	13.62%	Beta	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, reduced dose	22.73%	Beta	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, standard dose	23.53%	Beta	Lunenburg et al, 2018[7]
DPYD poor metabolizer, alternative regimen	13.62%	—	Assumed to be similar to wild-type
DPYD poor metabolizer, standard dose	100%	—	Lee et al, 2016[13]; Froehlich et al, 2015[88]; Toffoli et al, 2015[9]; Lee et al, 2014[58]; Boisdron-Celle et al, 2007[67] (4 compound heterozygous and 2 homozygous carriers received a standard dose; all had severe toxicity)
Probability of Treatment-Related Hospitalization in All Patients			
DPYD wild-type	7.8%	Beta	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, reduced dose	18.2%	Beta	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, standard dose	17.6%	Beta	Lunenburg et al, 2018[7]
DPYD poor metabolizer, alternative regimen	7.8%	—	Assume similar to that of wild-type
DPYD poor metabolizer, standard dose	66.7%	—	Lee et al, 2016[13]; Froehlich et al, 2015[13,57]; Toffoli et al, 2015[9,57]; Lee et al, 2014[9,58]; Boisdron-Celle et al, 2007[67] (4 compound heterozygous and 2 homozygous carriers received a standard dose; all had severe toxicity; 4 were fatal); assumed all fatal severity led to hospitalization

Model Parameter	Mean	Distribution	Reference
Days of Hospitalization for Patients Who Were Hospitalized			
DPYD wild-type	13	Normal[a]	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, reduced dose	4	Normal[a]	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, standard dose	23	Normal[a]	Lunenburg et al, 2018[7]
DPYD poor metabolizer, alternative regimen	13	Normal[a]	Assumed to be similar to that of wild-type
DPYD poor metabolizer, standard dose	29	Normal[a]	Assume 25% longer than that of intermediate metabolizer
Probability of Death Among Patients With Severe Toxicities			
DPYD wild-type	1.3%	Beta	Henricks et al, 2018[72]
DPYD intermediate metabolizer, reduced dose	1.3%	—	Assume similar to that of wild-type
DPYD intermediate metabolizer, standard dose	14.3%	Beta	Deenen et al, 2016[73]
DPYD poor metabolizer, alternative regimen	1.3%	—	Assumed to be similar to that of wild-type
DPYD poor metabolizer, standard dose	66.7%	Beta	Lee et al, 2016[13]; Froehlich et al, 2015[88]; Toffoli et al, 2015[9]; Lee et al, 2014[58]; Boisdron-Celle et al, 2007[67] (4 compound heterozygous and 2 homozygous carriers received a standard dose; all had severe toxicity; 4 were fatal)
Average Number of Severe Toxicities per Patient Who Had Severe Toxicity			
DPYD wild-type	1.5[b]	Normal[a]	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, reduced dose	1.4[b]	Normal[a]	Lunenburg et al, 2018[7]
DPYD intermediate metabolizer, standard dose	2.1[b]	Normal[a]	Lunenburg et al, 2018[7]
DPYD poor metabolizer, alternative regimen	1.5	—	Assumed to be similar to that of wild-type
DPYD poor metabolizer, standard dose	2.1	—	Assumed to be similar to that of intermediate metabolizers

[a]Assumed standard error to be 20% of mean.

[b]Derived by dividing the total number of adverse events reported (which were broken down by type of adverse event) by the number of patients who experienced an adverse event.

Utility Parameters

We considered patients' health-related quality of life over the course of their chemotherapy treatment. Utilities are numeric weights that represent a person's preference for a certain health state, such as being on chemotherapy for colorectal cancer. Utilities are often measured on a scale ranging from 0 (death) to 1 (perfect health). Disutilities represent the decrement in utility due to a particular symptom and are often expressed as negative values (e.g., −0.11 for a person experiencing an adverse event).

The utility and disutility parameters used in our model are presented in Table 12. We first estimated the baseline utility of patients with planned fluoropyrimidine treatment. Although each patient's quality of life may vary depending on their type of cancer, disease stage, and chemotherapy regimen, we calculated a weighted average value using utilities of the three most common cancers (colorectal, breast, and upper gastrointestinal) and used it as a proxy to represent the average baseline utility in this patient population. We obtained the utility of patients with metastatic colorectal cancer from Bennett et al.[89] This study analyzed data from the EQ-5D (a health-related quality-of-life instrument) collected from two phase III randomized controlled trials comparing different chemotherapy regimens. For patients who received a regimen containing 5-FU, leucovorin, and oxaliplatin, the baseline utility was 0.756. We obtained the utility of patients with metastatic breast cancer from Lloyd et al.[90] This study estimated the utility values of metastatic breast cancer plus six common toxicities using both the standard gamble method and the EQ-5D instrument. The utility of a breast cancer patient with stable disease and no toxicity was estimated to be 0.715. Last, we obtained the utility of gastric cancer from Curran et al.[91] In this study, the EQ-5D instrument was used to estimate the utility of patients with advanced gastric cancer who received two fluoropyrimidine-based chemotherapy regimens. For patients who received irinotecan, folinic acid, and 5-FU, the mean utility was 0.76. For patients who received cisplatin and 5-FU, the mean utility was 0.66. As a result, the weighted average utility of the three cancers was estimated to be 0.744.

Next, we obtained disutility values for fluoropyrimidine-related severe toxicities (e.g., gastrointestinal, hand-foot syndrome, and hematological) from Lloyd et al.[90] We applied the average disutility values to the proportion of patients expected to have severe toxicities.

For the reference case analysis, we assumed that the negative impact of severe toxicities on patients' quality of life (i.e., the disutility) would last about 4 weeks (Jason Yu, MD, email communication, June 21, 2020; Leta Forbes, MD, email communication, September 30, 2020). For sensitivity analysis, we assumed that disutility could last longer (up to 6 weeks). To account for the QALY loss from treatment-related death, we assumed that a fatal toxicity would occur after the first one to two cycles of chemotherapy.

Table 12: Utility Parameters

Parameter	Utility/Disutility Value	Distribution	Source
Baseline utility of patients with planned fluoropyrimidine treatment	0.744	Beta[a]	Calculated[b]
Colorectal cancer	0.756	—	Bennett et al, 2011[89]
Breast cancer	0.715	—	Lloyd et al, 2006[90]
Gastric cancer	0.710[c]	—	Curran et al, 2009[91]
Average disutility associated with a severe toxicity	−0.131	Beta[a]	Calculated
Gastrointestinal	−0.127[d]	—	Lloyd et al, 2006[90]
Hand-foot syndrome	−0.116	—	Lloyd et al, 2006[90]
Hematological	−0.150[e]	—	Lloyd et al, 2006[90]

[a]Assumed standard error to be 20% of mean.
[b]Weighted average of colorectal (55.6%), breast (30.5%), and gastric cancer (13.9%) utilities.
[c]Average utility of gastric cancer patients receiving irinotecan, folinic acid with 5-fluourouracil (0.76), and cisplatin with 5-fluourouracil (0.66).
[d]Average disutility of diarrhea and vomiting (−0.103) and stomatitis (−0.151).
[e]Disutility of febrile neutropenia.

Cost Parameters

We included direct medical costs related to:

- Physician visits
- *DYPD* genotyping tests
- Treatment of fluoropyrimidine-related toxicities
- Chemotherapy drugs

All costs are reported in 2020 Canadian dollars. When 2020 costs were not available, the health care component of the Canadian Consumer Price Index was used to adjust costs.[92]

PHYSICIAN VISIT

In the reference case analysis, we assumed that *DPYD* genotyping would not result in any additional physician visits. In a scenario analysis, we assumed that *DPYD* genotyping could lead to an additional visit with an oncologist before the start of chemotherapy (OHIP Schedule of Benefit A441, $70.90 for a complex medical specific re-assessment by a medical oncologist).[93]

DPYD *GENOTYPING*

We estimated the per-person cost of *DPYD* genotyping and considered costs related to:

- Sample collection
- Sample transportation
- Sample processing (to extract DNA) and testing (to generate *DPYD* genotype)
- Result interpretation and reporting

Detailed cost information is presented in Table 13. The cost of sample collection was obtained from the Schedule of Benefits for Laboratory Services in Ontario ($10.76 per sample).[94] The cost of sample shipping and handling ($52.50 per sample) was estimated from the literature.[95] For simplicity, we assumed that for a majority of the time, patient blood samples would be processed externally at a diagnostic laboratory. Shipping costs may vary from centre to centre. For example, a larger centre with more samples may have a lower cost per sample compared to a smaller centre with fewer samples. If *DPYD* genotyping is conducted on site (in a hospital laboratory, where there is also a cancer clinic), the shipping cost may be zero.

We estimated the cost of *DPYD* genotyping based on consultations with the two laboratories in Ontario that are currently conducting *DPYD* genotyping through research programs. Based on consultation with laboratory experts, the current cost in Ontario is about $100 per test (Theodore Wigle, MD, Lei Fu, PhD, Harriet Feilotter, PhD, personal communication, April to June 2020). This estimate included the cost of DNA extraction ($10), reagents and supplies for genotyping ($30; based on four samples per batch run using PCR), and laboratory personnel ($60). The cost of results interpretation and reporting is included in the labour and personnel costs. The patient's predicted genotype is usually automated based on the genotyping results, and the Clinical Pharmacogenetics Implementation Consortium guideline is used for treatment recommendations. We conducted sensitivity analyses using different costs, because we expected the test cost to vary depending on how testing is implemented in the province. According to laboratory experts, the cost per test may change depending on the annual volume of tests conducted and number of samples per run (Lei Fu, PhD, email communication, January 22, 2021; Table 14). If there is only one sample in each run, the cost can be as high as $250 per test. When more samples are batched in a single run, the cost per test decreases substantially (e.g., $26 per test with 89 samples per run).

We did not consider capital/fixed costs related to purchasing, installing, and maintaining the testing equipment (e.g., a Sanger sequencer or a real-time PCR machine). If the test is publicly funded, samples could be sent to a few sites where there is existing infrastructure, equipment, and specialized personnel (such as a hospital or community laboratory). We also did not include costs related to overhead, test validation, licensing, accreditation, and personnel training because those one-time or ongoing costs are usually included in the budgets of the laboratories providing those tests.

Table 13: Cost Parameters Related to Testing

Model Parameter	Mean Cost, $[a]	Distribution	Reference
Sample collection	10.76	Fixed	OHIP SOB for Laboratory Services (L700)[94]
Shipping and handling	56.11	Normal	Tsiplova et al, 2017[95]
DPYD genotyping test	100.00	Normal	Expert opinion[b] (based on 4 samples per batch run using PCR; $10 for DNA extraction, $30 for reagent/supplies, and $60 for labour/personnel)
Total	166.87		

Abbreviations: OHIP, Ontario Health Insurance Program; SOB, Schedule of Benefits.
[a]Costs in 2020 CAD.
[b]Clinical expert opinion (Lei Fu, PhD, email communication, January 22, 2021).

Table 14: Different Scenarios for *DPYD* Genotyping Test Cost

Model Parameter	*DPYD* Genotyping Cost Scenario						
Number of samples per run	1	2	4	10	17	41	89
Reagents + extraction[a]	$100	$65	$40	$22	$20	$17	$15
Labour cost per sample[b]	$150	$105	$60	$28	$20	$13	$11
Total cost per sample	$250	$170	$100	$50	$40	$30	$26

[a]Costs per sample in 2020 CAD.
[b]At $50 per hour.
Source: Clinical expert opinion (Lei Fu, PhD, email communication, January 22, 2021).

TREATMENT OF FLUOROPYRIMIDINE-RELATED TOXICITIES

We estimated the average costs of treating fluoropyrimidine-related toxicities (Table 15). For patients who were hospitalized due to severe toxicity, we estimated the hospitalization cost by multiplying the duration of hospitalization by the average hospital cost per day. We obtained the average hospital cost per day from a 2016 report published by the Canadian Institute for Health Informatics.[96]

Severe and non-severe toxicities that do not require hospitalization may require an extra follow-up visit, another blood draw, and/or a prescription for a common anti-diarrheal drug. Some patients may even need an emergency room or urgent care visit (Jason Yu, MD, email communication, June 21, 2020). To estimate these costs, we obtained the average non-hospitalization cost per event from a costing analysis conducted by Henricks et al[80] and converted it to Canadian dollars.

Table 15: Cost of Treatment-Related Toxicities

Model Parameter	Mean Cost, $	SE	Distribution	Reference
Hospital cost per day (for patients with severe toxicities requiring hospitalization)	1,232.10[a]	246.42	Gamma	CIHI 2016[96]
Non-hospitalization cost for non-severe toxicities (Grade 0–2)[c]	144.90[b]	28.98	Gamma	Henricks et al, 2019[80]
Non-hospitalization cost for severe toxicities that did not require hospitalization (grade ≥ 3)[c]	394.26[d]	78.85	Gamma	

Abbreviations: CIHI, Canadian Institute for Health Information; SE, standard error.

[a]Inflated from 2015 to 2020 CAD.

[b]Cost per event = €82, converted using purchasing power parity.[97]

[c]Grade score based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ratings system for level of toxicity.

[d]Cost per event = €234, converted using purchasing power parity.[97]

CHEMOTHERAPY COSTS

We estimated the costs of 5-FU, capecitabine, and alternative chemotherapy drugs for *DPYD* poor metabolizers. Similar to previous economic analyses,[79,80] we excluded costs that were unlikely to differ with *DPYD* genotyping. This included drug administration and clinical monitoring (e.g., costs of infusion clinics, consumables, nursing, and pharmacist time; Jason Yu, MD, email communication, June 21, 2020), as well as the costs of other drugs that may be used in combination with fluoropyrimidines in a chemotherapy regimen. We estimated chemotherapy drug costs per cycle using dosing information from the literature and unit prices from the Ontario Drug Benefit Formulary[98] or other published sources[99] (Table 16). We then calculated the weighted average cost of chemotherapy drugs using the estimated percentages of patients receiving 5-FU, capecitabine, and both in the target population (see Table 9, above). We then multiplied the per-cycle cost by the average number of cycles and the mean dose intensity.

We estimated the average per-cycle cost of 5-FU at the standard dose to be $15.11 per cycle. 5-FU is prescribed using a variety of dosing and administration schedules.[87] Using Ontario Health (Cancer Care Ontario)'s dosing recommendations for 5-FU as an intravenous bolus or intravenous infusion,[87] we identified the dosing schedules that resulted in the highest dose per cycle (i.e., 200 mg/m^2 on days 1–21, or 4,200 mg/m^2 per cycle) and the lowest dose per cycle (i.e., 500–600 mg/m^2 days 1 and 8, or 1,100 mg/m^2 per cycle).

We estimated the average cost of capecitabine at the standard dose to be $187.95 per cycle. We included an 8% markup because capecitabine is an oral drug.[100] We calculated the average dose based on an average body surface area of 1.9 m^2. Dosing information was from Ontario Health (Cancer Care Ontario)[101] and the *DPYD* genotyping study by Lunenburg et al.[7] For example, patients with advanced colorectal cancer usually receive a dose of 1,250 mg/m^2 twice daily for 14 days, followed by a 7-day rest period. Patients with rectal cancer usually receive a dose of 825 mg/m^2 twice daily.

We assumed that an alternative, fluoropyrimidine-free, chemotherapy would be given to patients who are poor metabolizers. This alternative chemotherapy may differ depending on cancer type and disease stage. For instance, raltitrexed may be used as an alternative for the treatment of colorectal cancer. For

metastatic breast cancer, a different type of cytotoxic drug such as vinorelbine or gemcitabine may be used. In the adjuvant setting, if breast cancer patients were intolerant of fluoropyrimidines, it is likely that no other drugs would be given (Jason Yu, MD, email communication, June 21, 2020; Leta Forbes, MD, email communication, September 30, 2020). To estimate drug costs in the reference case analysis, we used raltitrexed for the typical cost, because colorectal cancer is the most common cancer in this patient population. We estimated the average cost of raltitrexed to be $925.17 per cycle based on dosing guidelines from Ontario Health (Cancer Care Ontario), which indicate that adult patients should receive 3 mg/m^2 of raltitrexed in a 15-minute infusion.[102] We obtained the cost of raltitrexed from the Alberta Blue Cross drug price list[103] because there is limited information on the cost of raltitrexed in Ontario.

Table 16: Drug Acquisition Costs per 21-Day Cycle, Standard Dosing

	Dosing		Drug Costs			
Drug	Starting Dose	Dose per Day or Cycle[a]	Cost per mg	Cost per Day	Cost per Cycle	Reference
Capecitabine	Low: 825 mg/m^2 2× daily for 14 d	3,135 mg/d	$1.5250 per pill (500 mg); $0.4575 per pill (150 mg)	$10.38[b]	$145.32[b]	Henricks et al, 2018[81]; OH (CCO); ODB Formulary[98]
	High: 1,250 mg/m^2 2× daily for 14 d	4,750 mg/d		$16.47[b]	$230.58[b]	
					Average: $187.95[b]	
5-FU	Low: IV bolus, 500–600 mg/m^2 on days 1 and 8	2,090 mg/cycle	$0.003 per mg	—	$6.27	Henricks et al, 2018[81]; OH (CCO); pCODR[99]
	High: IV infusion, 200 mg/m^2 on days 1–21	7,980 mg/cycle		—	$23.94	
					Average: $15.11	
Raltitrexed	3 mg/m^2 on day 1	5.7 mg/cycle	$324.62 per 2 mg	—	$925.17	Alberta Blue Cross[103]; OH (CCO)[102,104]

Abbreviations: 5-FU, f-fluorouracil; CADTH, Canadian Agency for Drugs and Technologies in Health; ODB, Ontario Drug Benefit program; OH (CCO), Ontario Health (Cancer Care Ontario); pCODR, pan-Canadian Oncology Drug Review.

[a]Calculated assuming a mean body surface area of 1.9 m^2 (Lunenburg et al 2018[7]).

[b]An 8% markup was included for oral drugs (CADTH costing guidance document).

In the reference case analysis, we assumed that patients would undergo an average of five treatment cycles (Table 17).[80] We also obtained the mean dose intensity from Lunenburg et al.[7] Dose intensity is the amount of chemotherapy drugs received by the patient divided by the initial scheduled amount of chemotherapy.

Table 17: Additional Chemotherapy Cost Parameters

Model Parameter	Mean	Reference
Mean number of cycles	5	Henricks et al, 2019[80]
Mean dose Intensity[a]		
DPYD wild-type	97%	Lunenburg et al, 2018[7]
DPYD carrier receiving standard dose	91%	Lunenburg et al, 2018[7]
DPYD carrier receiving reduced dose	61%	Lunenburg et al, 2018[7]

[a]Dose intensity is the amount of chemotherapy drugs received by the patient divided by the initial scheduled amount of chemotherapy.

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis and Uncertainty

We conducted a reference case analysis and scenario analyses. Our reference case analysis adhered to CADTH guidelines[105] when appropriate and represents the analysis with the most likely set of input parameters and model assumptions. Our scenario analyses explored how the results are affected by varying input parameters and model assumptions.

For the reference case, we conducted a probabilistic analysis to capture parameter uncertainty. When possible, we specified distributions around input parameters using the mean and standard error. Selected cost parameters were characterized by lognormal or normal distributions, and probabilities were characterized by beta distributions. We ran a total of 5,000 simulations and calculated the expected values of costs and outcomes for each strategy. We presented the probability of each strategy being cost-effective over a range of willingness-to-pay values plotted on a cost-effectiveness acceptability curve. We also examined additional structural and parameter uncertainty by conducting several scenario analyses. These analyses are summarized in Table 18.

Table 18: Parameters for the Reference Case and Sensitivity Analyses

Parameter	Reference Case	Sensitivity Analysis
Prevalence of *DPYD* intermediate metabolizers	Pooled prevalence from the clinical evidence review (based on 4 variants): 6.60%	Lower estimate: 5.6% Upper estimate: 7.7%
Prevalence of *DPYD* poor metabolizers	Pooled prevalence from the clinical evidence review (based on 4 variants): 0.19%	Lower estimate: 0% Upper estimate: 0.6%
Source of effectiveness and resource use estimate	Lunenburg et al, 2018[7]	Henricks et al, 2018[72] (see details in Table A21)
Probability of treatment-related hospitalization	Poor metabolizers receiving standard dose: 66.7%	Poor metabolizers receiving standard dose: 100%
Days of hospitalization	Poor metabolizers receiving standard dose: 28.75 days	23 days 34.5 days
Impact of severe toxicities on quality of life	Assumed disutility would last for 4 weeks (28 days)	Assumed disutility would last for up to 6 weeks (42 days)
Alternative chemotherapy for poor metabolizers	Raltitrexed	No alternative drugs given
Cost of physician visit	Assumed no extra visit	Assumed 1 extra visit
Cost of *DPYD* genotyping (sample processing, sample testing, result interpretation, and reporting)	$100 per test	$50 and $150 per test

Results

Reference Case Analysis

Results of the reference case analysis are presented in Table 19. The average total cost was $1,920.82 (95% CrI: $1,308.71 to $2,743.56) for the *DPYD* genotyping strategy and $2,065.70 (95% CrI: $1,340.67 to $3,060.75) for usual care, resulting in a cost difference of −$144.88 (95% CrI: −$543.10 to $101.91) per patient.

The additional cost from *DPYD* genotyping ($169.11) was offset by cost reduction in the treatment of fluoropyrimidine-related toxicities (−$315.77). The average proportion of patients with severe toxicities was 14.20% (95% CrI: 11.76% to 16.92%) in the *DPYD* genotyping group and 14.42% (95% CrI: 12.06% to 16.94%) in the usual care group. The average QALYs associated with the *DPYD* genotyping strategy and the usual care strategy were 0.3674 (95% CrI: 0.1987–0.4781) and 0.3663 (95% CrI: 0.1978–0.4768), resulting in a small QALY gain of 0.0011 (95% CrI: 0.0003–0.0023) over a half-year time horizon. Because *DPYD* genotyping is slightly more effective and less costly than usual care, it is considered a dominant strategy.

Table 19: Reference Case Analysis Results

Parameter	*DPYD* Genotyping, Mean (95% CrI)	Usual Care (No Testing), Mean (95% CrI)	Difference, Mean (95% CrI)
Average total costs	$1,920.82 ($1,308.71 to $2,743.56)	$2,065.70 ($1,340.67 to $3,060.75)	−$144.88 (−$543.10 to $101.91)
Cost of *DPYD* genotyping test	$169.11	$0.00	$169.11
Cost of toxicities	$1,396.85	$1,712.62	−$315.77
Cost of chemotherapy drugs	$354.86	$353.08	$1.78
Average proportion of patients with severe toxicities	14.20% (11.76% to 16.92%)	14.42% (12.06% to 16.94%)	−0.22% (−1.63% to 1.37%)
Average number of severe toxicities	0.21 (0.13 to 0.30)	0.23 (0.15 to 0.32)	−0.02 (−0.05 to 0.02)
Average QALYs	0.3674 (0.1987 to 0.4781)	0.3663 (0.1978 to 0.4768)	0.0011 (0.0003 to 0.0023)
ICER ($/QALY)			Dominant

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Figure 21 presents the cost-effectiveness acceptability curve, which shows the probability of each strategy being cost-effective across a range of willingness-to-pay values. At the commonly used willingness-to-pay values of $50,000 and $100,000 per QALY, *DPYD* genotyping is highly likely to be cost-effective (91% and 96% probability, respectively).

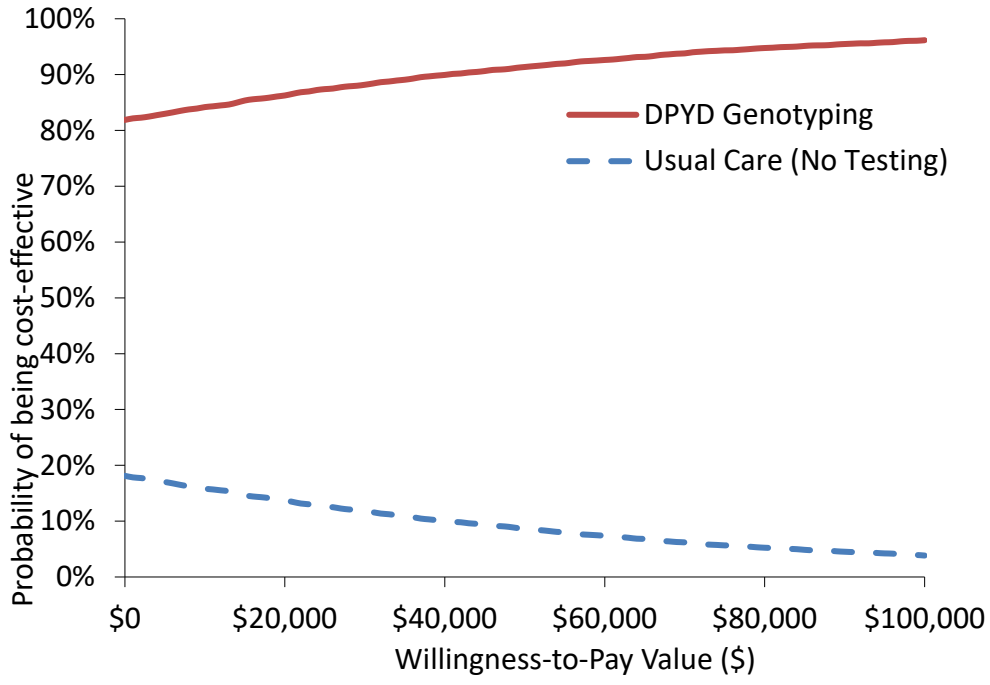

Figure 21: Cost-Effectiveness Acceptability Curve

Scenario Analyses

Results of the scenario analyses are shown in Table 20. *DPYD* genotyping remained cost-saving and slightly more effective (better QALYs) in all scenarios. When we assumed a lower prevalence of intermediate metabolizers (scenario 1a) or poor metabolizers (scenario 2a) in the target population, the cost savings and QALY gained from *DPYD* genotyping became smaller. If a higher prevalence was assumed, the cost savings and QALY gained from *DPYD* genotyping increased (scenarios 1b and 2b). When we used effectiveness and resource use data from an alternative clinical study (scenario 3), the cost savings decreased slightly because there was a smaller difference in hospital length of stay between *DPYD* carriers who received a standard dose and *DPYD* carriers who received a reduced dose. When the probability of hospitalization in poor metabolizers treated with a standard dose was increased to 100% (versus 66.7% in the reference case), the *DPYD* genotyping resulted in larger cost savings (scenario 4). When we assumed a shorter (23 days) hospital length of stay in poor metabolizers treated with a standard dose (versus 29 days in the reference case), the cost savings became smaller (scenario 5a). When disutility due to severe toxicity was assumed to last longer (8 vs. 4 weeks), the QALY gained became slightly larger (0.0012; scenario 6). In the *DPYD* genotyping strategy, if no alternative drug was given to poor metabolizers (remove fluoropyrimidines from the chemotherapy regimen without replacement with another drug), the cost savings increased only slightly (scenario 7). If *DPYD* genotyping required an extra physician visit (e.g., to discuss the test result with the patient), the cost savings decreased by half to $75.89 per patient (scenario 8). Similarly, if *DPYD* genotyping test was more expensive ($150 instead of $100 per test), the cost savings decreased to $97.10 per patient (scenario 9b).

Table 20: Scenario Analysis Results

Scenario	Total Cost			Proportion of Patients With Severe Toxicity			Total QALYs		
	DPYD Genotyping	Usual Care	Difference	*DPYD* Genotyping	Usual Care	Difference	*DPYD* Genotyping	Usual Care	Difference
Reference case	$1,920.82	$2,065.70	−$144.88	14.20%	14.42%	−0.22%	0.3674	0.3663	0.0011
1a: Prevalence of intermediate metabolizers, 5.6%	$1,937.26	$2,041.28	−$104.06	14.13%	14.34%	−0.21%	0.3743	0.3733	0.0010
1b: Prevalence of intermediate metabolizers, 7.7%	$1,901.37	$2,079.76	−$177.82	14.29%	14.52%	−0.23%	0.3728	0.3715	0.0012
2a: Prevalence of poor metabolizers, 0%	$1,923.02	$2,032.54	−$109.52	14.18%	14.23%	−0.04%	0.3677	0.3671	0.0007
2b: Prevalence of poor metabolizers, 0.6%	$1,941.42	$2,164.32	−$222.90	14.22%	14.79%	−0.57%	0.3694	0.3675	0.0020
3: Effectiveness and resource use based on Henricks et al, 2018[72]	$2,102.14	$2,172.23	−$70.08	23.75%	24.64%	−0.90%	0.3698	0.3680	0.0018
4: Probability of hospitalization in poor metabolizers, standard dose, 100%	$1,923.94	$2,093.98	−$170.04	14.22%	14.44%	−0.22%	0.3694	0.3683	0.0011
5a: Days of hospitalization in poor metabolizers, standard dose, 23 days	$1,923.94	$2,062.82	−$138.88	14.22%	14.44%	−0.22%	0.3694	0.3683	0.0011
5b: Days of hospitalization in poor metabolizers, standard dose, 34.5 days	$1,923.94	$2,080.77	−$156.83	14.22%	14.44%	−0.22%	0.3694	0.3683	0.0011
6: Assumed disutility would last for 8 weeks	$1,923.94	$2,071.79	−$147.85	14.22%	14.44%	−0.22%	0.3673	0.3661	0.0012
7: Assumed no alternative chemotherapy for poor metabolizers	$1,915.16	$2,071.79	−$156.63	14.22%	14.44%	−0.22%	0.3694	0.3683	0.0011
8: Assumed 1 extra physician visit	$1,995.90	$2,071.79	−$75.89	14.22%	14.44%	−0.22%	0.3694	0.3683	0.0011
9a: Cost of *DPYD* genotyping, $50 per test	$1,873.19	$2,071.79	−$198.60	14.22%	14.44%	−0.22%	0.3694	0.3683	0.0011
9b: Cost of *DPYD* genotyping, $150 per test	$1,974.69	$2,071.79	−$97.10	14.22%	14.44%	−0.22%	0.3694	0.3683	0.0011

Abbreviation: QALY, quality-adjusted life year.

Discussion

The results showed that pre-treatment *DPYD* genotyping could reduce severe fluoropyrimidine-related toxicity and save on cost, with some uncertainty. Overall, our results were consistent with findings in the literature. The two Dutch cost-minimization studies identified from the literature review (Deenen et al[79] and Henricks et al[80]) also found that *DPYD* genotyping yielded a small cost saving (approximately €45 to €51 EUR per patient). We found a smaller reduction in the proportion of patients experiencing severe toxicity (−0.22%, compared to the −0.54% found by Deenen et al[79] when only *DPYD**2A was genotyped, and with the −0.88% found by Henricks et al[80] when four variants were genotyped). This is because we used clinical data from a different observational study (Lunenburg et al[7]), which found a smaller reduction in the frequency of severe toxicity, but a shorter hospital length of stay in *DPYD* variant carriers receiving reduced dose.

COST OF DPYD GENOTYPE TESTING

The scenario analyses showed that results were sensitive to the cost of *DPYD* genotype testing. The cost of *DPYD* genotype testing may vary with many factors, such as the annual volume of tests conducted and number of samples per run (Table 21). In the reference case analysis, we used $100 per test based on expert opinion from two Ontario laboratories currently conducting the test under research programs. If *DPYD* genotyping is implemented at a larger scale in the province, the cost per test may go down further, although investment may be required to expand capacity. It is important to note that if a laboratory provides *DPYD* genotyping service to only one cancer center, the test volume may not be high enough to allow samples to be batched and the cost per test would be higher. In Quebec, *DPYD**2A was added to the provincial formulary in 2017. The variants *DPYD**13, c.2864A>T, and c.1236G>A were added in 2019 for patients who have planned cancer treatment with fluoropyrimidines. The experience with the first variant introduced has been published. According to the publication, the cost of genotyping for one variant, *DPYD**2A, is about $18.30 per test in Quebec (real-time PCR, tests run twice weekly at one laboratory). A centralized testing model was adopted, and the tests were run twice per week at one laboratory. This increase in throughput dramatically reduced the cost per sample while maintaining rapid turnaround time (about 6 days). Between March 2017 and August 2018, a total of 2,617 *DPYD**2A genotyping assays were performed, of which a majority (81%) were referred from 72 different hospitals in the province.[75]

The cost of *DPYD* genotyping in other countries varied widely in the literature, from about €6.40[82] to €177[83] EUR per test. Cortejoso et al[82] calculated a range of costs for *DPYD* genotyping in Spain based on the number of samples per run and the number of samples analyzed per year (not limited to *DPYD* testing) in the equipment used. The cost included reagents, equipment, and personnel (both clinical and laboratory). It was estimated that the per-patient cost of the *DPYD* genotype test could range from €43.1 to €3.5 EUR (1 sample per run, 100 samples per year to 20 samples per run, 2000 samples per year, respectively). In other studies, the reported costs of the *DPYD* genotype testing were higher (€75,[73] €100,[79] €177,[83] and €120[85] EUR). These costs were obtained through internal hospital data.

Because this is an active area of research, more *DPYD* variants could be added in the future, which might change the cost of testing, as well as the sensitivity and specificity of the test. The cost-effectiveness result may change accordingly. However, according to clinical experts, only minimal additional cost is expected if more variants are added. We expect the test to be more cost-effective if more people with increased risk of severe toxicity are identified as additional variants are added.

COST OF SEVERE TOXICITY

The cost of managing severe toxicity also varied in the literature, from about €75[84] (nausea and vomiting) to €46,412[83] (hospitalization related to gastrointestinal and hematologic toxicity) per event. Toffoli et al[84] reported the average cost of managing fluoropyrimidine-related toxicity to be about €930 per patient. For more severe toxicity, the highest cost was estimated to be about €6,102 per episode (e.g., hospitalization for febrile neutropenia). Fragoulakis et al[85] estimated the average cost of severe toxicity to be €1,150 in wild-type patients and €3,712 in carriers of any *DPYD* variant. Cortejoso et al[82] estimated the mean cost of treating grade ≥ 3 fluoropyrimidine-induced neutropenia to be €3044.18 (range €17.45 to €14,103.25).[82]

COST OF CHEMOTHERAPY DRUGS

The results were not sensitive to the cost of chemotherapy drugs. Fluoropyrimidines are considered to be inexpensive, so the change in drug cost due to fluoropyrimidine dose reduction (*DPYD* intermediate metabolizers) would be very small. *DPYD* poor metabolizers may receive alternative chemotherapy and the new regimen could be more expensive than fluoropyrimidines, but the change in cost to the system would be small because the proportion of poor metabolizers is very small.

MODEL STRUCTURE

Similar to previous economic studies, we used a decision-tree model to estimate the impact of *DPYD* genotyping on costs and outcomes. The effect of *DPYD* genotyping was modelled using observed rates of toxicity in populations before and after genotyping from Lunenburg et al[7] (which reflects clinical utility). An alternative modelling approach is to estimate the proportions of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) results using sensitivity and specificity of the test (clinical validity), and then predict the rate of toxicity post-genotyping based on different types of test results. However, additional assumptions may be required to estimate the impact of different test results on health outcomes (Table 21). How the test impacts clinical results may depend on many factors, such as clinical implementation. Data on hospitalization and resource use are also only available by wild-type versus *DPYD* variant carriers, and not by each test result category. Based on these considerations, we did not use sensitivity and specificity explicitly in the current model, although these test characteristics were inherently incorporated (i.e., the rate of severe toxicity in the overall population before receiving genotype-guided treatment adjustment is the sum of the proportions of patients with TP and FN results).

Table 21: Possible *DPYD* Genotyping Test Results and Potential Consequences

Results	Usual Care Strategy: All Patients Receive Standard Dose	Pre-Treatment *DPYD* Genotyping Strategy: Patients Receive Dose Adjustment Based on Genotype Results
TP results (1.60%)[a]	By definition,[b] all patients experienced severe toxicity	Patients receive dose reduction so toxicity may be reduced (assumption required to estimate how much toxicity can be reduced)
FP results (5.19%)[a]	By definition,[b] all patients did not experience severe toxicity	Patients receive dose reduction unnecessarily. Because clinical guidelines recommended dose titration to avoid underdosing, assume no change in treatment efficacy. These patients do not experience additional severe toxicity (no change in toxicity)
FN results (12.69%)[a]	By definition,[b] all patients experienced severe toxicity	Patients receive standard dose as with usual care, so all patients would experience severe toxicity (no change in toxicity)
TN results (80.52%)[a]	By definition,[b] all patients did not experience severe toxicity	Patients receive standard dose as with usual care (no change in toxicity)

Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive.

[a]The proportions of different test results are calculated using sensitivity/specificity derived from the Lunenburg study[7] (sensitivity: 7.1% [8/113], specificity: 96.2% [666/692]).

[b]The occurrence of severe toxicity was used as the reference standard to calculate sensitivity and specificity (i.e., using the *DPYD* genotyping test to predict severe toxicity in patients treated with a standard dose fluoropyrimidines). Sensitivity was defined as the proportion of patients identified as *DPYD* carriers among those who experienced severe toxicity. Specificity was defined as the proportion of wild-type patients among those who did not experience severe toxicity.

Strengths and Limitations

Our analysis has several strengths. First, we considered the impact of *DPYD* genotyping on both cost and effectiveness (i.e., the proportion of patients experiencing severe toxicity and QALYs). By using QALYs as an outcome, we were able to capture the impact of *DPYD* genotyping on both survival (due to avoidance of fatal toxicity) and patients' quality of life. Second, instead of estimating clinical and resource use parameters of *DPYD* variant carriers receiving standard dose based on historical controls, we selected Lunenburg et al[7] to inform the analysis because it included all three groups of patients in the same study (i.e., wild-type patients receiving standard dose, *DPYD* carriers receiving reduced dose, and *DPYD* carriers receiving standard dose). We considered that study to have less bias. Its results aligned well with the overall findings of the clinical evidence review. Finally, we included *DPYD* poor metabolizers in the analysis since *DPYD* genotyping is expected to be of greater importance for these patients than for intermediate metabolizers (i.e., heterozygous *DPYD* variant carriers).

There were some limitations to our analysis. Due to the lack of randomized clinical trial evidence, we relied on observational studies to estimate the impact of *DPYD* genotyping indirectly. The reference case analysis was based on a large observational study that compared the risks of severe toxicity in three groups of patients: wild-type patients receiving standard dose, *DPYD* carriers receiving standard dose, and *DPYD* carriers receiving reduced dose (Lunenburg et al[7]). All other clinical studies included only two groups. Clinical validity studies compared *DPYD* carriers receiving standard dose with wild-type patients, while clinical utility studies compared *DPYD* carriers receiving reduced dose with wild-type patients. Although Lunenburg et al[7] was the only study that included all three groups of patients without using historical controls, it had several important limitations. First, although the authors included a large number of patients overall (n = 828), the sample sizes of *DPYD* carriers were very small (34 patients

received a standard dose and 22 received a reduced dose), so it is difficult to draw firm conclusions from this comparison. Second, the distribution of different *DPYD* genotypes was not homogeneous across the two *DPYD* comparison groups. This might have affected the frequency of severe toxicity observed in the study. There was an overrepresentation of the variants that were expected to have the weakest effect on DPD in the *DPYD* carriers who received a standard dose (c.1236G>A and c.2846A>T). The authors speculated that more toxicity may have occurred in this group if *DPYD* variants were more equally distributed. Third, the study included patients from three different databases (some prospective and some retrospective), which could have led to biases. Finally, all patients included in the study received radiation therapy in addition to fluoropyrimidine-based regimens. According to the study authors, patients receiving radiation therapy usually receive lower fluoropyrimidine doses.

Furthermore, although it is a strength that we considered *DPYD* poor metabolizers in the analysis through modelling, there are very limited clinical data on these patients. We relied primarily on expert opinion to estimate the costs and outcomes associated with these patients. We assumed that if given standard-dose fluoropyrimidines, *DPYD* poor metabolizers would be more likely to have severe toxicities and hospitalizations, and even death. However, more research is needed to confirm those assumptions.

Finally, we did not model any potential long-term impacts of the test on cancer outcomes (e.g., differences in treatment efficacy associated with receiving reduced dose fluoropyrimidines or alternative treatment).

Conclusions

DPYD genotyping may be slightly more effective and less costly compared to usual care (no testing) because fewer patients would have severe fluoropyrimidine-related toxicity. At the commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained, *DPYD* genotyping is likely cost-effective compared to usual care (91% and 96% probability, respectively).

Budget Impact Analysis

Research Question

From the perspective of the Ontario Ministry of Health, what is the 5-year budget impact of publicly funding pre-treatment *DPYD* genotyping in patients who have planned cancer treatment with fluoropyrimidines in Ontario?

Methods

Analytic Framework

We estimated the budget impact of publicly funding pre-treatment *DPYD* genotyping using the cost difference between two scenarios: (1) current clinical practice without public funding for *DPYD* genotyping (the current scenario) and (2) anticipated clinical practice with public funding for *DPYD* genotyping (the new scenario). Figure 22 presents the budget impact model schematic.

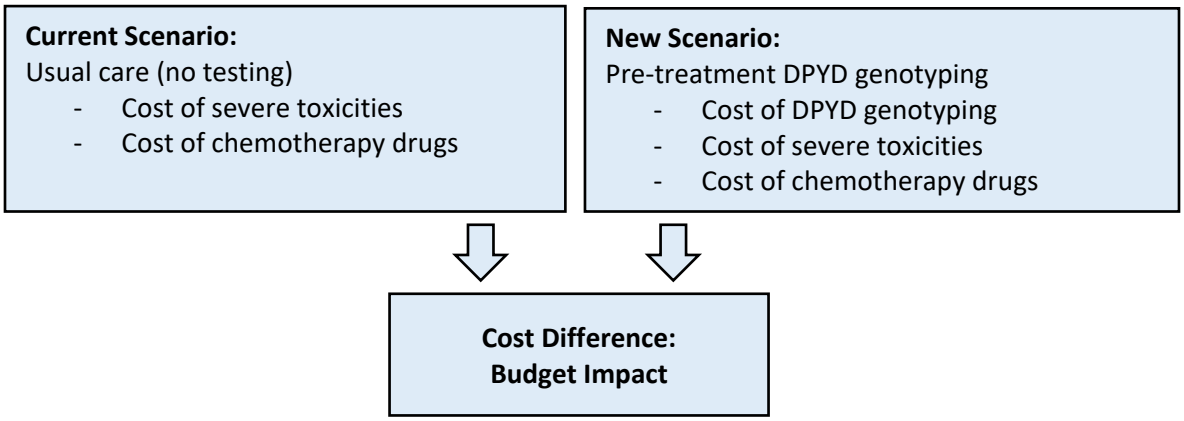

Figure 22: Schematic Model of Budget Impact

Key Assumptions

The following assumptions were made for the reference case analysis:

- In the current scenario, we assumed that *DPYD* genotyping is not publicly funded
- In the new scenario, we assumed there would be a slow uptake of pre-treatment *DPYD* genotyping in the next 5 years

Target Population

Our target population is patients who have planned cancer treatment with fluoropyrimidines (i.e., 5-fluorouracil [5-FU] and/or capecitabine). Both children and adults are included in the analysis, although the proportion of patients aged less than 18 years is very small (only 0.03%; Ontario Health Cancer Care Ontario; Ontario Cancer Registry, Cancer Activity Level Reporting and Ontario Drug Benefit datasets; prepared March 2020).

We obtained the number of patients administered fluoropyrimidines using data prepared by Ontario Health (Cancer Care Ontario) in March 2020. The data were obtained using the Ontario Cancer Registry to identify Ontario residents with a cancer diagnosis between April 1, 2009, and March 31, 2019. Then, using the Ontario Drug Benefit program and Cancer Activity Level Reporting, we identified the number of patients that were administered a fluoropyrimidine (i.e., 5-FU and/or capecitabine) between 2014/15 and 2018/19 (Table 22).

Table 22: Number of Patients Who Received Fluoropyrimidines From 2014/15 to 2018/19 in Ontario

	Fiscal Year				
Population	**2014/15**	**2015/16**	**2016/17**	**2017/18**	**2018/19**
Number of patients administered fluoropyrimidines	8,099	7,429	7,398	7,533	7,766

Source: Data provided by Ontario Health (Cancer Care Ontario) in March 2020 using Ontario Cancer Registry, Cancer Activity Level Reporting and Ontario Drug Benefit datasets.

We estimated the target population for our budget impact analysis by extrapolating the data in Table 22 over the next 5 years. We used linear extrapolation and excluded the 2014/15 fiscal year, because it was likely higher than the following years because of changes made in 2014 to the Cancer Activity Level Reporting dataset (Ontario Health [Cancer Care Ontario], email communication, March 23, 2020). We assumed that all patients who had planned fluoropyrimidine treatment would be eligible for *DPYD* genotyping. We estimated that a total of 40,809 patients would be eligible for *DPYD* genotyping over the next 5 years (Table 23).

Table 23: Number of Patients Projected to Receive Fluoropyrimidines From Year 1 to Year 5 in Ontario

	Year of Analysis					
Population	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Number of patients who have planned cancer treatment with fluoropyrimidines	7,933	8,047	8,162	8,276	8,391	40,809

Current Intervention Mix

Currently in Ontario, *DPYD* genotyping is used only in a research setting. Therefore, in our current scenario, we assumed that *DPYD* genotyping was not publicly funded and all patients were receiving usual care. Under usual care practices, all individuals receive standard-dose fluoropyrimidines without *DPYD* genotype testing.

Uptake of the New Intervention

The uptake of a new intervention such as *DPYD* genotyping could be limited by factors such as knowledge transfer, patterns of practice, and administrative barriers (Jason Yu, MD, email communication, June 21, 2020; Geoffrey Liu, MD, telephone communication, June 24, 2020). Based on the literature, international acceptance and implementation of *DPYD* genotyping as routine procedure for all patients with planned fluoropyrimidine treatment have been challenging. Therefore, we assumed the annual uptake rates for the reference case analysis to be 7%, 8%, 10%, 15%, and 20% in the next 5 years. We also explored the impact of higher uptake rates in sensitivity analyses (Table 24).

Table 24: Uptake Rates of *DPYD* Genotyping in the Next 5 Years

Uptake	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake rates for reference case	7%	8%	10%	15%	20%
Volume (N)	555	644	816	1,241	1,678
Intermediate uptake scenario	10%	20%	30%	40%	50%
Rapid uptake scenario	20%	40%	60%	80%	100%

Source: Estimated based on clinical expert opinion and extrapolation from current volume trends.

Resources and Costs

The cost per person was derived from the primary economic evaluation. The costs included are:

- *DYPD* genotyping (sample processing, testing, results interpretation, and reporting)
- Treatment of toxicity (hospitalization and non-hospitalization costs)
- Chemotherapy drugs
- Physician visits

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. In sensitivity analyses, we explored how the results are affected by varying input parameters and model assumptions.

Sensitivity analyses were conducted by varying:

- Prevalence of *DYPD* intermediate and poor metabolizers
- Uptake rate of *DYPD* genotyping test in years 1 to 5
- Cost of *DYPD* genotyping

Results

Reference Case

The reference case results are presented in Table 25. In the current scenario, the cost of usual care is about $16 million to $17 million per year. In the new scenario, the cost of usual care would decrease each year as the uptake of *DPYD* genotyping increased. The total health care cost for the *DPYD* genotyping group would range from $1.067 million in year 1 to $3.223 million in year 5. The annual budget impact was estimated to be a savings of $80,453 in year 1, increasing to a savings of $243,137 in year 5, for a total savings of $714,963 over 5 years. The cost of providing *DPYD* genotype testing alone was estimated to be $93,907 in year 1, increasing to $283,797 in year 5, for a total cost of $834,527 over 5 years.

Table 25: Budget Impact Analysis Results

	Budget Impact, $					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current Scenario						
Usual care	$16,387,218	$16,622,708	$16,860,264	$17,095,754	$17,333,310	$84,299,255
New Scenario						
Usual care	$15,240,113	$15,292,892	$15,174,238	$14,531,391	$13,866,648	$74,105,281
DPYD genotyping	$1,066,652	$1,236,549	$1,567,775	$2,384,509	$3,223,525	$9,479,010
Budget impact	−$80,453	−$93,268	−$118,251	−$179,854	−$243,137	−$714,963
Cost of *DPYD* genotype testing	$93,907	$108,865	$138,026	$209,931	$283,797	$834,527

Sensitivity Analysis

The sensitivity analysis results are presented in Table 26. When we assumed a lower prevalence of intermediate metabolizers (scenario 1a) or poor metabolizers (scenario 2a) in the target population, the cost savings from *DPYD* genotyping became smaller. If we assumed a higher prevalence, the cost savings from *DPYD* genotyping increased. If *DPYD* genotyping required an extra physician visit (e.g., to discuss test results with patients), the cost savings decreased by half. Similarly, if *DPYD* genotype testing were assumed to be more expensive ($150 instead of $100 per test), the cost savings also decreased. If the uptake rates were higher, the cost savings would increase.

Table 26: Budget Impact Sensitivity Analysis Results

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5	Total
1a: Prevalence of Intermediate Metabolizers, 5.6%						
Budget impact	−$57,763	−$66,964	−$84,901	−$129,130	−$174,566	−$513,325
Cost of test	$93,907	$108,865	$138,026	$209,931	$283,797	$834,527
1b: Prevalence of Intermediate Metabolizers, 7.7%						
Budget impact	−$99,062	−$114,840	−$145,602	−$221,453	−$299,374	−$880,331
Cost of test	$93,907	$108,865	$138,026	$209,931	$283,797	$834,527
2a: Prevalence of Poor Metabolizers, 0%						
Budget impact	−$60,818	−$70,505	−$89,390	−$135,958	−$183,796	−$540,467
Cost of test	$93,907	$108,865	$138,026	$209,931	$283,797	$834,527
2b: Prevalence of Poor Metabolizers, 0.6%						
Budget impact	−$123,779	−$143,494	−$181,931	−$276,708	−$374,071	−$1,099,983
Cost of test	$93,907	$108,865	$138,026	$209,931	$283,797	$834,527
3: Assume One Extra Physician Visit						
Budget impact	−$42,142	−$48,855	−$61,941	−$94,210	−$127,359	−$374,507
Cost of test	$93,907	$108,865	$138,026	$209,931	$283,797	$834,527
4a: Cost of *DPYD* Genotype Testing, $50 Per Test						
Budget impact	−$110,285	−$127,851	−$162,097	−$246,542	−$333,291	−$980,065
Cost of test	$66,142	$76,677	$97,216	$147,861	$199,887	$587,783
4b: Cost of *DPYD* Genotype Testing, $150 Per Test						
Budget impact	−$53,921	−$62,509	−$79,253	−$120,540	−$162,953	−$479,176
Cost of test	$121,673	$141,053	$178,836	$272,001	$367,707	$1,081,270
5a: Intermediate Uptake						
Budget impact	−$114,933	−$233,170	−$354,753	−$479,611	−$607,844	−$1,790,311
Cost of test	$134,154	$272,163	$414,078	$559,816	$709,493	$2,089,704
5b: Rapid Uptake						
Budget impact	−$229,867	−$466,340	−$709,506	−$959,222	−$1,215,688	−$3,580,622
Cost of test	$268,307	$544,325	$828,157	$1,119,631	$1,418,987	$4,179,407

Discussion

The budget impact analysis showed that publicly funding pre-treatment *DPYD* genotyping in patients with planned fluoropyrimidine treatment may be cost-saving (a total savings of $714,963 over the next 5 years). We estimated the cost of providing the *DPYD* genotyping test itself to be about $834,527 over the next 5 years. According to laboratory experts, the per-test cost may depend on how testing is implemented. A centralized testing model would increase the throughput, which would reduce the cost per sample dramatically while maintaining the rapid turnaround time (< 1 week). Centralized

testing would also reduce the number of trained personnel required and the need for validation at distributed sites.

Strengths and Limitations

Our analysis had several strengths. We estimated the size of the target population using real-world Ontario data from the Ontario Cancer Registry. We considered not only the cost of the *DPYD* genotyping test but also potential cost offsets related to fewer cases of severe toxicity. We also estimated the budget impact of several different scenarios by varying the prevalence, testing cost, and uptake rates. A limitation is that we did not estimate the costs related to implementation, service delivery, and program coordination, because these could vary substantially depending on how testing is implemented.

Conclusions

We estimated that publicly funding pre-treatment *DPYD* genotype testing may be cost-saving (a total of $714,963 saved over the next 5 years, provided that the implementation, service delivery, and program coordination costs do not exceed our estimated amounts). The cost of testing would be about $834,527 over the next 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience with fluoropyrimidine treatment, as well as the preferences and perceptions of those who have sought *DPYD* testing.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[106-108] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people who have been treated with fluoropyrimidines and who sought *DPYD* testing for treatment purposes in three ways:

- A review by the Canadian Agency for Drugs and Technologies in Health (CADTH) of the published qualitative evidence on patient preferences and values
- A survey by the Quebec Institut National de d'Excellence en Santé et en Services Sociaux (INESSS) exploring the perspectives on *DPYD* testing of people with cancer
- Direct engagement by Ontario Health through interviews with people who had lived experience with fluoropyrimidine treatment and those who sought *DPYD* testing

Qualitative Evidence

Ontario Health collaborated with CADTH to conduct this health technology assessment. *DPYD* testing is a type of pharmacogenomic test. Because the qualitative literature on *DPYD* testing is limited, CADTH conducted a review of the qualitative literature[109] on patient perspectives of pharmacogenomic testing more broadly. We have summarized the key findings of this review below.

Key Findings

- The rapid qualitative evidence synthesis included 13 primary studies that explored the views and understanding of patients and providers on pharmacogenomic testing
- Patients and providers saw pharmacogenomic testing as beneficial. Although they sometimes wanted more information, most patients and providers said that pharmacogenomic testing helped them narrow their choices to the "best" medication so they could avoid adverse reactions
- Patients and providers expressed worries about how pharmacogenomic testing would limit patient-centred care by limiting patients' choices of medications. They also raised concerns about having to select less effective or more expensive medications to avoid any potential adverse reactions flagged by the pharmacogenomic test results
- Patients and providers raised concerns about the potential for genetic discrimination by insurers and employers, and about privacy and confidentiality. Limiting access to medical records, particularly electronic ones, appeared to be the primary mechanism by which patients and providers thought privacy and confidentially could be mitigated.
- Pharmacogenomic test results can shape patient care over the life course. The potential for secondary findings from pharmacogenomic testing made patients worry about how results would affect them in the present and the future. The potential for pharmacogenomic test results to affect current and future family members also troubled patients and providers
- The review found limited information about the use of and views on pharmacogenomic testing by disease or type of test. Findings point to the need for faster results from pharmacogenomic testing in life-limiting or rapidly progressing conditions. In areas such as mental health, pharmacogenomic testing was used less routinely, and generally applied when patients experienced adverse reactions or limited effectiveness. Providers and patients expected pharmacogenomic test results to be just one of several types of information they used for decision-making

Survey Evidence

In 2019 INESSS conducted a survey[32] with cancer patients across Quebec who had been treated with fluoropyrimidines to ask them about their perspectives on fluoropyrimidine-based regimens and *DPYD* testing. We used some questions from the INESSS survey in our direct patient engagement interviews. We also requested and received the raw data from the survey to compare and contrast our results. The data shared by INESSS contained no information enabling the identification of patients who completed the survey.

Key Findings

- The INESSS survey yielded 38 respondents
- Several respondents indicated that they had not been informed about the potential risks associated with a standard fluoropyrimidine dose
- Most patients preferred being offered *DPYD* testing, despite the fact that their chances of testing positive were approximately 1%

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people who received fluoropyrimidine treatment and those of their families and other caregivers. We engaged people via phone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people who have received fluoropyrimidine treatment, as well as those of their families and caregivers.[110] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[111-114] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including Wellsprings, the University Health Network, Cancer Care Ontario, and London Health Sciences Centre, to spread the word about this engagement activity and to contact people who had been treated with fluoropyrimidines, family members, and caregivers, including those with experience of *DPYD* testing.

Inclusion Criteria

We sought to speak with people who had direct experience with fluoropyrimidines for the treatment of cancer, as well as their family or caregivers.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with 16 people who had been treated with fluoropyrimidines and were living in Ontario, as well as one family member and caregiver. Of the 17 people we spoke with, three had experience with *DPYD* testing, and the others had experience with pathology testing.

APPROACH

At the beginning of the interview, we explained the role of Ontario Health, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 9). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 30 to 90 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[115] Questions focused on the impact of cancer on people's quality of life, their experiences with treatments to manage or treat cancer, their experiences with the *DPYD* testing, and their perceptions of the benefits or limitations of *DPYD* testing. For family members and caregivers, questions

focused on their perceptions of the impact of cancer and treatments on the quality of life of the person with cancer, as well as the impact of the person's health condition and treatments on the family members and caregivers themselves. See Appendix 10 for our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[116,117] We used the qualitative data analysis software program NVivo[118] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of cancer and treatments on the people with cancer, family members, and caregivers we interviewed.

Results

DIAGNOSIS

Participants spoke about the varying symptoms they experienced, which led them to seek care and eventually to their cancer diagnosis. People had a variety of different experiences during their diagnosis journey. Some reported a positive, streamlined experience in which they were seen by a health care provider, sent for tests and diagnosed in a timely manner, and given treatment:

> *The stomach ache was not going away … I mentioned it to my family doctor, who immediately sent me for an ultrasound. Then the tumour that I had showed up immediately in the ultrasound.*

> *I had a mammogram, and they thought they saw something, and then they did an ultrasound and another mammogram. They determined it was aggressive after it came back from a lab.*

For a few participants, the search for a diagnosis was more difficult. Some were dismissed by physicians, some were misdiagnosed, and some did not have test results relayed in a timely manner. Two participants reported that it took years before they were given a proper diagnosis, during which time their cancer progressed. Patients expressed frustration with the process and felt they were not listened to or taken seriously until they advocated for themselves:

> *She showed me a pathology report from my appendix 10 months earlier that showed it was adenocarcinoma. So I was quite shocked, by both the fact that I had the cancer, plus the fact that it had been let go for 10 months. And basically I had gone from stage one to stage three at that point.*

> *For 3 to 4 years I fought to get a diagnosis. And by the time I started to have visible symptoms, which were rectal bleeding … I finally got a colonoscopy that was denied to me for 3 years. By that point, it had already gone into late stage three.*

> *I found it on my own and brought it to my family doctor's attention. We did an ultrasound and we just took it 6 months at a time, and we just watched the growth of it. I went through this for 2 years … I took matters in my own hands … I ended up finding a cancer doctor … and I was at stage four at that point.*

Many described the cancer diagnosis as a shock—unexpected and life-changing. They had concerns about their family and what the future would look like. Some had suspected the cancer diagnosis but still found the news devastating:

> *My first diagnosis was difficult. I was a single mom with teenage boys and a daughter with challenges.*
>
> *It was devastating to find out I had cancer. I kind of suspected it—I was almost expecting that answer from the way I felt and what I thought was going on in my body.*
>
> *You hear the diagnosis of cancer. It was surreal, because you know 24 hours earlier, it didn't exist. It wasn't even in our vocabulary and now it was a stage four cancer.*

A few participants said that they did not have a family history of cancer and highlighted their healthy lifestyle:

> *I'm a non-smoker, healthy lifestyle, active bodybuilder, into fitness. Probably the least likely person that you would expect to get colon cancer.*
>
> *But being such an active, healthy person my entire life, this kind of blindsided all of us. I'm still shocked.*

One patient felt relief at finding a diagnosis for their health concerns:

> *I actually felt better, because I had been struggling for the past year and had been asking for help to know what was going on and not getting anywhere … Well, at least I'm not crazy and there is really something wrong with me.*

TREATMENT JOURNEY

Once participants had been accurately diagnosed, they faced another care journey for treatment. Interviewees spoke about treatment options, searching for second or third opinions, and selecting a treatment plan. People reported a combination of treatment options offered to them, including surgery, chemotherapy, radiation, and immunotherapy:

> *I had both breasts removed. That was when the doctor told me what stage I was at … And I had the surgery, and then we waited 10 days, I believe. Then we started chemotherapy right away.*
>
> *The mastectomy was the only surgical option. And then I was 50–50 on both the chemo and radiation.*

SIDE EFFECTS

All participants experienced side effects from their treatments including surgery, chemotherapy, and radiation. Participants noted that the side effects from their treatment had a significant effect on their quality of life. The most commonly reported side effects they experienced were vomiting, hair loss, diarrhea, brain fog, memory loss, fatigue, and neuropathy:

I had some hair loss … I really didn't have very many side effects. I was very lucky.

When you do your own research on the chemotherapy treatments, it doesn't tell you that you're going to have a little bit of a memory loss or a blockage, or you're going to feel like a car just hit you.

The diarrhea kicked in fairly bad … and I had cartoon vomiting, is how I like to describe it.

A few participants experienced more severe side effects, such as myocardial infarction, blood clots, neuropathy, or severe diarrhea. Because of the severity of their side effects, they needed a reduction in their dosage or longer periods between treatments. In a few cases, the side effects led to hospitalizations:

So last week after I finished my 11 days of diarrhea, I called my doctor and I said, "You know, I don't think I can take the treatment this week. Can I have an extra week just to recover a bit from that before I start again for another?"

After the myocardial infarction, I had an emergency angiogram, a cardiogram, and various other tests, and was admitted for a while for that. So after that my chemo had to be changed.

A few participants mentioned latent side effects (such as trouble with cognitive function and neuropathy) that were still present years after their chemotherapy treatment:

For about 2½ years now I've been experiencing changes in my brain. I'm much more forgetful than I used to be. I can't concentrate like I used to. I can't multitask.

I still do have neuropathy in my feet. And that started once I had finished the treatment.

QUALITY OF LIFE

The side effects from treatment had a substantial impact on participants' quality of life. A majority mentioned that the side effects of chemotherapy limited their ability to do simple day-to-day tasks, especially household chores and errands. They had to get assistance from friends or family, or hire help:

I needed to be on bed rest for 48 hours until the chemo was out. That had a huge impact, because I basically just had to lie still and not do anything.

I had to hire a cleaning lady temporarily to come in and clean my house. I had family members dropping off dinners for my husband and me. When I was able to eat, I pretty much lived on soup broth.

He couldn't do very much for himself. Basically, I was doing almost everything for him.

Participants also noted that they had difficulty exercising. It was physically challenging for them because of the side effects of fatigue, neuropathy, and reduced lung capacity. Going for walks became difficult, and one person needed assistance:

I like to get out and walk and try to exercise. Not a stroll, but go for a good physical walk. Right now, as the treatments have come to a close, my lung capacity is not allowing that.

> *If I was to go out for a walk or something, I need somebody with me to hold me up, or I would use a walker.*
>
> *When you stand up it feels like your foot's on fire. You tend not to try to do a lot of stuff.*

One participant spoke about being unable to attend her son's wedding:

> *I had to cancel my son's wedding destination for me and my husband. He had to get married without us. I had to cancel family events. I had to cancel my vacation.*

EMPLOYMENT

Those interviewed described challenges with employment. Often, people took a leave of absence during their treatment because they were unable to meet the demands of their job while experiencing the side effects of their treatment. A few tried to schedule tasks and work duties around treatment, knowing that chemotherapy would affect their cognitive function. Others were unable to hold employment altogether because of neuropathy and a decline in cognitive function:

> *Between the brain fog and the struggle with neuropathy—my hands and feet—that affect my day-to-day activities. I already got a year to retirement. I'm probably just going to end up staying on disability until I hit retirement.*
>
> *I did 3 weeks' work in 3 days. It was a lot, but I knew I would have chemo brain.*
>
> *I did take a medical leave of absence from my job. I would not have been able to do the job for the demands physically, mentally, and also the risk of being in an [environment] full of germs.*

MENTAL HEALTH

Participants spoke about the emotional burden they felt. Patients reported struggling with feelings of depression, isolation, anxiety, and frustration. For some, the emotional toll was from getting a cancer diagnosis; others struggled with worry about experiencing adverse reactions to treatment:

> *It's very hard for someone who gets a diagnosis not to wander off into the black areas.*
>
> *I was incredibly anxious … in the end I got admitted to the oncology ward, and they monitored me there. And it was all fine, but there was a lot of anxiety leading up to that.*
>
> *You've seen people on chemo before, and sometimes the worst things happened—you know, all the hair falling out, and the severe vomiting, and things like that, and you hope you don't get that. But it's always in the back of your mind that you could be that severe. That definitely causes you a lot of anxiety.*

For others, the side effects from their cancer treatments limited their ability to do simple tasks:

> *I'm very frustrated with myself when I can't do things. I'll try and do something I think I can do and just struggle … And I get very upset with myself, very angry about it.*

Others tried to have a positive outlook on their situation:

> *I'm a very positive person. I have to be, because otherwise life would be miserable. I would be miserable. So no point in doing that.*

> *I know I had "poor me" days, but I'm the kind of person that says, okay, you've got 20 minutes to get over it and move on. And basically, that's what I did.*

DPYD TESTING

Toxicity From Fluoropyrimidines

A majority of participants emphasized that they were aware of the common side effects of fluoropyrimidines but were not aware of the possible level of toxicity. Participants noted that toxicity was not mentioned in the resources they were given, or in conversations with their care team:

> *I mean, they give you lists of side effects and things like that, but I don't recall the use of the word "toxicity."*

> *No, I was totally unaware. I just figured like everyone else going through chemo, I could possibly feel nauseous, be throwing up, have diarrhea … But no, I never knew it could be toxic.*

> *I never knew there could be such a reaction to a drug that it could be to the point of being dangerous … I mean, side effects are uncomfortable. Yeah. But to the point of really being a health hazard.*

DPYD Testing in Ontario

At the time of completing this health technology assessment, *DPYD* testing was conducted through at one hospital in Ontario. Of the 17 participants, three had direct experience with *DPYD* testing. They said that the process was a simple blood test, and they felt it was just one of many the tests they took as part of their care journey. Because *DPYD* testing is commonly done before starting chemotherapy treatment, two of the three participants were not aware of their results, because they had just had their test done:

> *I don't have the results of the test. The results went to the doctor. I'm interested in knowing. I'll find out tomorrow when I start chemo.*

Only one participant knew their test result, and it was negative. This participant had researched and asked for a *DPYD* test after having an adverse reaction to their chemotherapy treatment:

> *I requested* DPYD *testing because, again, the cardiac thing is a bit iffy as to whether it's classic* DPYD *deficiency. The cardiac stuff is not well represented in the literature as much as the classic symptoms.*

Non-users of DPYD Testing

Most of the participants did not have direct experience with *DPYD* testing. We gave participants basic information about the test, including the logistics of the test, the type of information it can provide, and how the information would be used to inform the treatment path. We then asked for their thoughts on *DPYD* testing and whether such a test would be of value to them.

Participants who had no direct experience with *DPYD* testing were open to testing and commented about its perceived benefits. Most participants acknowledged that the test would give them more information before they started treatment. They thought it would aid in their decision-making, especially because of the toxic nature of chemotherapy. The review of the qualitative literature[109] illustrated this as well, reporting that "Some providers and patients described that they saw test results as useful in that they provided more information."

People also spoke about how *DPYD* testing might prepare their care team to face any risks associated with fluoropyridines or avoid those risks altogether. They spoke about the importance of being as informed as possible:

> *My care team would have been forearmed with the knowledge if there was an issue that was beyond the normal parameters of what should be occurring. Medication could have been adjusted.*

> *If you can get treatment—the correct treatment—to a patient initially, and cure or provide a curative response, or at least improve the quality of life right at the beginning, it's going to cost less than having to take care of somebody in our system for 5 or 10 years.*

> *I don't know how I'm going to react to any of the drugs that I'm going to be given, but if I can alleviate one of the problems I could possibly have, then absolutely I would do it.*

The INESSS survey[32] contained the question, "Do you believe that this test should be offered to patients who are candidates for fluoropyrimidine treatment, knowing that about 1% of individuals will have a positive result for this test (this proportion could reach 7% with the inclusion of the three proposed genetic variations)?" (INESSS survey, raw data; February 12, 2021). We asked our interviewees the same question. A majority of the participants we interviewed agreed that *DPYD* testing should be offered even if only 1% of individuals received positive results:

> *I think it's important to test everybody so that you know if you are in the 1%. You'd want to know.*

> *Cancer itself is such a horrible thing for people to have to go through, that even if it's only 1%, everybody should have that chance and not have to experience those side effects.*

> *I think knowing what the possible side effects are and hearing the horror stories of what some people have to go through, I think if there was a way to help those patients … how many patients stop chemotherapy because they can't handle the chemotherapy? I think it should be offered.*

A couple of participants did not completely agree that *DPYD* testing should be offered if only 1% of people tested positive, although both took into account the different perspectives and were not able to give a definite answer:

> *No, because it is just 1%, and how many sail through without any big worries. That said, if I was in that 1% I'd feel a lot differently.*

> *1% is pretty low, in my opinion, if you're someone like myself who doesn't have a history of reactions to a lot of drugs. On the other hand, everybody's circumstances are different, and I*

> *don't think money should be a barrier for a solution for a cure or better outlook on life … I'm of two minds.*

BARRIERS TO *DPYD* TESTING

Awareness of DPYD *Testing*

Most of the non-users of *DPYD* testing were not aware of the test and said that this option was never brought up during their care journey:

> *There was no discussion of the testing that you're talking about … I never heard of it before.*

> *No, I didn't even know it existed.*

A few participants expressed frustrations over not being made aware of *DPYD* testing before they started their fluoropyrimidine treatment and talked about how important the results from this test could have been to them:

> *I'm just kind of wondering why I was not made aware of it. Why an oncologist or cancer clinic wouldn't be making that information available to people that this testing is available in case you want to take advantage of it.*

> *To me, it's really important. And I don't know why every oncologist wouldn't want to send their patients to find out before they start giving them the medication.*

> *Four and a half years with Folfox and what I went through with it, and at no point was I ever offered any testing.*

Access to DPYD *Testing*

Participants were asked if they would have been willing to travel within Ontario , to get *DPYD* testing if it were offered to them. All interviewees said that they would have been open to travelling to get tested before they started their chemotherapy treatment:

> *The cost of getting there and the cost of staying overnight, because you can't drive up and back [from where I am]. But I really wouldn't mind at all.*

> *It's 2 hours [to the test facility]. That's not a big deal for us. And if we decided it was something that was worthwhile, we would do it no matter what.*

One of the participants who had experience with *DPYD* testing reflected on how surprised they were to be asked to travel for the test, especially when they lived in Toronto:

> *He told me about the blood test [location], which to me sounded like a crazy thing to do, because I had to go all the way to [that location] … I presume that there are enough doctors in Toronto or enough labs in Toronto who could do the test.*

A couple of patients said that they would have been able to get to London to get *DPYD* testing, but that others might not have access to the same resources:

> *I would first ask why can't they just ship my blood over there and get it tested. But if that's logistically not possible, then yes, I would. But I'm reasonably healthy, I have the time, and I'm not old. I don't know how different it would be for someone older.*

> *Most often than not, if a doctor said, "Go do it," you [would] do it, but maybe not. Maybe people can't get there.*

ETHICAL CONCERNS

Storage of Genetic Data

The qualitative literature review[109] found that "patients and providers expressed worries around who would have access to patients' genetic information and the potential for it to be accessed and misused by unauthorized persons. These concerns around confidentiality and privacy were often raised in reference to fears of discrimination by insurers."

In contrast, when we asked interviewees their opinions about the storage of genetic information, most were not concerned about the privacy and confidentiality of their genetic data. Participants noted that because the data were used for health purposes to benefit the patient, and because a health care organization was storing it, they had trust that their information would not be given to third parties such as insurance companies:

> *There's a code of ethics in every profession … and most of them adhere to the code of ethics of their profession.*

> *You just end up weighing privacy concerns over health concerns or life and death concerns, and I guess for me, life and death always trumps privacy.*

Sharing Information With Relatives

Participants were also asked their opinions about sharing their test results with relatives. All interviewees were open to sharing their results and noted that it would provide their loved ones with more information so they could make more informed decisions about their health:

> *I wouldn't have any problem sharing it with my children or my brother and sister. Anything that might be helpful in their decisions about their life, about having children, or about how it might even affect their lifestyle and their choices. Any kind of information is good as long as it doesn't depress you.*

> *I would actually want them to know that, as it would have implications for them if they were needing to have chemotherapy. But my personal opinion is, yes, I would. I would believe in it, but I understand people's hesitation in sharing that with family members.*

> *Absolutely. I have shared my genetic report, I have shared all my data with all of my cousin, and my sister.*

Preferences and Values Evidence Discussion

We compared the findings from different types of recruitment and engagement with the results from our direct patient engagement. This included CADTH's qualitative literature rapid review[109] on pharmacogenomics and the survey results from INESSS[32] exploring patient perspectives on *DPYD* testing.

Participants in our direct patient engagement discussed and reflected on their diagnosis, the impacts of living with cancer, and their treatment journey. Interviewees spoke about their struggles with the side effects of from their cancer treatment. They also shared the burden of their condition and its disruption of their quality of life, including its effects on their daily life, mental health, and employment.

Participants also discussed their perspectives on *DPYD* testing. They mentioned a lack of awareness among cancer patients about the toxicity of fluoropyrimidines and the existence of the *DPYD* test. Respondents to the INESSS survey further reinforced the message that lack of awareness was a barrier. A majority of the people we interviewed said that they were not offered *DPYD* testing as an option, although they were very open to it and willing to take the test. Most noted that they would have made travel within Ontario to the health care facility the test is available at, to take the test if it were offered. Most of the people we interviewed spoke about the significance of having *DPYD* test results before starting their fluoropyrimidine treatment to provide guidance on dosage and reduce the risk of adverse effects. This finding was also reflected in the CADTH qualitative literature review.[109] Participants we interviewed noted that the fact that *DPYD* testing was offered only at one health care facility in Ontario would be a barrier to those who did not have the resources to get there.

In contrast to the findings of the qualitative literature review,[109] the patients and caregivers we interviewed were not concerned about privacy, confidentiality, or the storage of their genetic data, and interviewees were not reluctant to share their test results with relatives. Because we spoke to only a small number of interviewees, this finding may or may not reflect the views of all patients.

The applicability of our results is limited because of the small number of participants with direct experience of *DPYD* testing, and because most of those who had had the test were not yet aware of their results and their potential effect on treatment. As well, most participants lived in large urban areas and we presumed that they had high socioeconomic status, because no one mentioned resource barriers when asked about travelling within Ontario to access the *DPYD* test.

Preferences and Values Evidence Conclusions

Participants we interviewed who had been treated with fluoropyrimidines described the substantial impact of cancer and the treatment side effects on their quality of life and mental health. Most reflected on the perceived value of *DPYD* testing to reduce the risk of serious adverse events as a result of fluoropyrimidine treatment—a finding that was also reflected in the INESSS survey results[32] and the qualitative literature review.[109] Barriers included lack of awareness and limited access to *DPYD* testing.

Conclusions of the Health Technology Assessment

Studies found that carriers of any one of the variants under assessment treated with a standard fluoropyrimidine dose may have a higher risk of severe toxicity versus wild-type patients treated—this may lead to dose reduction, treatment discontinuation and hospitalization. *DPYD* genotyping led to changes in clinical conduct by allowing fluoropyrimidine treatment modifications. It was uncertain whether the genotype-guided dose reduction in heterozygous *DPYD* carriers led to a risk of severe toxicity and hospitalization that was either comparable to wild-type patients, or lower than *DPYD* carriers, treated with a standard dose. The length of hospital stay was shorter in carriers treated with a reduced versus standard dose, but the evidence was uncertain. It is uncertain whether the treatment effectiveness of a reduced dose in carriers is comparable to that in wild-type patients.

For patients with planned fluoropyrimidine treatment, *DPYD* genotyping is likely cost-effective compared to usual care (no testing). Publicly funding *DPYD* genotyping in Ontario may be cost-saving, with an estimated saving of $714,963 over the next 5 years, provided that the costs of implementation, service delivery, and program coordination do not exceed this amount.

Participants we interviewed who had been treated with fluoropyrimidines described the substantial impact of cancer and the treatment side effects on their quality of life and mental health. Most reflected on the perceived value of *DPYD* testing to prevent serious adverse events as a result of fluoropyrimidine treatment. Barriers expressed by patients to accessing the test included lack of awareness and limited access to *DPYD* testing.

Abbreviations

CI	Confidence interval
DPD	Dihydropyrimidine dehydrogenase
EMA	European Medicines Agency
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NICE	The National Institute for Health and Care Excellence
PCR	Polymerase chain reaction
QALY	Quality-adjusted life-year
RR	Relative risk
SD	Standard deviation

Glossary

Adverse event	An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.
Allele	A gene is the basic unit of heredity (humans have approximately 20,000 genes). An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene—one from each parent.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Chromosome	A chromosome is a highly organized molecule of DNA in the cells of living organisms. Chromosomes are made up of genes (see alleles, above) that contain the codes for creating molecules that are required by an organism to function and survive. Cells of the body that contain two sets of chromosomes are called diploid.
Cost–benefit analysis	A cost–benefit analysis is a type of economic evaluation that expresses the effects of a health care intervention in terms of a monetary value so that these effects can be compared with costs. Results can be reported either as a ratio of costs to benefits or as a simple sum that represents the net benefit (or net loss) of one intervention over another. The monetary valuation of the different intervention effects is based on either prices that are revealed by markets or an individual or societal willingness-to-pay value.
Cost–consequence analysis	A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve	In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.
Cost-effectiveness analysis	Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.
Cost-minimization analysis	In economic evaluations, a cost-minimization analysis compares the costs of two or more health care interventions. It is used when the intervention of interest and its relevant alternative(s) are determined to be equally effective.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.
Decision tree	A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.
Discounting	Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.
Disutility	A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).
Dominant	A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

DPD deficiency	DPD deficiency is a condition in which the activity of the DPD enzyme in the body is reduced or absent. One expression of this condition is in the reduced ability to process the fluoropyrimidine class of chemotherapy drugs, sometimes leading to toxic reactions requiring adjustment of chemotherapy treatment and potentially hospitalization and death.
EQ-5D	The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.
Exon	An exon is the portion of a gene that codes for amino acids, which are compounds that combine to form proteins.
Genotyping	Testing to determine whether a genetic variant (genotype) that underlies an observable characteristic (phenotype) of a person is present.
Health-related quality of life	Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.
Health state	A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.
Heterozygous	Having two different alleles for a particular gene.
Homozygous	Having the same pair of alleles for a particular gene.
Incremental cost	The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Negative predictive value (NPV)	A test performance characteristic, defined as the proportion of persons who do not have the disease among those who have a negative diagnostic test result; it is calculated as follows: true negatives ÷ (true negatives + false negatives).
One-way sensitivity analysis	A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.
Phenotype	The observable characteristics (e.g., appearance, development, behaviour) resulting from a person's genetic profile (their genotype).
Positive predictive value (PPV)	A test performance characteristic, defined as the proportion of persons with a positive result in a diagnostic test who have the disease; it is calculated as follows: true positives ÷ (true positives + false positives).
Probabilistic analysis	A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Standard gamble	In economic evaluations, standard gamble is a direct method of measuring people's preferences for various health states. In a standard gamble, respondents are asked about their preference for either (a) remaining in a certain health state for the rest of their life, or (b) a gamble scenario in which there is a chance of having optimal health for the rest of one's life but also a chance of dying immediately. Respondents are surveyed repeatedly, with the risk of immediate death varying each time (e.g., 75% chance of optimal health, 25% chance of immediate death) until they are indifferent about their choice. The standard gamble is considered the gold standard for eliciting preferences as it incorporates individual risk attitudes, unlike other methods of eliciting preferences.
Time horizon	In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.
Uptake rate	In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.
Utility	A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Clinical Literature Search for Systematic Reviews

Search date: February 20, 2020

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 11, 2020>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2020 Week 07>, Ovid MEDLINE(R) ALL <1946 to February 19, 2020>

Search Strategy:

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1 Fluorouracil/ (171324)
2 (5 FU* or 5FU* or fluorouracil* or fluoro uracil* or fluoruracil* or fluouracil* or fluoroplex* or fluracedyl* or flurodex* or floxuridin* or fluoroblastin* or fluoxan* or flurablastin* or fluracil* or fluracilium* or fluril* or fluro uracil* or fluroblastin* or adrucil* or carac* or efudex* or efudix* or haemato FU* or neofluor* or onkofluor* or ribofluor*).ti,ab,kf. (117421)
3 Capecitabine/ (32280)
4 (capecitabin* or fluorocytidin* or xeloda* or apecitab* or ecansya*).ti,ab,kf. (18633)
5 (Fluoropyrimidin* or (fluoro adj3 pyrimidinedion*)).ti,ab,kf. (8608)
6 Tegafur/ (11704)
7 (tegafur* or florafur* or fluorofur* or futraful* or ftorafur* or sunfural* or uftoral* or utefos*).ti,ab,kf. (5175)
8 or/1-7 (234811)
9 Dihydropyrimidine Dehydrogenase Deficiency/ (471)
10 "Dihydrouracil Dehydrogenase (NADP)"/ (3232)
11 ((dihydropyrimidin* adj2 dehydrogenas*) or DPD* or ?DPYD*).ti,ab,kf. (13245)
12 (Dihydropyrimidinas* or DHP or DHPDHASE*).ti,ab,kf. (6254)
13 ((dihydrothymin* or dihydrouracil) adj2 dehydrogenas*).ti,ab,kf. (100)
14 ((Pyrimidin* adj2 familial) or thymine uraciluri*).ti,ab,kf. (48)
15 (c?1679?T* or c?2846?A* or c?1129?* or c?1236?G* or c?1905* or I560S* or D949V* or E412E*).ti,ab,kf. (296)
16 ((dihydrouracil or DHU) adj3 (uracil or U) adj3 ratio*).ti,ab,kf. (94)
17 or/9-16 (20288)
18 8 and 17 (4127)
19 exp Animals/ not Humans/ (16500883)

20 18 not 19 (3014)
21 limit 20 to english language [Limit not valid in CDSR; records were retained] (2628)
22 21 use coch,clhta,cleed (1)
23 (Systematic Reviews or Meta Analysis).pt. (110870)
24 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (597167)
25 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (406428)
26 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (408046)
27 (evidence adj (review* or overview* or synthes#s)).ti,ab,kf. (15235)
28 (review of reviews or overview of reviews).ti,ab,kf. (1428)
29 umbrella review*.ti,ab,kf. (725)
30 GRADE Approach/ (357)
31 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (432364)
32 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (454968)
33 cochrane.ti,ab,kf. (192787)
34 (meta regress* or metaregress*).ti,ab,kf. (18895)
35 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (25228)
36 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (64004)
37 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (43199)
38 or/23-37 (1195660)
39 21 and 38 (76)
40 39 use medall (31)
41 or/22,40 (32)
42 fluorouracil/ (171324)
43 (5 FU* or 5FU* or fluorouracil* or fluoro uracil* or fluoruracil* or fluouracil* or fluoroplex* or fluracedyl* or flurodex* or floxuridin* or fluoroblastin* or fluoxan* or flurablastin* or fluracil* or fluracilium* or fluril* or fluro uracil* or fluroblastin* or adrucil* or carac* or efudex* or efudix* or haemato FU* or neofluor* or onkofluor* or ribofluor*).tw,kw. (119326)
44 capecitabine/ (32280)
45 (capecitabin* or fluorocytidin* or xeloda* or apecitab* or ecansya*).tw,kw. (20145)
46 fluoropyrimidine/ (3900)
47 fluoropyrimidine derivative/ (2009)
48 (Fluoropyrimidin* or (fluoro adj3 pyrimidinedion*)).tw,kw. (8769)
49 tegafur/ (11704)

50 (tegafur* or florafur* or fluorofur* or futraful* or ftorafur* or sunfural* or uftoral* or utefos*).tw,kw. (5366)
51 or/42-50 (236382)
52 dihydropyrimidine dehydrogenase deficiency/ (471)
53 dihydropyrimidine dehydrogenase/ (3478)
54 ((dihydropyrimidin* adj2 dehydrogenas*) or DPD* or ?DPYD*).tw,kw,dv. (13362)
55 (Dihydropyrimidinas* or DHP or DHPDHASE*).tw,kw,dv. (6337)
56 ((dihydrothymin* or dihydrouracil) adj2 dehydrogenas*).tw,kw,dv. (110)
57 ((Pyrimidin* adj2 familial) or thymine uraciluri*).tw,kw,dv. (49)
58 (c?1679?T* or c?2846?A* or c?1129?* or c?1236?G* or c?1905* or I560S* or D949V* or E412E*).tw,kw,dv. (296)
59 ((dihydrouracil or DHU) adj3 (uracil or U) adj3 ratio*).tw,kw,dv. (95)
60 or/52-59 (20531)
61 51 and 60 (4219)
62 (exp animal/ or nonhuman/) not exp human/ (10570073)
63 61 not 62 (4011)
64 limit 63 to english language [Limit not valid in CDSR; records were retained] (3557)
65 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (578482)
66 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (573556)
67 ((systematic* or methodologic*) adj3 (review* or overview*)).tw,kw. (418056)
68 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw. (435063)
69 (evidence adj (review* or overview* or synthes#s)).tw,kw. (15631)
70 (review of reviews or overview of reviews).tw,kw. (1628)
71 umbrella review*.tw,kw. (765)
72 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).tw,kw. (457621)
73 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (454968)
74 cochrane.tw,kw. (196339)
75 (meta regress* or metaregress*).tw,kw. (19823)
76 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).tw,kw. (26126)
77 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (64004)
78 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw. (44866)
79 or/65-78 (1215984)
80 64 and 79 (128)

81 80 use emez (94)
82 41 or 81 (126)
83 82 use medall (31)
84 82 use coch (0)
85 82 use clhta (1)
86 82 use cleed (0)
87 82 use emez (94)
88 remove duplicates from 82 (97)

Clinical Literature Search Update of Primary Studies from 2018–Present

Search date: February 27, 2020

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2020>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 21, 2020>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2020 Week 08>, Ovid MEDLINE(R) ALL <1946 to February 26, 2020>

Search Strategy:

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1 Fluorouracil/ (176301)
2 (5 FU* or 5FU* or fluorouracil* or fluoro uracil* or fluoruracil* or fluouracil* or fluoroplex* or fluracedyl* or flurodex* or floxuridin* or fluoroblastin* or fluoxan* or flurablastin* or fluracil* or fluracilium* or fluril* or fluro uracil* or fluroblastin* or adrucil* or carac* or efudex* or efudix* or haemato FU* or neofluor* or onkofluor* or ribofluor*).ti,ab,kf. (128574)
3 Capecitabine/ (33465)
4 (capecitabin* or fluorocytidin* or xeloda* or apecitab* or ecansya*).ti,ab,kf. (22073)
5 (Fluoropyrimidin* or (fluoro adj3 pyrimidinedion*)).ti,ab,kf. (9745)
6 Tegafur/ (12284)
7 (tegafur* or florafur* or fluorofur* or futraful* or ftorafur* or sunfural* or uftoral* or utefos*).ti,ab,kf. (5825)
8 or/1-7 (250907)
9 Dihydropyrimidine Dehydrogenase Deficiency/ (473)
10 "Dihydrouracil Dehydrogenase (NADP)"/ (3267)
11 ((dihydropyrimidin* adj2 dehydrogenas*) or DPD* or ?DPYD*).ti,ab,kf. (13677)
12 (Dihydropyrimidinas* or DHP or DHPDHASE*).ti,ab,kf. (6333)
13 ((dihydrothymin* or dihydrouracil) adj2 dehydrogenas*).ti,ab,kf. (101)
14 ((Pyrimidin* adj2 familial) or thymine uraciluri*).ti,ab,kf. (48)

15 (c?1679?T* or c?2846?A* or c?1129?* or c?1236?G* or c?1905* or I560S* or D949V* or E412E*).ti,ab,kf. (308)
16 ((dihydrouracil or DHU) adj3 (uracil or U) adj3 ratio*).ti,ab,kf. (98)
17 or/9-16 (20802)
18 8 and 17 (4269)
19 exp Animals/ not Humans/ (16503427)
20 18 not 19 (3156)
21 limit 20 to english language [Limit not valid in CDSR; records were retained] (2734)
22 limit 21 to yr="2018 -Current" (243)
23 22 use medall,coch,cctr,clhta,cleed (126)
24 fluorouracil/ (176301)
25 (5 FU* or 5FU* or fluorouracil* or fluoro uracil* or fluoruracil* or fluouracil* or fluoroplex* or fluracedyl* or flurodex* or floxuridin* or fluoroblastin* or fluoxan* or flurablastin* or fluracil* or fluracilium* or fluril* or fluro uracil* or fluroblastin* or adrucil* or carac* or efudex* or efudix* or haemato FU* or neofluor* or onkofluor* or ribofluor*).tw,kw. (130532)
26 capecitabine/ (33465)
27 (capecitabin* or fluorocytidin* or xeloda* or apecitab* or ecansya*).tw,kw. (23603)
28 fluoropyrimidine/ (3905)
29 fluoropyrimidine derivative/ (2013)
30 (Fluoropyrimidin* or (fluoro adj3 pyrimidinedion*)).tw,kw. (9910)
31 tegafur/ (12284)
32 (tegafur* or florafur* or fluorofur* or futraful* or ftorafur* or sunfural* or uftoral* or utefos*).tw,kw. (6027)
33 or/24-32 (252546)
34 dihydropyrimidine dehydrogenase deficiency/ (473)
35 dihydropyrimidine dehydrogenase/ (3513)
36 ((dihydropyrimidin* adj2 dehydrogenas*) or DPD* or ?DPYD*).tw,kw,dv. (13796)
37 (Dihydropyrimidinas* or DHP or DHPDHASE*).tw,kw,dv. (6416)
38 ((dihydrothymin* or dihydrouracil) adj2 dehydrogenas*).tw,kw,dv. (111)
39 ((Pyrimidin* adj2 familial) or thymine uraciluri*).tw,kw,dv. (49)
40 (c?1679?T* or c?2846?A* or c?1129?* or c?1236?G* or c?1905* or I560S* or D949V* or E412E*).tw,kw,dv. (308)
41 ((dihydrouracil or DHU) adj3 (uracil or U) adj3 ratio*).tw,kw,dv. (99)
42 or/34-41 (21047)
43 33 and 42 (4363)
44 (exp animal/ or nonhuman/) not exp human/ (10577094)
45 43 not 44 (4155)
46 limit 45 to english language [Limit not valid in CDSR; records were retained] (3665)
47 limit 46 to yr="2018 -Current" (356)
48 47 use emez (229)
49 23 or 48 (355)
50 49 use medall (113)
51 49 use emez (229)

52 49 use coch (0)
53 49 use cctr (13)
54 49 use clhta (0)
55 49 use cleed (0)
56 remove duplicates from 49 (248)

Economic Evidence Search

Economic Evaluation and Cost Effectiveness Search

Search date: February 20, 2020

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2020>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 11, 2020>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2020 Week 07>, Ovid MEDLINE(R) ALL <1946 to February 19, 2020>

Search Strategy:

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1 Fluorouracil/ (176163)
2 (5 FU* or 5FU* or fluorouracil* or fluoro uracil* or fluoruracil* or fluouracil* or fluoroplex* or fluracedyl* or flurodex* or floxuridin* or fluoroblastin* or fluoxan* or flurablastin* or fluracil* or fluracilium* or fluril* or fluro uracil* or fluroblastin* or adrucil* or carac* or efudex* or efudix* or haemato FU* or neofluor* or onkofluor* or ribofluor*).ti,ab,kf. (128498)
3 Capecitabine/ (33412)
4 (capecitabin* or fluorocytidin* or xeloda* or apecitab* or ecansya*).ti,ab,kf. (22042)
5 (Fluoropyrimidin* or (fluoro adj3 pyrimidinedion*)).ti,ab,kf. (9736)
6 Tegafur/ (12278)
7 (tegafur* or florafur* or fluorofur* or futraful* or ftorafur* or sunfural* or uftoral* or utefos*).ti,ab,kf. (5823)
8 or/1-7 (250717)
9 Dihydropyrimidine Dehydrogenase Deficiency/ (472)
10 "Dihydrouracil Dehydrogenase (NADP)"/ (3262)
11 ((dihydropyrimidin* adj2 dehydrogenas*) or DPD* or ?DPYD*).ti,ab,kf. (13670)
12 (Dihydropyrimidinas* or DHP or DHPDHASE*).ti,ab,kf. (6332)
13 ((dihydrothymin* or dihydrouracil) adj2 dehydrogenas*).ti,ab,kf. (101)

14 ((Pyrimidin* adj2 familial) or thymine uraciluri*).ti,ab,kf. (48)
15 (c?1679?T* or c?2846?A* or c?1129?* or c?1236?G* or c?1905* or I560S* or D949V* or E412E*).ti,ab,kf. (308)
16 ((dihydrouracil or DHU) adj3 (uracil or U) adj3 ratio*).ti,ab,kf. (97)
17 or/9-16 (20794)
18 8 and 17 (4266)
19 exp Animals/ not Humans/ (16500893)
20 18 not 19 (3153)
21 limit 20 to english language [Limit not valid in CDSR; records were retained] (2731)
22 21 use coch,clhta,cleed (1)
23 economics/ (255908)
24 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (852651)
25 economics.fs. (430085)
26 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (929299)
27 exp "costs and cost analysis"/ (592564)
28 (cost or costs or costing or costly).ti. (273338)
29 cost effective*.ti,ab,kf. (342723)
30 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (225084)
31 models, economic/ (13318)
32 markov chains/ or monte carlo method/ (84845)
33 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (44747)
34 (markov or markow or monte carlo).ti,ab,kf. (136012)
35 quality-adjusted life years/ (41946)
36 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (78715)
37 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (128516)
38 or/23-37 (2641736)
39 21 and 38 (104)
40 39 use medall,cctr (33)
41 or/22,40 (34)
42 fluorouracil/ (176163)
43 (5 FU* or 5FU* or fluorouracil* or fluoro uracil* or fluoruracil* or fluouracil* or fluoroplex* or fluracedyl* or flurodex* or floxuridin* or fluoroblastin* or fluoxan* or flurablastin* or fluracil* or fluracilium* or fluril* or fluro uracil* or fluroblastin* or adrucil* or carac* or efudex* or efudix* or haemato FU* or neofluor* or onkofluor* or ribofluor*).tw,kw. (130452)
44 capecitabine/ (33412)
45 (capecitabin* or fluorocytidin* or xeloda* or apecitab* or ecansya*).tw,kw. (23571)
46 fluoropyrimidine/ (3900)
47 fluoropyrimidine derivative/ (2009)

48 (Fluoropyrimidin* or (fluoro adj3 pyrimidinedion*)).tw,kw. (9901)
49 tegafur/ (12278)
50 (tegafur* or florafur* or fluorofur* or futraful* or ftorafur* or sunfural* or uftoral* or utefos*).tw,kw. (6025)
51 or/42-50 (252354)
52 dihydropyrimidine dehydrogenase deficiency/ (472)
53 dihydropyrimidine dehydrogenase/ (3508)
54 ((dihydropyrimidin* adj2 dehydrogenas*) or DPD* or ?DPYD*).tw,kw,dv. (13789)
55 (Dihydropyrimidinas* or DHP or DHPDHASE*).tw,kw,dv. (6415)
56 ((dihydrothymin* or dihydrouracil) adj2 dehydrogenas*).tw,kw,dv. (111)
57 ((Pyrimidin* adj2 familial) or thymine uraciluri*).tw,kw,dv. (49)
58 (c?1679?T* or c?2846?A* or c?1129?* or c?1236?G* or c?1905* or I560S* or D949V* or E412E*).tw,kw,dv. (308)
59 ((dihydrouracil or DHU) adj3 (uracil or U) adj3 ratio*).tw,kw,dv. (98)
60 or/52-59 (21039)
61 51 and 60 (4360)
62 (exp animal/ or nonhuman/) not exp human/ (10570089)
63 61 not 62 (4152)
64 limit 63 to english language [Limit not valid in CDSR; records were retained] (3662)
65 Economics/ (255908)
66 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (131026)
67 Economic Aspect/ or exp Economic Evaluation/ (464763)
68 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (955437)
69 exp "Cost"/ (592564)
70 (cost or costs or costing or costly).ti. (273338)
71 cost effective*.tw,kw. (355233)
72 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (236617)
73 Monte Carlo Method/ (67433)
74 (decision adj1 (tree* or analy* or model*)).tw,kw. (48599)
75 (markov or markow or monte carlo).tw,kw. (141087)
76 Quality-Adjusted Life Years/ (41946)
77 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (82603)
78 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (149458)
79 or/65-78 (2267662)
80 64 and 79 (157)
81 80 use emez (124)
82 41 or 81 (158)
83 82 use medall (32)
84 82 use emez (124)
85 82 use cctr (1)

86 82 use coch (0)
87 82 use clhta (1)
88 82 use cleed (0)
89 remove duplicates from 82 (125)

Grey Literature Search

Performed: February 20–25, 2020

Websites searched:
HTA Database Canadian Repository, Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Health Technology Assessment Database, Epistemonikos, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, Health Technology Wales, Oregon Health Authority Health Evidence Review Commission, Veterans Affairs Health Services Research and Development, Italian National Agency for Regional Health Services (AGENAS), Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Ministry of Health Malaysia Health Technology Assessment Section, Swedish Agency for Health Technology Assessment and Assessment of Social Services, PROSPERO, EUnetHTA, Tuft's Cost-Effectiveness Analysis Registry, SickKids Paediatric Economic Database Evaluation (PEDE) database

Keywords used:
DPYD, DPD, Dihydropyrimidine Dehydrogenase, Fluorouracil, Fluoropyrimidine, 5FU, toxicity

Clinical results (included in PRISMA): 5
Economic results (included in PRISMA): 5
Ongoing HTAs (PROSPERO/EUnetHTA/MSAC): 4
Ongoing RCTs (clinicaltrials.gov): 91

Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included Studies: Clinical Validity

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Dose Adjustments	Outcomes
Wigle et al, 2021[71] N = 1,388 Canada	Patients identified retrospectively (c.1236G>A) Retrospective genotyping (c.1236G>A); pre-treatment genotyping (wild-type) 2013–2019	c.1236G>A	• Different cancer types • Fluoropyrimidine-based regimen, alone or in combination with other drugs or radiotherapy	*DPYD* carriers Wild-type	Standard fluoropyrimidine dose	Grade ≥ 3 toxicity (NCI-CTCAE v5.0) Treatment discontinuation Treatment-related mortality
Iachetta et al, 2019[52] N = 366 Italy	Retrospective patient selection from database Retrospective genotyping 2011–2016	c.2846A>T *DPYD**13	• Different cancer types • Fluoropyrimidine-based chemoradiation therapy • Not carrying *DPYD**2A • Controls were matched by primary tumour location, stage, and age	*DPYD* carriers Wild-type	Information on dose reduction not provided	Toxicity (NCI-CTCAE, v4.0)
Maharjan et al, 2019[53] N = 113 United States	Retrospective patient selection from database Prospective genotyping 2011–2018	*DPYD**2A c.2846A>T *DPYD**13	• Different cancer types • Fluoropyrimidine-based regimens • Patients genotyped for *DPYD;* decision to genotype was at the investigator's discretion and may have been associated with the risk of developing toxicity	*DPYD* carriers Wild-type	*DPYD**2A and c.2846A>T received full-dose chemotherapy	Toxicity (NCI-CTCAE v5.0)
Cremolini et al, 2018[55] N = 443 Italy	Based on patients included in RCT Prospective genotyping Period NR	*DPYD**2A *DPYD**13 c.2846A>T	• Metastatic colorectal cancer • 5-FU-based regimens	*DPYD* carriers Wild-type	Dose modified before start of therapy based on prespecified adverse events, not based on genotyping	Severe toxicity grade ≥ 3

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Dose Adjustments	Outcomes
Lunenburg et al, 2018[7] N = 828 Netherlands	Retrospective patient selection (3 databases) Prospective or retrospective genotyping depending on database 1993–2017 depending on database	*DPYD**2A c.2846A>T *DPYD**13 c.1236G>A	• Different cancer types • Fluoropyrimidine-based chemoradiation therapy	*DPYD* carriers Wild-type	Standard fluoropyrimidine dose	Grade ≥ 3 toxicity (NCI-CTCAE v3.0 and v4.03) Treatment modification Treatment-related hospitalization Length of stay
Nahid et al, 2018[54] N = 161 Bangladesh	Prospective recruitment Unclear whether genotyping was prospective or retrospective Period NR	*DPYD**2A	• Colorectal cancer • 5-FU-based regimens • WHO performance status < 3	*DPYD* carriers Wild-type	Dose reductions allowed	Toxicity (NCI-CTCAE, v3.0) Treatment modification
Etienne-Grimaldi et al, 2017[56] N = 243 France	Prospective recruitment Pre-treatment genotyping and phenotype test 2009–2011	DPYD*2A c.2846A>T *DPYD**13 c.1236G>A	• Women > 18 y old • Advanced breast cancer • Capecitabine alone or in combination with an antiangiogenic drug • Available *DPYD* genotyping results	*DPYD* carriers Wild-type	Dose at investigator's discretion	Grade ≥ 3 toxicity (NCI-CTCAE v3) Sensitivity, specificity, PPV, NPV
Meulendijks et al, 2017[18] N = 550 Netherlands	Prospective recruitment Serum collected before start of treatment Period NR	c.2846A>T *DPYD**13 c.1236G>A	• Different cancer types • Fluoropyrimidine-based chemoradiation therapy • Excluded *DPYD**2A carriers and patients undergoing chemoradiotherapy	*DPYD* carriers Wild-type	NR	Sensitivity, specificity, PPV, NPV (grade ≥ 3; NCI-CTCAE v3.0)

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Dose Adjustments	Outcomes
Meulendijks et al, 2017[70] N = 185 Netherlands	Based on patients included in 3 clinical studies Retrospective genotyping (sample collected for studies) 2003–2014	c.2846A>T c.1236G>A	• Advanced gastric cancer • Capecitabine-based regimens • WHO performance status 0–2	*DPYD* carriers Wild-type	Dosing according to study protocol	Grade ≥ 3 toxicity (NCI-CTCAE v 3.0 and 4.3)
Boige et al, 2016[15] N = 1,545 France	Based on patients included in RCT Retrospective genotyping Period NR	*DPYD**2A *DPYD**13 c.2846A>T	• Resected stage III colorectal cancer • 5-FU-based regimens	*DPYD* carriers Wild-type	Some patients had dose adjustment, not based on *DPYD* genotyping	Grade ≥ 3 toxicity (NCI-CTCAE v3.0)
Lee et al, 2016[13] N = 1,953 United States	Based on patients included in RCT Retrospective genotyping (sample collected for RCT) Period NR	*DPYD* variants of hapB3	• Caucasian patients • Stage III colon cancer • 5-FU-based regimens • With available DNA sample • Excluded: Carriers or unknown status for *DPYD**2A, c.2846A>T, and *DPYD**13	*DPYD* carriers Wild-type	Dose adjustment according to study guidelines (age and presence of toxicity, *KRAS* carrier status, cetuximab)	Grade ≥ 3 toxicity (NCI-CTCAE v3)
Froehlich et al, 2015[57] N = 500 Switzerland	Retrospective patient selection from database Unclear if genotyping was prospective or retrospective 2006–2013	*DPYD**2A *DPYD**13 c.2846A>T c.1236G>A	• Different cancer types • 5-FU- or capecitabine-based regimens	*DPYD* carriers Wild-type	Dose reduction related to toxicity (grade ≥ 2) after 1st or 2nd cycles	Toxicity (NCI-CTCAE v3.0) Treatment modification
Toffoli et al, 2015[9] N = 603 Italy	Retrospective patient selection from database Genotyping on previously collected sample 2006–2013	*DPYD**2A *DPYD**13 c.2846A>T	• Solid tumours • Fluoropyrimidine-based regimens (≥ 3 cycles unless interrupted due to toxicity)	*DPYD* carriers Wild-type	Some patients had dose adjustment because of toxicity	Grade ≥ 3 toxicity Sensitivity, specificity, PPV, NPV for severe toxicity Treatment modification

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Dose Adjustments	Outcomes
Lee et al, 2014[58] N = 2,594 United States	Based on patients included in RCT Genotyping on previously collected blood sample Period NR	*DPYD**2A *DPYD**13 c.2846A>T	• Resected stage III colon cancer • 5-FU-based regimen, within 10 wk of surgery • Only *KRAS* wild-type patients included	*DPYD* carriers Wild-type	Dose reduction in some patients because of toxicity, according to study guidelines	Grade ≥ 3 toxicity (NCI-CTCAE v3) Sensitivity, specificity, PPV, NPV Treatment modification
Jennings et al, 2013[59] N = 254 United Kingdom	Retrospective patient selection from database Genotyping after start of treatment (email communication with author) 2008–2011	*DPYD**2A *DPYD**13 c.2846A>T c.1236G>A	• Colorectal cancer • 5-FU or capecitabine alone or in combination as adjuvant, neoadjuvant, or palliative • WHO performance status 0–2	*DPYD* carriers Wild-type	Dose modification and treatment withdrawal allowed as standard hospital protocol; not based on genotyping (email communication with author)	Grade ≥ 3 toxicity (NCI-CTCAE v4.0) Delays and dose reductions due to adverse events
Loganayagam et al, 2013[60] N = 430 United Kingdom	Retrospective patient selection from database Unclear if prospective or retrospective genotyping Period NR	*DPYD**2A *DPYD**13 c.2846A>T	• Different cancer types • Fluoropyrimidine-based regimens • WHO performance status < 2	*DPYD* carriers Wild-type	Dose reduction allowed before start of treatment because of comorbidities and after start of treatment because of toxicity	Grade ≥ 3 toxicity (NCI-CTCAE) Sensitivity, specificity, PPV, NPV Treatment modification Hospitalization
Cellier et al, 2011[62] N = 85 France	Based on patients included in study Prospective testing 2002–2004	*DPYD**2A *DPYD**13 c.2846A>T	• Locally advanced rectal cancer • Tegafur-uracil + leucovorin + radiotherapy • WHO performance status 0–2	*DPYD* carriers and phenotype test Wild-type and phenotype test	Dose reduction or interruption not based on test results but on toxicity (grade 2–4) Careful monitoring of diarrhea and neutropenia if DPD deficiency identified; both clinician and patient informed of the risk, but no dose change	Toxicity (WHO criteria for chemotherapy and early radiotherapy)

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Dose Adjustments	Outcomes
Deenen et al, 2011[61] N = 568 Netherlands	Based on patients included in RCT Genotyping after treatment started Period NR	*DPYD**2A *DPYD**13 c.2846A>T c.1236G>A	• Metastatic colorectal cancer • Capecitabine-based regimens	*DPYD* carriers Wild-type	Dose modifications allowed because of toxicity	Capecitabine-related grade ≥ 3 toxicity (NCI-CTCAE v3) Treatment modifications
Cerić et al, 2010[63] N = 50 Bosnia-Herzegovina	Data prospectively collected Genotyping performed after treatment started 2006–2007	*DPYD**2A	• Different cancer types • Fluoropyrimidine-based regimens	*DPYD* carriers Wild-type	NR	Grade 3–4 toxicity (NCI-CTCAE)
Braun et al, 2009[64] N = 1,181 United Kingdom	Based on patients included in RCT Blood sample collection for RCT 2000–2003	*DPYD**2A	• Metastatic colorectal cancer • 5-FU alone or in combination	*DPYD* carriers Wild-type	Ongoing grade ≥ 2 toxicity at start of cycle: 1 wk treatment delay Grade ≥ 3 toxicity or 2 delays after grade 2 toxicity: 20% dose reduction (all drugs)	Grade ≥ 3 toxicity (NCI-CTCAE v2.0) Delay and/or dose reduction because of toxicity
Schwab et al, 2008[65] N = 683 Germany	Data prospectively collected Blood samples collected before treatment Period NR	*DPYD**2A	• Colon, other GI, breast, or cancer of unknown primary • 5-FU alone or in combination with folinic acid or levamisole	*DPYD* carriers Wild-type	NR	5-FU-related toxicity (WHO criteria) Sensitivity, specificity, PPV, NPV for severe toxicity
Sulzyc-Bielicka et al, 2008[66] N = 252 Poland	Data prospectively collected Unclear if prospective or retrospective genotyping 1998–2005	*DPYD**2A	• Colorectal cancer	*DPYD* carriers Wild-type	NR	Toxicity (NCI-CTCAE v2.0)

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Dose Adjustments	Outcomes
Boisdron-Celle et al, 2007[67] N = 252 France	Data prospectively collected Blood samples collected before treatment; genotyping results not provided to treating physician Period NR	*DPYD**2A c.2846A>T	• Advanced colorectal carcinomas or in adjuvant setting • 5-FU–leucovorin • WHO performance status < 2 • Age < 80 y	*DPYD* carriers Wild-type	No pre-treatment dose adjustment Dose adjustment allowed starting at 2nd cycle based on 5-FU plasma concentration in previous cycle	Grade ≥ 3 toxicity Treatment modifications based on toxicity and 5-FU levels
Largillier et al, 2006[68] N = 105 France	Data prospectively collected Unclear if prospective or retrospective genotyping 2003–2004	*DPYD**2A	• Advanced breast cancer • Capecitabine alone	*DPYD* carriers Wild-type	Dose reduction at 2nd and 3rd cycle in some patients	Grade 3–4 toxicity (NCI-CTCAE)
Salgueiro et al, 2004[69] N = 73 Portugal	Data prospectively collected Unclear if prospective or retrospective genotyping Period NR	*DPYD**2A	• Colorectal cancer • Adjuvant 5-FU-based chemotherapy	*DPYD* carriers Wild-type	NR	Grade ≥ 3 toxicity (NCI-CTCAE)

Abbreviations: 5-FU, 5-fluorouracil; DPD, dihydropyrimidine; GI, gastrointestinal; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; RCT, randomized controlled trial; WHO, World Health Organization.

Table A2: Characteristics of Included Studies: Clinical Utility

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Outcomes
Wigle et al, 2021[71] N = 1,394 Canada	Pre-treatment genotyping Patients identified prospectively 2013–2019	*DPYD**2A c.2846A>T *DPYD**13 c.1236G>A	• Planned fluoropyrimidine-based regimen, alone or in combination with other drugs or radiotherapy • Different cancer types	*Intervention* • Heterozygous *DPYD**2A, DPYD*13, and c.2846A>T carriers: 50% dose reduction before start of treatment • Heterozygous c.1236G>A: 25% to 50% initial dose reduction before start of treatment • Dose increase allowed after 2 cycles based on tolerance for heterozygous carriers • Homozygous or compound heterozygous carriers: avoidance of fluoropyrimidines *Control* • Wild-type • Fluoropyrimidine dose as per standard of care	Grade ≥ 3 toxicity (NCI-CTCAE v5.0) Treatment discontinuation Treatment-related mortality
Henricks et al, 2019[11] N = 1,732 Netherlands	Pre-treatment genotyping Patients identified prospectively and retrospectively 2007–2015	*DPYD**2A	• Planned fluoropyrimidine-based regimen, alone or in combination with other drugs or radiotherapy • Different cancer types	*Intervention* • Heterozygous *DPYD**2A carriers: 50% dose reduction before start of treatment • Dose increase allowed after 2 cycles based on tolerance *Control* • Wild-type • Standard fluoropyrimidine dose	Grade ≥ 3 (NCI-CTCAE) Hospitalization for treatment-related toxicity Treatment discontinuation Treatment-related death

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Outcomes
Kleinjan et al, 2019[12] N = 184 Netherlands	Pre-treatment genotyping Patients identified retrospectively through databases of laboratories performing *DPYD* testing and hospital pharmacy database of genotype-guided dose adjustment 2006--2017	*DPYD**2A c.2846A>T *DPYD**13 c.1236G>A	• Capecitabine-based regimens • Receiving ≥ 1 cycle • Different cancer types • Those who underwent *DPYD* genotyping (all patients as part of standard care)	*Intervention* • Heterozygous *DPYD**2A and *DPYD**13 carriers: 50% dose reduction • Heterozygous c.2846A<T and c.1236G>A carriers: 25% dose reduction • After 1–2 cycles dose could be further reduced, maintained, or increased (by 15%, up to standard dose) based on capecitabine-related toxicity • Treatment stopped in case of disease progression; outcomes of subsequent treatment NR *Control* • Wild-type • Treated according to standard practice; dose reductions allowed according to age and comorbidities • Treatment stopped in case of disease progression; outcomes of subsequent treatment NR	Grade ≥ 3 toxicity (NCI-CTCAE v5.0): except for hand–foot syndrome (grade ≥ 2) Treatment-related hospitalizations

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Outcomes
Stavraka et al, 2019[23] N = 66 United Kingdom	Retrospective patient identification Pre-treatment *DPYD* genotyping 2014–2017	*DPYD**2A c.2846A>T *DPYD**13	• Planned capecitabine with or without lapatinib treatment • Consecutive metastatic breast cancer	*Intervention* • *DPYD* carriers • Heterozygous *DPYD**2A carriers: 50% dose reduction • Heterozygous c.2846A<T carriers: 25% dose reduction • Subsequent dose increase allowed *Control* • Wild-type • Dose modification if needed	Toxicity (NCI-CTCAE v4.0) Toxicity-related hospitalizations Treatment decisions
Henricks et al, 2018[72] N = 1,103 Netherlands	Prospective patient identification Pre-treatment *DPYD* genotyping 2015–2017	*DPYD**2A c.2846A>T *DPYD**13 c.1236G>A	• Planned fluoropyrimidine-based regimen + radiotherapy • Different cancer types • Adults (≥ 18 y old) • WHO performance status 0–2 • Excluded: homozygous and compound heterozygous *DPYD* variant carriers	*Intervention* • Heterozygous *DPYD**2A and *DPYD**13 carriers: 50% dose reduction • Heterozygous c.2846A<T and c.1236G>A carriers: 25% dose reduction • Dose increase allowed after 1st 2 cycles if treatment well tolerated at physician's discretion *Control* • Wild-type • Dose reduction and increase allowed at physician's discretion	Grade ≥ 3 toxicity (NCI-CTCAE v4.03) Treatment-related hospitalization Treatment discontinuation

Author, Year N Country	Study Design Methods Study Period	Variants Evaluated	Participants	Intervention Control	Outcomes
Lunenburg et al, 2018[7] Netherlands N = 828	Patients originated from 3 different cohorts Genotyping prospectively and retrospectively depending on variant and cohort 1993–2017 depending on database	*DPYD**2A c.2846A>T *DPYD**13 c.1236G>A	• Planned fluoropyrimidine-based chemoradiation therapy • Different cancer types	*Intervention* • *DPYD* carriers on pre-treatment testing • Dose reduction 25% or 50% (≥ 50% for some *DPYD**2A carriers) • Dose increase permitted *Control* • *DPYD* variant carriers (retrospective testing) • Wild-type • Standard fluoropyrimidine chemoradiation dose used • Dose reduction and increase allowed at treating physician's discretion	Toxicity (NCI-CTCAE grade ≥ 3) Dose reductions and increases Treatment delay and discontinuation Treatment-related hospitalizations Length of stay

Abbreviations: DPD, dihydropyrimidine; NCI-CTCAE; National Cancer Institute Common Terminology Criteria for Adverse Events; NR = not reported; PK = pharmacokinetic; WHO, World Health Organization.

Appendix 3: Critical Appraisal of Clinical Evidence

Table A3: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

	Phase 2				Phase 3
Author, Year	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal[b]	Synthesis and Findings[b]	Risk of Bias in the Review[c]
INESSS, 2019[32]	Low	Low	NA	NA	Low
HAS, 2018[10]	Low	Low	NA	NA	Low
Campbell et al, 2016[46]	Low	Low	NA	NA	Low
Meulendijks et al, 2015[47]	Low[d]	Low[e]	NA	NA	Low
Li et al, 2014[48]	Low[d]	Low[e]	NA	NA	Low
Terrazzino et al, 2013[49]	Low[d]	Low[e]	NA	NA	Low
Technology Evaluation Center, 2010[50]	Low[d]	Low[e]	NA	NA	Low

Abbreviations: HAS, Haute Autorité de Santé; INESS, Institut National de d'Excellence en Santé et en Services Sociaux; NA, not applicable; ROBIS, Risk of Bias in Systematic Reviews.

[a]Possible risk-of-bias levels: low, high, unclear.

[b]We used only domains 1 and 2 (study eligibility criteria and identification and selection of studies) of the tool because we were using the selected systematic reviews to generate a list of included studies (i.e., the results synthesis and conclusions sections were not used).

[c]Based on the domains assessed.

[d]Did not search the grey literature, but this may not necessarily have affected the risk of bias; for this reason, the risk of bias for this domain was considered low.

[e]Lack of a double reviewer could have led to missing relevant studies, but we could not determine whether this occurred; this did not warrant increasing the risk of bias.

Table A4: Risk of Bias[a] Among Cohort Studies

Author, Year	Selection				Comparability	Outcome		
	Representative-ness of the Exposed Cohort	Selection of the Non-exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts (Design or Analysis)	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow-up of Cohorts
Clinical Validity								
Wigle et al, 2021[71]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Iachetta et al, 2019[52]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Maharjan et al, 2019[53]	C[c]	A (*)	A (*)	B	Not controlled[b]	B (*)	A (*)	A (*)
Cremolini et al, 2018[55]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Lunenburg et al, 2018[7]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	B(*)[d]	A (*)	A (*)
Nahid et al, 2018[54]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Etienne-Grimaldi et al, 2017[56]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Meulendijks et al, 2017[18]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Meulendijks et al, 2017[70]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Boige et al, 2016[15]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Lee et al, 2016[13]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Froehlich et al, 2015[57]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Toffoli et al, 2015[9]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Lee et al, 2014[58]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Jennings et al, 2013[59]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Loganayagam et al, 2013[60]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Cellier et al, 2011[62]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Deenen et al, 2011[61]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Cerić et al, 2010[63]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Braun et al, 2009[64]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Schwab et al, 2008[65]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)

Author, Year	Selection				Comparability	Outcome		
Sulzyc-Bielicka et al, 2008[66]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Boisdron-Celle et al, 2007[67]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Largillier et al, 2006[68]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Salgueiro et al, 2004[69]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Clinical Utility								
Wigle et al, 2021[71]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Henricks et al, 2019[11]	A (*)	A (*) or B	A (*)	A (*)	Not controlled[b]	B (*)	A (*)	A (*)
Kleinjan et al, 2019[12]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	B (*)	A (*)	A (*)
Stavraka et al, 2019[23]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	B (*)	A (*)	A (*)
Henricks et al, 2018[72]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	A (*)	A (*)	A (*)
Lunenburg et al, 2018[7]	A (*)	A (*)	A (*)	A (*)	Not controlled[b]	B (*)	A (*)	A (*)

[a]Risk of bias assessed using the Newcastle-Ottawa Scale.[44] The ratings range from A to B, A to C, or A to D depending on the parameter and the level of quality for each parameter; A is the highest level of quality. The scale then uses a "star system" to rate each domain overall. For the selection and outcome domains, a star (*) is given if the rating is either A or A/B, depending on the parameter. For the comparability domain, a star may be given depending on the degree of control for confounders.[44]

[b]Analysis comparing the frequency of toxicity in carriers vs. wild-type patients was not controlled for potential confounders.

[c]Decision to genotype was at the investigator's discretion and may have been associated with the risk of developing toxicity.

[d]Some differences in types of toxicity collected from each of the three databases included.

Table A5: GRADE Evidence Profile for the Comparison of *DPYD* Variant Carriers Who Received a Standard Fluoropyrimidine Dose and Wild-Type Patients (Severe Toxicity)

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Overall Severe Toxicity, Carriers of One of the *DPYD* Variants Under Assessment							
7 (observational)[7,9,57-60,62]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Neutropenia, Carriers of One of the *DPYD* Variants Under Assessment							
2 (observational)[7,9]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Diarrhea, Carriers of One of the *DPYD* Variants Under Assessment							
2 (observational)[7,9]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Hand–Foot Syndrome, Carriers of One of the *DPYD* Variants Under Assessment							
1 (observational)[7]	No serious limitations	Could not be evaluated	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Overall Severe Toxicity, *DPYD2A Carriers**							
17 (observational)[9,15,54-65,67-69]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations[c]	Undetected	NA	⨁⨁ Low
Severe Neutropenia, *DPYD2A Carriers**							
9 (observational)[9,15,53-55,58,63,68,69]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations[c]	Undetected	NA	⨁⨁ Low
Severe Diarrhea, *DPYD2A Carriers**							
11 (observational)[9,15,53-55,58,61,63,65,68,69]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations[c]	Undetected	NA	⨁⨁ Low
Severe Hand–Foot Syndrome, *DPYD2A Carriers**							
3 (observational)[61,62,68]	No serious limitations	Serious limitations (−1)[d]	No serious limitations	No serious limitations[c]	Undetected	NA	⨁ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Overall Severe Toxicity, *DPYD13 Carriers**							
7 (observational)[9,15,52,57,58,60,62]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Neutropenia, *DPYD13 Carriers**							
2 (observational)[9,15]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Severe Diarrhea, *DPYD13 Carriers**							
3 (observational)[9,15,62]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Overall Severe Toxicity, c.2846A>T Carriers							
13 (observational)[9,15,52,55-62,67,70]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations[c]	Undetected	NA	⨁⨁ Low
Severe Neutropenia, c.2846A>T Carriers							
5 (observational)[9,15,53,55,58]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations[c]	Undetected	NA	⨁⨁ Low
Severe Diarrhea, c.2846A>T Carriers							
6 (observational)[9,15,53,55,58,61]	No serious limitations	No serious limitations[b]	No serious limitations	No serious limitations[c]	Undetected	NA	⨁⨁ Low
Severe Hand–Foot Syndrome, c.2846A>T Carriers							
1 (observational)[61]	No serious limitations	Could not be evaluated	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Overall Severe Toxicity, c.1236G>A Carriers, Heterozygous							
6 (observational)[13,57,59,61,70,71]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[e]	Undetected	NA	⨁ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Overall Severe Toxicity, c.1236G>A Carriers, Homozygous							
2 (observational)[13,57]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Neutropenia, c.1236G>A Carriers, Heterozygous							
1 (observational)[13]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Diarrhea, c.1236G>A Carriers, Heterozygous							
2 (observational)[13,61]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Nausea and/or Vomiting, c.1236G>A Carriers, Homozygous							
1 (observational)[13]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Hand–Foot Syndrome, c.1236G>A Carriers, Heterozygous							
2 (observational)[13,71]	No serious limitations	Could not be evaluated	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Overall Severe Toxicity, Compound Heterozygous							
4 (observational)[9,57,58,67]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Severe Diarrhea, Compound Heterozygous							
1 (observational)[9]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.

[a]Insufficient statistical power to detect a difference between groups.

[b]Decision not to downgrade based on the consistency in the direction of effect. Despite the range of point estimates obtained from the studies, they were consistent in their direction of effect and the variation in magnitude observed would not have affected the overall conclusion.

[c]Not downgraded because in most studies the 95% confidence interval excluded the possibility of no effect or lower risk in carriers vs. wild-type patients.

[d]Substantial inconsistency in the direction of effect among studies.

[e]Insufficient statistical power to detect a difference between groups in most studies.

Table A6: GRADE Evidence Profile for the Comparison of *DPYD* Variant Carriers Who Received a Standard Fluoropyrimidine Dose and Wild-Type Patients (Toxicity-Related Dose Reduction, Treatment Discontinuation, Hospitalization, and Mortality)

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Toxicity-Related Dose Reduction, Carriers of One of the *DPYD* Variants Under Assessment							
1 (observational)[60]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Toxicity-Related Dose Reduction, *DPYD2A Carriers**							
2 (observational)[58,60]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Toxicity-Related Dose Reduction, *DPYD13 Carriers**							
2 (observational)[58,60]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Toxicity-Related Dose Reduction, c.2846A>T Carriers							
2 (observational)[58,60]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Treatment Discontinuation, Carriers of One of the *DPYD* Variants Under Assessment							
1 (observational)[60]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Treatment Discontinuation, *DPYD2A Carriers**							
3 (observational)[58,60,68]	No serious limitations	No serious limitations	No serious limitations	No serious limitations[b]	Undetected	NA	⨁⨁ Low
Treatment Discontinuation, *DPYD13 Carriers**							
2 (observational)[58,60]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Treatment Discontinuation, c.2846A>T Carriers							
2 (observational)[58,60]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Treatment Discontinuation, c.1236G>A Carriers							
1 (observational)[71]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Hospitalization, Carriers of One of the *DPYD* Variants Under Assessment							
3 (observational)[7,60,67]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Hospitalization, Compound Heterozygous							
1 (observational)[67]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Mortality, Carriers of One of the *DPYD* Variants Under Assessment							
2 (observational)[63,68]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low
Mortality, Compound Heterozygous							
1 (observational)[67]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.

[a]Insufficient statistical power to detect a difference between groups.

[b]Not downgraded because in most studies the 95% confidence interval excluded the possibility of no effect or lower risk in carriers vs. wild-type patients.

Table A7: GRADE Evidence Profile for the Comparison of *DPYD* Variant Carriers Who Received a Genotype-Guided Reduced Fluoropyrimidine Dose and Wild-Type Patients or *DPYD* Variant Carriers who Received a Standard Dose (Severe Toxicity, Treatment Discontinuation, and Hospitalization)

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Overall Severe Toxicity, *DPYD* Variants Under Assessment vs. Wild-Type Patients							
6 (observational)[7,11,12,23,71,72]	No serious limitations	No serious limitations[a]	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Overall Severe Toxicity, *DPYD* Variants Under Assessment vs. *DPYD* Carriers Who Received a Standard Fluoropyrimidine Dose							
1 (observational)[7]	Serious limitations (−1)[c]	Could not be evaluated	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Severe Hematological Toxicity, *DPYD* Variants Under Assessment vs. Wild-Type Patients							
6 (observational)[7,11,12,23,71,72]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Severe Hematological Toxicity, *DPYD* Variants Under Assessment vs. *DPYD* Carriers Who Received a Standard Fluoropyrimidine Dose							
1 (observational)[7]	Serious limitations (−1)[c]	Could not be evaluated	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Severe Gastrointestinal Toxicity, *DPYD* Variants Under Assessment vs. Wild-Type Patients							
6 (observational)[7,11,12,23,71,72]	No serious limitations	No serious limitations[a]	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Severe Gastrointestinal Toxicity, *DPYD* Variants Under Assessment vs. *DPYD* Carriers Who Received a Standard Fluoropyrimidine Dose							
1 (observational)[7]	Serious limitations (−1)[c]	Could not be evaluated	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Severe Hand–Foot Syndrome, *DPYD* Variants Under Assessment vs. Wild-Type Patients							
6 (observational)[7,11,12,23,71,72]	No serious limitations	No serious limitations[a]	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Treatment Discontinuation, *DPYD* Variants Under Assessment vs. Wild-Type Patients							
5 (observational)[7,11,23,71,72]	No serious limitations	No serious limitations[a]	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Hospitalization, *DPYD* Variants Under Assessment vs. Wild-Type Patients							
5 (observational)[7,11,12,23,72]	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low
Hospitalization, *DPYD* Variants Under Assessment vs. *DPYD* Carriers Who Received a Standard Fluoropyrimidine Dose							
1 (observational)[7]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	NA	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.

[a]Some inconsistency in the direction of point estimates; however, given the wide confidence intervals, this was considered to be due to imprecision. As a result, we downgraded the evidence for this outcome.

[b]Insufficient statistical power to detect a difference between groups.

[c]Downgraded because of the imbalance in the distribution of *DPYD* variants between the reduced-dose carrier and standard-dose carrier groups; the two variants that were expected to have a weaker effect on dihydropyrimidine (DPD) activity were overrepresented in the latter group. This may have led to an underestimate in the frequency of severe toxicity in the standard-dose group and an underestimate in the difference between groups.

Table A8: GRADE Evidence Profile for the Comparison of *DPYD* Variant Carriers Who Received a Genotype-Guided Reduced Fluoropyrimidine Dose and Wild-Type Patients (Survival)

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Overall Survival, *DPYD2A Carriers**							
1 (observational)[11]	No serious limitations	Could not be evaluated	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low
Progression-Free Survival, *DPYD2A Carriers**							
1 (observational)[11]	No serious limitations	Could not be evaluated	No serious limitations	Serious limitations (−1)[a]	Undetected	NA	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.

[a]Insufficient statistical power to detect a difference between groups.

Appendix 4: Clinical Evidence Review—Patient Characteristics

Table A9: Characteristics of Patients Included in Clinical Validity Studies

Author, Year N (Carrier/Wild-Type)	Age, y	Male, n (%)	Race/Ethnicity, n (%)	Type of Cancer, n (%)	Treatment Regimen, n (%)
Wigle et al, 2021[71] 1,388 (41/1,347)	*Mean ± SD* Carriers: 66 ± 10 Wild-type: 64 ± 12	Carriers: 28 (68.3) Wild-type: 742 (55.1)	*White* Carriers: 40 (97.6) Wild-type: 1,267 (94.1) *Other* Carriers: 1 (2.4) Wild-type: 32 (2.4) *Unknown* Carriers: 0 Wild-type: 48 (3.6)	*Colorectal* Carriers: 21 (51.2) Wild-type: 779 (57.8) *Breast* Carriers: 1 (2.4) Wild-type: 89 (6.6) *Gastroesophageal* Carriers: 5 (12.2) Wild-type: 189 (14.0) *Pancreas* Carriers: 2 (4.9) Wild-type: 106 (7.9) *Other* Carriers: 12 (29.3) Wild-type: 184 (13.7)	*5-FU* Carriers: 19 (46.3) Wild-type: 643 (47.7) *Capecitabine* Carriers: 22 (53.7) Wild-type: 704 (52.3) *Patients treated with capecitabine who also received radiotherapy* Carriers: 11 (26.8) Wild-type: 277 (20.6)
Iachetta et al, 2019[52] 366 (2/364)	*Median (range)* Carriers: 67 (32–84) Wild-type: 65 (22–88)	Carriers: 68 (46) Wild-type: 125 (57)	NR	*Colorectal* Carriers: 66 (45.2) Wild-type: 118 (53.6) *Breast* Carriers: 4 (3) Wild-type: 9 (4) *Gastroesophageal* Carriers: 61 (41.8) Wild-type: 74 (33.6) *Other* Carriers: 15 (10.3) Wild-type: 19 (8.6)	Both 5-FU or capecitabine used; detailed information not provided
Maharjan et al, 2019[53] 113 (5/108)	*Median (range)* 59 (21–90)	62 (54.9)	Caucasian: 75 (66.4) African American: 35 (31.0) Other: 3 (2.6)	Colorectal: 79 (69.9) Breast: 0 Gastric: 23 (20.4) Other: 11 (9.7)	5-FU: 79 (69.9) Capecitabine: 34 (30.1)

Author, Year N (Carrier/Wild-Type)	Age, y	Male, n (%)	Race/Ethnicity, n (%)	Type of Cancer, n (%)	Treatment Regimen, n (%)
Cremolini et al, 2018[55] 443 (10/433)	*Median (range)* 61 (29–75)	235 (53.0)	NR	Colorectal: 443 (100.0)	5-FU: 443 (100.0)
Lunenburg et al, 2018[7] 805 (34/771)	*Median (range)* Carriers: 64 (45–79) Wild-type: 63 (23–88)	Carriers: 20 (58.8) Wild-type: 432 (56.0)	NR	*Colorectal* Carriers: 22 (64.7) Wild-type: 554 (71.9) *Gastrointestinal* Carriers: 12 (35.3) Wild-type: 169 (21.9) *Other* Carriers: 0 (0.0) Wild-type: 48 (6.3)	*5-FU* Carriers: 5 (14.7) Wild-type: 103 (13.4) *Capecitabine* Carriers: 29 (85.3) Wild-type: 668 (86.6) Number of patients with concomitant radiotherapy not provided
Nahid et al, 2018[54] 161 (8/153)	*Median (range)* 47 (25–75)	97 (60.2)	NR	Colorectal: 161 (100.0)	5-FU: 161 (100.0)
Etienne-Grimaldi et al, 2017[56] 243 (6/237)	*Mean (range)* 61.2 (30–88)	0 (0.0)	NR	Breast: 243 (100.0)	Capecitabine: 243 (100.0)
Meulendijks et al, 2017[18] 550 (30/520)	*Median (range)* 61 (30–88)	232 (42.2)	Caucasian: 521 (94.7) Other: 29 (5.3)	Colorectal: 190 (34.5) Breast: 175 (31.8) Gastric: 126 (22.9) Other: 59 (10.7)	5-FU: 70 (12.7) Capecitabine: 480 (87.3)
Meulendijks et al, 2017[70] 185 (5/180)	*Mean (range)* 59 (22–77)	135 (73.0)	NR	Advanced gastric: 185 (100.0)	Capecitabine: 185 (100.0)
Boige et al, 2016[15] 1,545 (36/1,509)	*Median (range)* 60 (19–75)	1,135 (73.5)	NR	Colon: 1,545 (100.0)	5-FU: 1,545 (100.0)
Lee et al, 2016[13] 1,953 (78/1,875)	*Mean ± SD* 57 ± 11	1,069 (54.7)	Caucasian: 1,953 (100.0)	Colon: 1,953 (100.0)	5-FU: 1,953 (100.0)

Author, Year N (Carrier/Wild-Type)	Age, y	Male, n (%)	Race/Ethnicity, n (%)	Type of Cancer, n (%)	Treatment Regimen, n (%)
Froehlich et al, 2015[57] 500 (32/468)	*n (%)* 18–49 y: 47 (12.1) 50–69 y: 260 (66.8) > 69 y: 82 (21.1)	230 (59.1)	Caucasian: 493 (98.6)	Colorectal: 275 (55.0) Esophageal: 97 (19.4) Breast: 26 (5.2) Gastric: 46 (9.2) Head and neck: 31 (6.2) Other: 25: (5.0)	5-FU: 397 (79.4) Capecitabine: 103 (20.6)
Toffoli et al, 2015[9] 603 (18/585)	*Median (range)* 62 (17–99)	310 (51.4)	Caucasian: 603 (100.0)	NR	5-FU: 546 (90.5) Capecitabine: 55 (9.1) Other: 2 (0.4)
Lee et al, 2014[58] 2,594 (62/2,532)	*Median (range)* 58 (19–86)	1,385 (53.4)	Caucasian: 2,248 (87.8) Black/African American: 170 (6.6) Asian: 121 (4.7) Other: 22 (0.9) Missing: 33 (12.7)	Colon: 2,619 (100.0)	5-FU: 2,619 (100.0)
Jennings et al, 2013[59] 253 (15/238)	*Median (range)* 67 (23–88)	145 (57.3)	NR	Colorectal: 253 (100.0)	5-FU: 94 (37.1) Capecitabine: 159 (62.9)
Loganayagam et al, 2013[60] 430 (10/420)	*Mean (range)* 62 (20–83)	247 (57.4)	Caucasian: 364 (84.7) Afro-Caribbean: 50 (11.6) South Asian: 12 (2.8) Southeast Asian: 4 (0.9)	Colorectal: 364 (84.7) Gastrointestinal: 62 (14.4) Other: 4 (0.9)	5-FU: 186 (43.3) Capecitabine: 244 (56.7)
Cellier et al, 2011[62] 85 (3/82)	*Median (range)* 67 (25–81)	56 (65.9)	NR	Rectal: 85 (100.0)	5-FU + radiotherapy: 85 (100.0)
Deenen et al, 2011[61] 568 (44/524)	*Median (range)* 63 (31–83)	345 (60.7)	Mostly Caucasian as reported by the authors, but figures not provided	Colorectal: 568 (100.0)	Capecitabine: 568 (100.0)
Cerić et al, 2010[63] 50 (1/49)	NR	27 (54.0)	NR	Colorectal: 41 (82.0) Breast: 3 (6.0) Gastric: 3 (6.0) Other: 3 (6.0)	5-FU: 42 (84.0) Capecitabine: 8 (16.0)
Braun et al, 2009[64] 750 (7/743)	*Median (range)* 64 (27–85)	803 (68.0)	NR	Colorectal: 750 (100.0)	5-FU: 750 (100.0)

Author, Year N (Carrier/Wild-Type)	Age, y	Male, n (%)	Race/Ethnicity, n (%)	Type of Cancer, n (%)	Treatment Regimen, n (%)
Schwab et al, 2008[65] 683 (13/670)	NR	383 (56.1)	NR	Colon: 470 (68.8) Breast: 32 (4.7) Gastric: 66 (9.7) Other: 28 (4.1) Unclear: 87 (12.7)	5-FU: 683 (100.0)
Sulzyc-Bielicka et al, 2008[66] 252 (1/251)	62 (SD NR)	146 (57.9)	NR	Colorectal: 252 (100.0)	5-FU: 252 (100.0)
Boisdron-Celle et al, 2007[67] 252 (10/242)	*Mean ± SD* 67 ± 11	140 (56)	Caucasian: 252 (100.0)	Colorectal: 252 (100.0)	5-FU: 252 (100.0)
Largillier et al, 2006[68] 105 (1/104)	*Mean (range)* 61 (33–84)	0	NR	Breast: 105 (100.0)	Capecitabine: 105 (100.0)
Salgueiro et al, 2004[69] 73 (1/72)	*Mean (range)* 59 (31–85)	34 (46.6)	NR	Colorectal: 73 (100.0)	5-FU: 73 (100.0)

Abbreviations: 5-FU, 5-fluorouracil; NR = not reported; SD, standard deviation.

Table A10: Characteristics of Patients Included in Clinical Utility Studies

Author, Year N (Carriers/Wild-Type)	Age, y	Male, n (%)	Race/Ethnicity, n (%)	Type of Cancer, n (%)	Treatment Regimens, n (%)
Wigle et al, 2021[71] 1,394 (47/1,347)	*Mean ± SD* Carriers: 62 ± 13 Wild-type: 64 ± 12	Carriers: 22 (46.8) Wild-type: 742 (55.1)	*White* Carriers: 45 (95.7) Wild-type: 1,267 (94.1) *Other* Carriers: 1 (2.1) Wild-type: 32 (2.4) *Unknown* Carriers: 1 (2.1) Wild-type: 48 (3.6)	*Colorectal* Carriers: 21 (51.2) Wild-type: 779 (57.8) *Breast* Carriers: 1 (2.4) Wild-type: 89 (6.6) *Gastroesophageal* Carriers: 5 (13.4) Wild-type: 189 (14.0) *Pancreas* Carriers: 2 (4.9) Wild-type: 106 (7.9) *Other* Carriers: 12 (29.3) Wild-type: 184 (13.7)	*5-FU* Carriers: 24 (51.1) Wild-type: 643 (47.7) *Capecitabine* Carriers: 23 (48.9) Wild-type: 704 (52.3) *Patients treated with capecitabine who also received radiotherapy* Carriers: 11 (23.4) Wild-type: 277 (20.6)
Henricks et al, 2019[11] 1,646 (40/1,606)	*Median (range)* Carriers: 62 (34–91) Wild-type: 61 (21–89)	Carriers: 14 (35) Wild-type: 720 (45)	*Caucasian* Carriers: 39 (98) Wild-type: 1,540 (96) *Southeast Asian* Carriers: 1 (2.5) Wild-type: 14 (0.9) *African* Carriers: 0 (0.0) Wild-type: 21 (1.3) *Other* Carriers: 0 (0.0) Wild-type: 31 (1.9)	*Colorectal* Carriers: 13 (32.5) Wild-type: 854 (53.2) *Breast* Carriers: 15 (37.5) Wild-type: 369 (23.0) *Gastric* Carriers: 2 (5.0) Wild-type: 227 (14.1) *Other* Carriers: 10 (25.0) Wild-type: 156 (14.1)	*5-FU* Carriers: 2 (5.0) Wild-type: 168 (10.5) *Capecitabine* Carriers: 38 (95.0) Wild-type: 1,438 (89.5) *Patients treated with either 5-FU or capecitabine who also received radiotherapy* Carriers: 12 (30.0) Wild-type: 490 (30.5)

Author, Year N (Carriers/Wild-Type)	Age, y	Male, n (%)	Race/Ethnicity, n (%)	Type of Cancer, n (%)	Treatment Regimens, n (%)
Kleinjan et al, 2019[12] 185 (11/174)	*Median (range)* Carriers: 65 (36–77) Wild-type: 67 (32–85)	Carriers: 5 (45.5) Wild-type: 92 (52.9)	*White* Carriers: 11 (100) Wild-type: 171 (98.3) *Other* Carriers: 0 Wild-type: 3 (1.7)	*Colorectal* Carriers: 8 (72.7) Wild-type: 134 (77.0) *Breast* Carriers: 1 (9.1) Wild-type: 21 (12.1) *Other* Carriers: 2 (18.2) Wild-type: 19 (10.9)	Capecitabine: 185 (100.0)
Stavraka et al, 2019[23] 63 (2/61)	*Median (range)* 58 (28–85)	2 (3.0)	NR	Metastatic: 63 (100.0)	Capecitabine: 63 (100.0)
Henricks et al, 2018[72] 1,103 (85/1,018)	*Median (range)* Carriers: 63 (54–71) Wild-type: 64 (56–71)	Carriers: 48 (52.9) Wild-type: 545 (53.5)	*White* Carriers: 84 (98.8) Wild-type: 964 (94.7) *Black* Carriers: 0 (0.0) Wild-type: 19 (1.9) *Asian* Carriers: 1 (1.2) Wild-type: 23 (2.3) *Other* Carriers: 0 (0.0) Wild-type: 12 (1.2)	*Colorectal* Carriers: 56 (65.9) Wild-type: 648 (63.7) *Breast* Carriers: 10 (11.8%) Wild-type: 131 (12.9%) *Gastric* Carriers: 6 (7.1) Wild-type: 57 (5.6%) *Other* Carriers: 13 (15.3) Wild-type: 182 (17.9%)	*5-FU* Carriers: 17 (20.0) Wild-type: 171 (16.8) *Capecitabine* Carriers: 68 (80.0) Wild-type: 847 (83.2) *Patients treated with either 5-FU or capecitabine who also received radiotherapy* Carriers: 24 (28.2) Wild-type: 303 (29.8)

Author, Year N (Carriers/Wild-Type)	Age, y	Male, n (%)	Race/Ethnicity, n (%)	Type of Cancer, n (%)	Treatment Regimens, n (%)
Lunenburg et al, 2018[7] 828 (23/771/34[a])	*Median (range)* Carriers: 66 (50–78) Carriers[a]: 64 (45–79) Wild-type: 63 (23–88)	Carriers: 13 (56.5) Carriers[a]: 20 (58.8) Wild-type: 432 (56.0)	NR	*Colorectal* Carriers: 18 (78.3) Carriers[a]: 22 (64.7) Wild-type: 554 (71.9) *Gastrointestinal* Carriers: 4 (17.3) Carriers[a]: 12 (35.3) Wild-type: 169 (21.9) *Other* Carriers: 1 (4.3) Carriers[a]: 0 (0.0) Wild-type: 48 (6.3)	*5-FU* Carriers: 3 (13.0) Carriers[a]: 5 (14.7) Wild-type: 103 (13.4) *Capecitabine* Carriers: 20 (87.0) Carriers[a]: 29 (85.3) Wild-type: 668 (86.6) *Radiotherapy* All patients received radiotherapy

Abbreviations: 5-FU, 5-fluorouracil; NR = not reported; SD, standard deviation.

[a]*DPYD* carriers who received a standard dose.

Appendix 5: Clinical Evidence Review—Study Results

Table A11: Prevalence of *DPYD* Variants (Results for Heterozygous Carriers Unless Otherwise Specified)

Author, Year N	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterozygous, n (%)	Combined (3 variants[a]), n (%)	Combined (4 variants), n (%)
Wigle et al, 2021[71] 1,397	9 (0.6)	1 (0.07)	19 (1.4)	59 (4.2)	2 (0.14) Variants not specified	29 (2.1)	88 (6.3)
Iachetta et al, 2019[52] 366	NA	2 (0.6)	5 (1.4)	NA	NA	NA	NA
Kleinjan et al, 2019[12] 185	4 (2.2)	0	1 (0.5)	6 (3.2)	0	5 (2.7)	11 (5.9)
Maharjan et al, 2019[53] 113	3 (2.7)	0	2 (1.8)	NA	NA	5 (4.4)	NA
Stavraka et al, 2019[23] 66	1 (1.5)	0	2 (3.0)	NA	0	3 (4.5)	NA
Cremolini et al, 2018[55] 443	5 (1.1)	0	5 (1.1)	NA	NA	10 (2.2)	NA
Henricks et al, 2018[72] 1,103	16 (1.5)	1 (0.09)	17 (1.5)	51 (4.6)	NA	33 (3.1)	85 (7.7)
Lunenburg et al, 2018[7] 828	13 (1.6)	1 (0.1)	10 (1.2)	31 (3.7) Ht 2 (0.2) Hm	NA	24 (2.9)	57 (6.9[72,74])
Nahid et al, 2018[54] 161	8 (5.0)	NA	NA	NA	NA	NA	NA
Etienne-Grimaldi et al, 2017[56] 243	3 (1.2)	1 (0.4)	3 (1.2)	4 (1.6)	0	7 (2.9) Ht	11 (4.5) Ht
Meulendijks et al, 2017[70] 185	NA	NA	5 (2.3)	15 (8.1)	NA	NA	NA
Boige et al, 2016[15] 1,545	11 (0.7)	4 (0.3)	21 (1.4)	NA	NA	36 (2.4)	NA
Lee et al, 2016[13] 1,953	NA	NA	NA	77 (3.9) Ht 1 (0.05) Hm	NA	NA	NA

Author, Year N	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterozygous, n (%)	Combined (3 variants[a]), n (%)	Combined (4 variants), n (%)
Froehlich et al, 2015[57] 500	4 (0.8)	2 (0.4)	3 (0.6)	22 (4.4) Ht 1 (0.2) Hm	*DPYD**13/c.1236G>A 1 (0.2)	9 (1.8)	31 (6.4)
Toffoli et al, 2015[9] 603	11 (1.8)	1 (0.2)	5 (0.8)	NA	*DPYD**2A/*DPYD**13 1 (0.2)	18 (3.0)	NA
Lee et al, 2014[58] 2,886	27 (0.9)	4 (0.1)	32 (1.1)	NA	*DPYD**2A/c.2846A>T 1 (0.03)	64 (2.2)	NA
Jennings et al, 2013[59] 253	3 (1.2)	NA	2 (0.8)	10 (3.9)	NA	NA	NA
Loganayagam et al, 2013[60] 430	4 (0.9)	1 (0.2)	5 (1.1)	NA	0	10 (2.2)	NA
Cellier et al, 2011[62] 85	1 (1.2)	1 (1.2)	1 (1.2)	NA	NA	3 (3.5)	NA
Deenen et al, 2011[61] 568	7 (1.2)	0	8 (1.4)	27 (4.8) Ht 1 (0.2) Hm	NA	NA	42 (7.4)
Cerić et al, 2010[63] 50	1 (2.0)	NA	NA	NA	NA	NA	NA
Braun et al, 2009[64] 750	7 (0.9)	NA	NA	NA	NA	NA	NA
Schwab et al, 2008[65] 683	13 (1.9)	NA	NA	NA	NA	NA	NA
Sulzyc-Bielicka et al, 2008[66] 252	1 (0.4)	NA	NA	NA	NA	NA	NA
Boisdron-Celle et al, 2007[67] 252	2 (0.8)	NA	7 (2.8)	NA	*DPYD**2A/c.2846A>T 1 (0.4)	NA	NA
Largillier et al, 2006[68] 105	1 (1.0)	NA	NA	NA	NA	NA	NA
Salgueiro et al, 2004[69] 73	1 (1.4)	NA	NA	NA	NA	NA	NA

Abbreviations: Hm, homozygous; Ht, heterozygous; NA, not applicable.

[a]*DPYD**2A, *DPYD**13, and c.2846A>T.

Table A12: Fluoropyrimidine Dose Reduction, Treatment Delay, and Discontinuation Due to Toxicity

Author, Year N (Carrier/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterogeneous, n (%)	Combined (3–4 variants), n (%)
Wigle et al, 2021[71] 1,388 (41/1,347)	NR	NR	NR	*Treatment discontinuation* Carriers: 7 (17.1) Wild-type: 232 (17.2) RR (95% CI): 0.99 (0.44–1.83)	NR	NR
Nahid et al, 2018[54] 161 (8/153)	*Dose reduction* Carriers: 8 (100.0) Wild-type: NR *Treatment delay* NR *Treatment discontinuation* Carriers: 4 (50.0) Wild-type: NR	NR	NR	NR	NR	NR
Froehlich et al, 2015[57] 500 (32/468)	*Any treatment modification*[a] Carriers: 2 (50.0)	*Any treatment modification*[a] Carriers: 2 (100.0)	*Any treatment modification*[a] Carriers: 1 (33.3)	*Any treatment modification*[a] Carriers: 12 (50.0)	NR	*Any treatment modification*[a] Carriers (4 variants): 16 (48.5) Carriers (3 variants: *DPYD**2A, *DPYD**13, c.2846A>T): 5 (55.6)
Toffoli et al, 2015[9] *DPYD**2A 596 (11/585) *DPYD**13 586 (1/585) c.2846A>T 590 (5/585) *DPYD**2A/ *DPYD**13 586 (1/585)	*Dose reduction* Carriers: 1 (9.1) Wild-type: NR *Treatment delay* Carriers: 4 (36.4) Wild-type: NR *Treatment discontinuation* Carriers: 6 (54.5) Wild-type: NR	*Dose reduction* Carriers: 1 (100) Wild-type: NR *Treatment delay* Carriers: 1 (100) Wild-type: NR *Treatment discontinuation* Carriers: 0 Wild-type: NR	*Dose reduction* Carriers: 1 (20.0) Wild-type: NR *Treatment delay* Carriers: 3 (60.0) Wild-type: NR *Treatment discontinuation* Carriers: 1 (20.0) Wild-type: NR	Not evaluated	*Dose reduction* Carriers: 0 Wild-type: NR *Treatment delay* Carriers: 0 Wild-type: NR *Treatment discontinuation* Carriers: 1 (100); fatal toxicity Wild-type: NR	NR

Author, Year N (Carrier/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterogeneous, n (%)	Combined (3–4 variants), n (%)
Lee et al, 2014[58] *DPYD**2A 2,589 (25/2,564) *DPYD**13 2,568 (4/2,564)[b] c.2846A>T 2,589 (27/2,562) *DPYD**2A/ c.2846A>T 2,565 (1/2,564)[b]	*Dose reduction* Carriers: 20 (80.0) Wild-type: 1884 (74.3) RR (95% CI): 1.08 (0.82–1.26) *Treatment delay* NR *Treatment discontinuation* Carriers: 11 (44.0) Wild-type: 653 (25.5) RR (95% CI): 1.73 (1.00–2.51)	*Dose reduction* Carriers: 3 (75.0) Wild-type: 1904 (74.3) RR (95% CI): 1.01 (0.27–1.23) *Treatment delay* NR *Treatment discontinuation* Carriers: 3 (75.0) Wild-type: 1,921 (74.9) RR (95% CI): 1.00 (0.27–1.32)	*Dose reduction* Carriers: 20 (74.1) Wild-type: 1,884 (73.5) RR (95% CI): 1.01 (0.74–1.20) *Treatment delay* NR *Treatment discontinuation* Carriers: 8 (29.6) Wild-type: 656 (25.6) RR (95% CI): 1.16 (0.57–1.91)	NR	NR	NR
Loganayagam et al, 2013[60] *DPYD**2A 424 (4/420) *DPYD**13 421 (1/420) c.2846A>T 425 (5/420)	*Dose reduction* Carriers: 2 (50.0) Wild-type: 98 (23.3) RR (95% CI): 2.15 (0.34–4.58) *Treatment delay* NR *Treatment discontinuation* Carriers: 2 (50.0) Wild-type: 27 (6.4) RR (95% CI): 7.81 (1.36–23.30)	*Dose reduction* Carriers: 1 (100.0) Wild-type: 98 (23.3) RR (95% CI): 4.29 (1.93–5.06) *Treatment delay* NR *Treatment discontinuation* Carriers: 0 Wild-type: 27 (6.4) *P* = 1.00	*Dose reduction* Carriers: 3 (60.0) Wild-type: 98 (23.3) RR (95% CI): 2.58 (0.73–4.58) *Treatment delay* NR *Treatment discontinuation* Carriers: 2 (40.0) Wild-type: 27 (6.4) RR (95% CI): 6.25 (1.06–20.44)	NR	None observed	3 variants (*DPYD**2A, *DPYD**13, c.2846A>T) *Dose reduction* Carriers: 6 (60.0) Wild-type: 98 (23.3) RR (95% CI): 2.58 (1.23–4.38) *Treatment delay* NR *Treatment discontinuation* Carriers: 4 (40.0) Wild-type: 27 (6.4) RR (95% CI): 6.25 (2.08–16.41)

Author, Year N (Carrier/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterogeneous, n (%)	Combined (3–4 variants), n (%)
Deenen et al, 2011[61] *DPYD**2A 567 (7/560) *DPYD**13 561 (1/560) c.2846A>T 568 (8/560) c.1236G>A 568 (28/540)	*Mean dose reduction* Carriers: 50% Wild-type: 10% *Treatment delay* NR *Treatment discontinuation* NR	No carrier identified	*Mean dose reduction* Carriers: 25% Wild-type: 10%	NR	NR	NR
Braun et al, 2009[64] 750 (7/743)	*Dose reduction or delay* Carriers: 4 (57.1) Wild-type: 265 (35.7) RR (95% CI): 1.60 (0.56–2.54) *Treatment discontinuation* NR	NR	NR	NR	NR	NR
Largillier et al, 2006[68] 105 (1/104)	*Dose reduction* NR *Treatment delay* NR *Treatment discontinuation* Carriers: 1 (100); death Wild-type: 15 (14.4); severe toxicity (13), death (2) RR (95% CI): 6.94 (2.43–11.51)	NR	NR	NR	NR	NR

Author, Year N (Carrier/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterogeneous, n (%)	Combined (3–4 variants), n (%)
Salgueiro et al, 2004[69] 73 (1/72)	*Dose reduction* NR *Treatment delay* NR *Treatment discontinuation* Carriers: 1 (100); 2nd cycle due to grade 4 febrile neutropenia and grade 3 gastrointestinal toxicity Wild-type: NR	NR	NR	NR	NR	NR

Abbreviations: CI, confidence interval; NR, not reported; RR, risk ratio.

[a]Can include dose reduction, therapy delay, or withdrawal due to toxicity.

[b]Denominator not provided; we assumed that it would be the same as for *DPYD**2A.

Table A13: Clinical Validity Study Results—Overall Severe (Grade ≥ 3) Toxicity (All Variants)

Author, Year N (Carriers/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterozygous, n (%)	Combined (3–4 variants), n (%)
Wigle et al, 2021[71] 1,388 (41/1,347)	NR	NR	NR	Carriers: 14 (34.1) Wild-type: 418 (31.0) RR (95% CI): 1.10 (0.67–1.62)	NR	NR
Iachetta et al, 2019[52] *DPYD**13: 366 (2/364) c.2846A>T: 366 (5/361)	NR	Carriers: 2 (100.0) Wild-type: 144 (39.6) RR (95% CI): 2.53 (1.18–2.90) *Time of occurrence, median cycle* Carriers: 2 Wild-type: 8 *P* < .0001	Carriers: 5 (100.0) Wild-type: 141 (39.1) RR (95% CI): 2.56 (1.36–2.92) *Time of occurrence, median cycle* Carriers: 1 Wild-type: 8 *P* < .0001	NR	NR	NR
Cremolini et al, 2018[55] *DPYD**2A: 438 (5/433) *DPYD**13: 433 (0/433) c.2846A>T: 438 (5/433)	Carriers: 4 (80.0) Wild-type: 217 (50.1) RR (95% CI): 1.60 (0.63–2.10)	NR	Carriers: 4 (80.0) Wild-type: 217 (50.1) RR (95% CI): 1.60 (0.63–2.10)	NR	NR	NR
Lunenburg et al, 2018[7] 805 (34/771)	NR	NR	NR	NR	NR	*4 variants under study* Carriers: 8 (23.5) Wild-type: 105 (13.6) RR (95% CI): 1.72 (0.82–3.06)
Nahid et al, 2018[54] 161 (8/153)	Carriers: 7 (87.5) Wild-type: 71 (46.4) RR (95% CI): 1.88 (1.05–2.46)	NR	NR	NR	NR	NR
Etienne-Grimaldi et al, 2017[56] *DPYD**2A: 242 (3/239) c.2846A>T: 242 (3/239)	Carriers: 2 (66.7) Wild-type: 28 (11.7) RR (95% CI); 5.70 (1.06–11.23)	NR	Carriers: 2 (66.7) Wild-type: 28 (11.7) RR (95% CI): 5.70 (1.06–11.23)	NR	NR	NR

Author, Year N (Carriers/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterozygous, n (%)	Combined (3–4 variants), n (%)
Meulendijks et al, 2017[70] c.2846A>T: 185 (5/180) c.1236G>A: 185 (15/170)	NR	NR	Carriers: 3 (60.0) Wild-type: 85 (47.0) RR (95% CI): 1.28 (0.35–2.20)	Carriers: 6 (40.0) Wild-type: 82 (48.0) RR (95% CI): 0.83 (0.37–1.63)	NR	NR
Lee et al, 2016[13] c.1236G>A: 1,953 (77 Ht/1 Hm/1,875)	NR	NR	NR	Carriers (Ht): 31 (40.3) Carriers (Hm): 1 (100.0) Wild-type: 606 (32.3) RR (95% CI; Ht): 1.25 (0.91–1.61) RR (95% CI; Hm): 3.10 (1.47–3.31)	NR	NR
Boige et al, 2016[15] *DPYD**2A: 1,545 (11/1,534) *DPYD**13 = 1,544 (4/1,540) c.2846A>T: 1,545 (21/1,524) Combined: 1,545 (36/1,509)	Carriers: 8 (72.7) Wild-type: 757 (49.3) RR (95% CI): 1.47 (0.83–1.89)	Carriers: 2 (50.0) Wild-type: 763 (49.5) RR (95% CI): 1.01 (0.14–1.83)	Carriers: 18 (85.7) Wild-type: 747 (49.0) RR (95% CI): 1.75 (1.33–2.04)	NR	NR	Could not be calculated because the number of events in wild-type patients for the combined analysis was unknown

Author, Year N (Carriers/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterozygous, n (%)	Combined (3–4 variants), n (%)
Froehlich et al, 2015[57] *DPYD**2A: 472 (4/468) *DPYD**13: 469 (1/468) c.2846A>T: 471 (3/468) c.1236G>A: 480 (22/468) c.1236G>A: 469 (1/468) *DPYD**13/c.1236G>A: 469 (1/468) Combined: 498 (30/468; excludes compound heterozygous and homozygous)	Carriers: 0 Wild-type: 40 (8.5) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 40 (8.5) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 40 (8.5) RR could not be calculated *P* = 1.00	*Heterozygous* Carriers: 9 (40.9) Wild-type: 40 (8.5) RR (95% CI): 4.81 4.79 (2.42–8.93) *Homozygous* Carriers: 1 (100.0) Wild-type: 38 (8.5) RR (95% CI): 11.76 (4.73–14.91)	DPYD**13/c.1236G>A* Carriers: 1 (100.0) Wild-type: 40 (8.5) RR (95% CI): 11.76 (4.73–14.91)	4 variants under study (excludes compound heterozygous and homozygous) *Grade ≥ 3* Carriers: 9 (30.0) Wild-type: 38 (8.2) RR (95% CI): 3.66 (1.73–7.02)
Toffoli et al, 2015[9] *DPYD**2A: 596 (11/585) *DPYD**13: 586 (1/585) c.2846A>T: 590 (5/585) *DPYD**2A/ *DPYD**13 : 586 (1/585) Combined: 602 (17/585; excludes compound heterozygous)	Carriers: 7 (63.6) Wild-type: 84 (14.4) RR (95% CI): 4.42 (2.32–7.07)	Carriers: 0 Wild-type: 84 (14.4) RR could not be calculated *P* = 1.00	Carriers: 3 (60.0) Wild-type: 84 (14.4) RR (95% CI): 4.42 (1.19–7.87)	NR	Carriers: 1 (100); fatal Wild-type: 84 (14.4) RR (95% CI): 6.94 (3.07–8.34)	3 variants: *DPYD**2A, *DPYD**13, c.2846A>T (excludes compound heterozygous) Carriers: 10 (58.8) Wild-type: 84 (14.4) RR (95% CI): 4.08 (2.36–6.41)
Lee et al, 2014[58] *DPYD**2A: 2,589 (25/2,564) *DPYD**13 = 2,568 (4/2,564)[a] c.2846A>T: 2,589 (27/2,562) *DPYD**2A/ c.2846A>T: 2,565 (1/2,564)[a] Combined: 2,618 (56/2,562; excludes compound heterozygous)	Carriers: 22 (88.0) Wild-type: 834 (32.5) RR (95% CI): 2.70 (2.16–3.11)	Carriers: 2 (50.0) Wild-type: 834 (32.5) RR (95% CI): 1.54 (0.22–2.78)	Carriers: 22 (81.5) Wild-type: 835 (32.6) RR (95% CI): 2.50 (1.94–2.98)	NR	*DPYD**2A/ c.2846A>T Carriers: 1 (100.0) Wild-type: 834 (32.5)[a] RR (95% CI): 3.08 (1.47–3.25)	3 variants: *DPYD**2A, *DPYD**13, c.2846A>T (excludes compound heterozygous) Carriers: 46 (82.5) Wild-type: 835 (32.6) RR (95% CI): 2.53 (2.14–2.89)

Author, Year N (Carriers/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterozygous, n (%)	Combined (3–4 variants), n (%)
Jennings et al, 2013[59] *DPYD**2A: 253 (3/250) c.2846A>T: 253 (2/251) c.1236G>A: 253 (10/243) Combined (carrier/wild-type): 253 (15/238)	Carriers: 2 (66.7) Wild-type: 42 (16.8) RR (95% CI): 3.97 (0.72–7.56)	Not evaluated	Carriers: 2 (100.0) Wild-type: 42 (16.7) RR (95% CI): 5.99 (2.63–7.60)	Carriers: 3 (30.0) Wild-type: 41 (16.8) RR (95% CI): 1.79 (0.47–5.21)	NR	3 variants: *DPYD**2A, c.2846A>T, c.1236G>A Carriers: 7 (46.7) Wild-type: 37 (15.5) RR (95% CI): 3.01 (1.41–6.00)
Loganayagam et al, 2013[60] *DPYD**2A: 424 (4/420) *DPYD**13: 421 (1/420) c.2846A>T: 425 (5/420) Combined: 430 (10/420)	Carriers: 4 (100.0) Wild-type: 94 (22.4) RR (95% CI): 4.46 (2.18–5.29)	Carriers: 1 (100.0) Wild-type: 94 (22.4) RR (95% CI): 4.46 (2.01–5.29)	Carriers: 5 (100.0) Wild-type: 94 (22.4) RR (95% CI): 4.46 (2.40–5.29)	NR	NR	3 variants: *DPYD**2A, *DPYD**13, c.2846A>T Carriers: 10 (100.0) Wild-type: 94 (22.4) RR (95% CI): 4.46 (3.26–5.29)
Cellier et al, 2011[62] *DPYD**2A: 83 (1/82) *DPYD**13: 83 (1/82) c.2846A>T: 83 (1/82) Combined: 85 (3/82)	Carriers: 1 (100.0) Wild-type: 34 (41.5) RR (95% CI): 2.41 (1.00–3.14)	Carriers: 1 (100.0) Wild-type: 34 (41.5) RR (95% CI): 2.41 (1.00–3.14)	Carriers: 1 (100.0) Wild-type: 34 (41.5) RR (95% CI): 2.41 (1.00–3.14)	NR	NR	3 variants: *DPYD**2A, *DPYD**13, c.2846A>T Carriers: 3 (100) Wild-type: 34 (41.5) RR (95% CI): 2.41 (1.11–3.14)
Deenen et al, 2011[61] *DPYD**2A: 567 (7/560) *DPYD**13: 561 (1/560) c.2846A>T: 568 (8/560) c.1236G>A: 568 (28/540)	Carriers: 7 (100.0) Wild-type: 477 (85.2) RR (95% CI): 1.17 (0.72–1.23)	NR	Carriers: 7 (87.5) Wild-type: 478 (85.4) RR (95% CI): 1.02 (0.59–1.19)	Carriers: 26 (92.9) Wild-type: 459 (85.0) RR (95% CI): 1.09 (0.91–1.19)	NR	NR
Cerić et al, 2010[63] *DPYD**2A: 50 (1/49)	Carriers: 1 (100.0) Wild-type: 25 (51.0) RR (95% CI): 1.96 (0.82–2.67)	NR	NR	NR	NR	NR
Braun et al, 2009[64] *DPYD**2A: 750 (7/743)	Carriers: 4 (57.1) Wild-type: 427 (57.5) RR (95% CI): 0.99 (0.34–1.54)	NR	NR	NR	NR	NR

Author, Year N (Carriers/Wild-Type)	*DPYD**2A, n (%)	DPYD*13, n (%)	c.2846A>T, n (%)	c.1236G>A, n (%)	Compound heterozygous, n (%)	Combined (3–4 variants), n (%)
Schwab et al, 2008[65] *DPYD**2A: 683 (13/670)	Carriers: 6 (46.2) Wild-type: 104 (15.5) RR (95% CI): 2.98 (1.34–5.54)	NR	NR	NR	NR	NR
Boisdron-Celle et al, 2007[67] *DPYD**2A: 244 (2/242) c.2846A>T: 249 (7/242) Compound heterozygous: 243 (1/242)	Carriers: 1 (50.0) Wild-type: 8 (3.3) RR (95% CI): 15.15 (0.63–75.94)	NR	Carriers: 5 (71.4) Wild-type: 8 (3.3) RR (95% CI): 21.64 (8.30–52.26)	NR	*DPYD**2A/ c.2846A>T Carriers: 1 (100.0) Wild-type: 8 (3.3) RR (95% CI): 30.30 (9.10–52.26)	NR
Largillier et al, 2006[68] 105 /1/104) 1st cycle	Carriers: 1 (100.0) Wild-type: 18 (17.3) RR (95% CI): 5.78 (2.12–7.96)	NR	NR	NR	NR	NR
Salgueiro et al, 2004[69] *DPYD**2A: 73 (1/72)	Carriers: 1 (100.0) Wild-type: 7 (9.7) RR (95% CI): 10.31 (3.14–18.51)	NR	NR	NR	NR	NR

Abbreviations: CI, confidence interval; Hm, homozygous; Ht, heterozygous; NR, not reported; RR, risk ratio.

[a]Denominator not reported specifically for this group; assumed it would be the same as wild-type for other variants in this study.

Table A14: Clinical Validity Study Results—Severe (Grade ≥ 3) Hematological Toxicity (*DPYD**2A)

Author, Year N (Carriers/Wild-Type)	Neutropenia, n (%)	Leukopenia, n (%)	Anemia	Thrombocytopenia	Febrile Neutropenia	Overall Hematological
Maharjan et al, 2019[53] *DPYD**2A: 55 (3/52)	Carriers: 1 (33.3) Wild-type: 4 (7.7) RR (95% CI): 4.32 (0.20–38.56)	NR	Carriers: 0 Wild-type: 0 RR could not be calculated	Carriers: 0 Wild-type: 0 RR could not be calculated	Carriers: 0 Wild-type: 0 RR could not be calculated	NR
Cremolini et al, 2018[55] DPYD*2A: 438 (5/433)	Carriers: 4 (80.0) Wild-type: 156 (36.0) RR (95% CI): 2.22 (0.90–3.04)	NR	Carriers: 0 Wild-type: 6 (1.4) RR could not be calculated *P* = 1.00	Carriers: 1 (20.0) Wild-type: 5 (1.2) RR (95% CI): 16.67 (0.77–143.35)	Carriers: 1 (20.0) Wild-type: 34 (7.9) RR (95% CI): 2.53 (0.09–16.45)	Carriers: 4 (80.0) Wild-type: 163 (37.6) RR (95% CI): 2.13 (0.86–2.90)
Nahid et al, 2018[54] 161 (8/153)	Carriers: 5 (62.5) Wild-type: 40 (26.1) RR (95% CI): 2.39 (1.04–4.42)	Carriers: 1 (12.5) Wild-type: 15 (9.8) RR (95% CI): 1.28 (0.05–10.46)	Carriers: 4 (50.0) Wild-type: 31 (20.3) RR (95% CI): 2.46 (0.88–5.86)	Carriers: 2 (25.0) Wild-type: 11 (7.2) RR (95% CI): 3.47 (0.60–15.85)	NR	NR
Boige et al, 2016[15] 1,545 (11/1,534)	Carriers: 7 (63.7) Wild-type: 555 (36.2) RR (95% CI): 1.76 (0.90–2.43)	NR	NR	NR	NR	Carriers: 7 (63.7) Wild-type: 610 (39.7) RR (95% CI): 1.60 (0.82–2.21)
Toffoli et al, 2015[9] 596 (11/585)	Carriers: 5 (45.5) Wild-type: 38 (6.5) RR (95% CI): 7.00 (2.81–15.14)	Carriers: 1 (9.1) Wild-type: 8 (1.4) RR (95% CI): 6.50 (0.28–63.87)	NR	Carriers: 1 (9.1) Wild-type: unclear RR could not be calculated	NR	Carriers: 5 (45.5) Wild-type: 45 (7.7) RR (95% CI): 5.91 (2.40–12.82)
Lee et al, 2014[58] 2,589 (25/2,564)	Carriers: 16 (64.0) Wild-type: 288 (11.2) RR (95% CI): 5.71 (3.89–7.94)	Carriers: 2 (8.0) Wild-type: 47 (1.8) RR (95% CI): 4.44 (0.67–14.79)	NR	Carriers: 1 (4.0) Wild-type: 8 (0.3) RR (95% CI): 13.33 (0.53–130.48)	Carriers: 2 (8.0) Wild-type: 42 (1.6) RR (95% CI): 5.00 (0.75–16.74)	NR
Cerić et al, 2010[63] 50 (1/49)	Carriers: 1 (100.0) Wild-type: 13 (26.5) RR (95% CI): 3.77 (1.38–5.47)	NR	NR	NR	NR	NR

Author, Year N (Carriers/Wild-Type)	Neutropenia, n (%)	Leukopenia, n (%)	Anemia	Thrombocytopenia	Febrile Neutropenia	Overall Hematological
Schwab et al, 2008[65] 683 (13/670)	NR	Carriers: 4 (30.8) Wild-type: 28 (4.2) RR (95% CI): 7.33 (2.44–19.45)	NR	NR	NR	Carriers: 4 (30.8) Wild-type: 28 (4.2) RR (95% CI): 7.33 (2.44–19.45)
Sulzyc-Bielicka et al, 2008[66] 252 (1/251)	Not evaluated	Not evaluated	NR	NR	NR	Carriers: 1 (100.0) Wild-type: 3 (1.2) RR (95% CI): 83.33 (17.94–221.92)
Largillier et al, 2006[68] 105 (1/104)	Carriers: 1 (100.0) Wild-type: 2 (1.9) RR (95% CI): 52.63 (10.40–120.90)	NR	NR	NR	NR	NR
Salgueiro et al, 2004[69] 73 (1/72)	Carriers: 1 (100.0) Wild-type: 5 (6.9) RR (95% CI): 14.49 (3.78–25.19)	NR	Carriers: 0 Wild-type: 1 (1.4) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 1 (1.4) RR could not be calculated *P* = 1.00	Carriers: 1 (100.0) Wild-type: 0 RR could not be calculated *P* = .01	Carriers: 1 (100.0) Wild-type: 5 (6.9) RR (95% CI): 14.49 (3.78–25.19)

Abbreviations: C, carrier; CI, confidence interval; NR, not reported; RR, risk ratio.

Table A15: Clinical Validity Study Results—Severe (Grade ≥ 3) Gastrointestinal Toxicity (*DPYD**2A)

Author, Year N (Carriers/Wild-Type)	Mucositis and Stomatitis, n (%)	Nausea, n (%)	Vomiting, n (%)	Diarrhea, n (%)	Overall Gastrointestinal, n (%)
Maharjan et al, 2019[53] *DPYD**2A: 55 (3/52)	Carriers: 0 Wild-type: 2 (3.8) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 3 (5.8) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 2 (3.8) RR could not be calculated *P* = 1.00	Carriers: 3 (100.0) Wild-type: 10 (19.2) RR (95% CI): 5.21 (1.96–9.37)	NR
Cremolini et al, 2018[55] 438 (5/433)	Carriers: 2 (40.0) Wild-type: 26 (6.0) RR (95% CI): 6.67 (1.14–21.94)	Carriers: 0 Wild-type: 14 (3.2) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 18 (4.2) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 64 (14.8) RR could not be calculated *P* = 1.00	Carriers: 2 (40) Wild-type: 96 (22.2) RR (95% CI): 1.83 (0.28–4.40)
Nahid et al, 2018[54] 161 (8/153)	Carriers: 1 (12.5) Wild-type: 8 (5.2) RR (95% CI): 2.40 (0.10–20.63)	Carriers: 3 (37.5) Wild-type: 18 (11.8) RR (95% CI): 3.18 (0.88–10.07)	Carriers: 3 (37.5) Wild-type: 22 (14.4) RR (95% CI): 2.60 (0.70–7.42)	Carriers: 5 (62.5) Wild-type: 42 (27.5) RR (95% CI): 2.27 (0.99–4.18)	NR
Boige et al, 2016[15] 1,545 (11/1,534)	Carriers: 0 Wild-type: 73 (4.8) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 34 (2.2) RR could not be calculated *P* = 1.00	NR	Carriers: 5 (45.5) Wild-type: 187 (12.2) RR (95% CI): 3.73 (1.51–6.91)	Carriers: 5 (45.5) Wild-type: 264 (17.2) RR (95% CI): 2.65 (1.06–4.36)
Toffoli et al, 2015[9] 596 (11/585)	Carriers: 0 Wild-type: 7 (1.2) RR could not be calculated *P* = 1.00	*Nausea and vomiting* Carriers: 1 (9.1) Wild-type: 7 (1.2) RR (95% CI): 7.58 (0.32–82.00)		Carriers: 3 (27.3) Wild-type: 34 (5.8) RR (95% CI): 4.71 (1.16–14.43)	NR
Lee et al, 2014[58] 2,589 (25/2,564)	Carriers: 3 (12.0) Wild-type: 107 (4.2) RR (95% CI): 2.86 (0.71–7.39)	*Nausea and vomiting* Carriers: 5 (20.0) Wild-type: 124 (4.8) RR (95% CI): 4.17 (1.54–8.42)		Carriers: 3 (12.0) Wild-type: 305 (11.9) RR (95% CI): 1.01 (0.24–2.51)	NR
Deenen et al, 2011[61] 567 (7/560)	NR	NR	NR	Carriers: 5 (71.4) Wild-type: 134 (23.9) RR (95% CI): 2.99 (1.35–4.44)	NR

Author, Year N (Carriers/Wild-Type)	Mucositis and Stomatitis, n (%)	Nausea, n (%)	Vomiting, n (%)	Diarrhea, n (%)	Overall Gastrointestinal, n (%)
Cerić et al, 2010[63] 50 (1/49)	Carriers: 1 (100.0) Wild-type: 6 (12.2) RR (95% CI): 8.20 (2.43–15.04)	NR	NR	Carriers: 1 (100.0) Wild-type: 12 (24.5) RR (95% CI): 4.08 (1.45–5.94)	NR
Schwab et al, 2008[65] 683 (13/670)	Carriers: 4 (30.8) Wild-type: 48 (7.2) RR (95% CI): 4.28 (1.38–10.88)	NR	NR	Carriers: 3 (23.1) Wild-type: 56 (8.4) RR (95% CI): 2.75 (0.72–8.28)	NR
Largillier et al, 2006[68] 105 (1/104)	Carriers: 1 (100.0) Wild-type: 1 (1.0) RR (95% CI): 100.00 (13.32–150.75)	*Nausea and vomiting* Carriers: 0 Wild-type: 6 (5.8) RR could not be calculated		Carriers: 1 (100.0) Wild-type: 5 (4.8) RR (95% CI): 20.83 (5.56–35.60)	NR
Salgueiro et al, 2004[69] 73 (1/72)	Carriers: 0 Wild-type: 2 (2.8) RR could not be calculated *P* = 1.00	*Nausea and vomiting* Carriers: 0 Wild-type: 0	NR	Carriers: 0 Wild-type: 1 (1.4) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 3 (4.2) RR could not be calculated *P* = 1.00

Abbreviations: CI, confidence interval; NR, not reported; RR, risk ratio.

Table A16: Clinical Validity Study Results—Severe (Grade ≥ 3) Hematological Toxicity (c.2846A>T)

Author, Year N (Carriers/Wild-Type)	Neutropenia, n (%)	Leukopenia, n (%)	Anemia, n (%)	Thrombocytopenia, n (%)	Febrile Neutropenia, n (%)	Overall Hematological, n (%)
Maharjan et al, 2019[53] 54 (2/52)	Carriers: 0 Wild-type: 4 (7.7) RR could not be calculated *P* = 1.00	NR	Carriers: 0 Wild-type: 0	Carriers: 0 Wild-type: 0	Carriers: 0 Wild-type: 0	Carriers: 0 Wild-type: 4 (7.7) RR could not be calculated *P* = 1.00
Cremolini et al, 2018[55] 438 (5/433)	Carriers: 3 (60.0) Wild-type: 156 (36.0) RR (95% CI): 1.67 (0.46–2.75)	NR	Carriers: 0 Wild-type: 6 (1.4) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 5 (1.2) RR could not be calculated *P* = 1.00	Carriers: 1 (20.0) Wild-type: 34 (7.9) RR (95% CI): 2.53 (0.87–16.45)	Carriers: 3 (60.0) Wild-type: 163 (37.6) RR (95% CI): 1.60 (0.44–2.56)
Meulendijks et al, 2017[70] c.2846A>T: 185 (5/180)	NR	NR	NR	NR	NR	Carriers: 2 (40.0) Wild-type: 58 (32.0) RR (95% CI): 1.25 (020–3.38)
Boige et al, 2016[15] 1,545 (21/1,524)	Carriers: 13 (61.9) Wild-type: 549 (36.0) RR (95% CI): 1.72 (1.11–2.26)	NR	NR	NR	NR	Carriers: 16 (76.2) Wild-type: 601 (39.4) RR (95% CI): 1.93 (1.38–2.38)
Toffoli et al, 2015[9] 590 (5/585)	Carriers: 1 (20.0) Wild-type: 38 (6.5) RR (95% CI): 3.08 (0.10–19.69)	NR	NR	NR	NR	Carriers: 1 (20.0) Wild-type: 45 (7.7) RR (95% CI): 2.60 (0.09–13.90)
Lee et al, 2014[58] 2,589 (27/2,562)	Carriers: 15 (55.6) Wild-type: 289 (11.3) RR (95% CI): 4.92 (3.22–6.72)	Carriers: 4 (14.8) Wild-type: 46 (1.8) RR (95% CI): 8.22 (2.54–20.07)	NR	Carriers: 3 (11.1) Wild-type: 6 (0.2) RR (95% CI): 55.50 (10.69–223.31)	Carriers: 2 (7.4) Wild-type: 42 (1.6) RR (95% CI): 4.63 (0.70–15.65)	NR

Abbreviations: CI, confidence interval; NR, not reported; RR, risk ratio.

Table A17: Clinical Validity Study Results—Severe (Grade ≥ 3) Gastrointestinal Toxicity (c.2846A>T)

Author, Year N (Carriers/Wild-Type)	Mucositis, n (%)	Nausea, n (%)	Vomiting, n (%)	Diarrhea, n (%)	Overall Gastrointestinal, n (%)
Maharjan et al, 2019[53] 54 (2/52)	Carriers: 0 Wild-type: 2 (3.8) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 3 (5.8) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 2 (3.8) RR could not be calculated *P* = 1.00	Carriers: 2 (100) Wild-type: 10 (19.2) RR (95% CI): 5.21 (1.67–9.37)	NR
Cremolini et al, 2018[55] 438 (5/433)	*Stomatitis* Carriers: 2 (40.0) Wild-type: 26 (6.0) RR (95% CI): 6.67 (1.14–21.94)	Carriers: 0 Wild-type: 14 (3.2) RR could not be calculated *P* = 1.00	Carriers: 0 Wild-type: 18 (4.2) RR could not be calculated *P* = 1.00	Carriers: 2 (40.0) Wild-type: 64 (14.8) RR (95% CI): 2.70 (0.43–7.26)	Carriers: 4 (80.0) Wild-type: 96 (22.2) RR (95% CI): 3.60 (1.49–5.32)
Meulendijks et al, 2017[70] c.2846A>T: 185 (5/180)	NR	NR	NR	NR	Carriers: 0 Wild-type: 25 (14.0) RR could not be calculated *P* = 1.00
Boige et al, 2016[15] 1,545 (21/1,524)	Carriers: 5 (23.8) Wild-type: 68 (4.5) RR (95% CI): 5.29 (2.00–11.07)	Carriers: 0 Wild-type: 34 (2.2) RR could not be calculated	NR	Carriers: 3 (14.3) Wild-type: 189 (12.4) RR (95% CI): 1.15 (0.28–2.83)	Carriers: 7 (33.3) Wild-type: 262 (17.2) RR (95% CI): 1.94 (0.91–3.26)
Toffoli et al, 2015[9] 590 (5/585)	*Stomatitis* Carriers: 0 Wild-type: 7 (1.2) RR could not be calculated *P* = 1.00	*Nausea and vomiting* Carriers: 0 Wild-type: 8 (1.4) RR could not be calculated *P* = 1.00		Carriers: 2 (40.0) Wild-type: 34 (5.8) RR (95% CI): 6.90 (1.15–22.19)	NR
Lee et al, 2014[58] 2,589 (27/2,562)	*Mucositis/stomatitis* Carriers: 2 (7.4) Wild-type: 106 (4.1) RR (95% CI): 1.80 (0.26–5.76)	*Nausea and vomiting* Carriers: 2 (7.4) Wild-type: 127 (5.0) RR (95% CI): 1.48 (0.21–4.77)		Carriers: 9 (33.3) Wild-type: 299 (11.7) RR (95% CI): 2.85 (1.49–4.57)	NR
Deenen et al, 2011[61] 568 (8/560)	NR	NR	NR	Carriers: 5 (62.5) Wild-type: 134 (23.9) RR (95% CI): 2.62 (1.13–4.27)	NR

Abbreviations: CI, confidence interval; NR, not reported; RR, risk ratio.

Table A18: Clinical Utility Study Results—Severe (Grade ≥ 3) Toxicity

Author, Year N (Carriers/Wild-Type)	Hematological Toxicity, n (%)	Gastrointestinal Toxicity, n (%)	Hand–Foot Syndrome, n (%)	Overall Toxicity, n (%)	Treatment-Related Mortality, n (%)	Toxicity-Related Hospitalizations, n (%)
Wigle et al, 2021[71] 1,394 (47/1,347)	Carriers: 6 (12.8) Wild-type: 157 (11.7) RR (95% CI): 1.09 (0.44–2.18) *By genotype* *DPYD**2A: 2 (22.2) *DPYD**13: 0 c.2846A>T: 2 (10.5) c.1236G>A: 2 (11.1)	Carriers: 6 (12.8) Wild-type: 167 (12.4) RR (95% CI): 1.03 (0.42–2.05) *By genotype* *DPYD**2A: 2 (22.2) *DPYD**13: 0 c.2846A>T: 2 (10.5) c.1236G>A: 2 (11.1)	Carriers: 1 (2.1) Wild-type: 35 (2.6) RR (95% CI): 0.81 (0.03–4.68) *By genotype* *DPYD**2A: 0 *DPYD**13: 0 c.2846A>T: 1 (5.3) c.1236G>A: 0	Carriers: 11 (23.4) Wild-type: 418 (31.0) RR (95% CI): 0.75 (0.41–1.21) *By genotype* *DPYD**2A: 3 (33.3) *DPYD**13: 0 c.2846A>T: 5 (26.3) c.1236G>A: 3 (16.7)	Carriers: 0 Wild-type: 10 (0.7) RR could not be calculated *P* > .99[a]	NR
Henricks et al, 2019[11] 1,646 (40/1,606) *DPYD**2A	Carriers: 4 (10.0) Wild-type: 158 (10.0) RR (95% CI): 1.00 (0.32–2.35)	Carriers: 4 (10.0) Wild-type: 150 (9.3) RR (95% CI): 1.08 (0.34–2.48)	Carriers: 2 (5.0) Wild-type: 84 (5.2) RR (95% CI): 0.96 (0.14–3.21)	Carriers: 7 (17.5) Wild-type: 372 (23.2) RR (95% CI): 0.75 (0.34–1.38)	Carriers: 0 Wild-type: 2 (0.1) RR could not be calculated *P* > .99	Carriers: 6 (15.0) Wild-type: 179 (11.1) RR (95% CI): 1.35 (0.55—2.64)
Kleinjan et al, 2019[12] 185 (11/174) 4 variants	Carriers: 1 (9.1) Wild-type: 6 (3.4) RR (95% CI): 2.68 (0.11–28.11)	<u>*Diarrhea*</u> Carriers: 2 (18.2) Wild-type: 34 (19.5) RR (95% CI): 0.93 (0.15–3.93)	Carriers: 0 Wild-type: 35 (20.1) RR could not be calculated *P* = .13	Carriers: 3 (27.3) Wild-type: 66 (37.9) RR (95% CI): 0.72 (0.18—2.02) *Cycle of 1st toxicity, median (range)* Carriers: 2 (1–2) Wild-type: 2 (1–6) *P* = .33 *Toxicity after dose increase* Carriers: 1 (9.1) Wild-type: NA	NR	Carriers: 2 (18.2) Wild-type: 20 (11.5) (diarrhea in both groups) RR (95% CI): 1.58 (0.26–7.39) *Days in hospital, median (range)* Carriers: 6.5 (6–7) Wild-type: 8 (1–34) *P* = .62
Stavraka et al, 2019[23] 63 (2/61) 3 variants, but none had *DPYD**13	Carriers: 1 (50.0) Wild-type: 0 RR could not be calculated *P* = .03	Carriers: 1 (50.0) Wild-type: 5 (8.2) RR (95% CI): 6.10 (0.27–35.23)	Carriers: 1 (50.0) Wild-type: 9 (14.8) RR (95% CI): 3.38 (0.14–16.79)	Carriers: 1 (50.0) Wild-type: 14 (23.0) RR (95% CI): 2.17 (0.08–9.17)	Carriers: 0 Wild-type: 0 RR could not be calculated	Carriers: 1 (50.0) Wild-type: 0 RR could not be calculated *P* = .03

Author, Year N (Carriers/Wild-Type)	Hematological Toxicity, n (%)	Gastrointestinal Toxicity, n (%)	Hand–Foot Syndrome, n (%)	Overall Toxicity, n (%)	Treatment-Related Mortality, n (%)	Toxicity-Related Hospitalizations, n (%)
Henricks et al, 2018[72] 1,103 (85/1,018) 4 variants *DPYD**2A: 16 *DPYD**13: 1 c.2846A>T: 17 c.1236G>A: 51	Carriers: 13 (15.3) Wild-type: 65 (6.4) RR (95% CI): 2.39 (1.29–4.09) *By genotype* *DPYD**2A: 2 (12.5) *DPYD**13: 0 c.2846A>T: 4 (23.5) c.1236G>A: 7 (13.7)	Carriers: 17 (20.0) Wild-type: 86 (8.4) RR (95% CI): 2.38 (1.41–3.73) *By genotype* *DPYD**2A: 2 (12.5) *DPYD**13: 0 c.2846A>T: 4 (23.5) c.1236G>A: 11 (21.6)	Carriers: 1 (1.2) Wild-type: 36 (3.5) RR (95% CI): 0.34 (0.01–1.92) *By genotype* *DPYD**2A: 0 *DPYD**13: 0 c.2846A>T: 1 (5.9) c.1236G>A: 0	Carriers: 33 (38.8) Wild-type: 231 (22.7) RR (95% CI): 1.71 (1.25–2.25) *By genotype* *DPYD**2A: 5 (31.3) *DPYD**13: 0 c.2846A>T: 8 (47.1) c.1236G>A: 20 (39.2)	Carriers: could not be determined (1 death in a carrier who was wrongly treated with a full dose for 2 cycles) Wild-type: 3 (0.3) *P* = .55	Carriers: 16 (18.8) Wild-type: 140 (13.8) RR (95% CI): 1.36 (0.82—2.13) *P* = 0.21 *Days in hospital, median (IQR)* Carriers: 5 (3–7) Wild-type: 5 (3–10)
Lunenburg et al, 2018[7] 827 (22[b]/771/34[c]) 4 variants	Carriers: 2 (8.7) Wild-type: 22 (2.9) Carriers[c]: 4 (11.8) RR (95% CI) vs. wild-type: 3.00 (0.49–11.66) RR (95% CI) vs. Carriers[c]: 0.74 (0.12–5.72)	Carriers: 2 (8.7) Wild-type: 62 (8.0) Carriers[c]: 6 (17.6) RR (95% CI) vs. wild-type: 1.08 (0.16–3.52) RR (95% CI) vs. carriers[c]: 0.49 (0.08–2.28)	*Grade ≥ 2* Carriers: 1 (4.3) Wild-type: 24 (3.1) Carriers[c]: NR RR (95% CI) vs. wild-type: 1.40 (0.05–8.27)	Carriers: 5 (22.7) Wild-type: 105 (13.6) Carriers[c]: 8 (23.5) RR (95% CI) vs. wild-type: 1.60 (0.59–3.22) RR (95% CI) vs. carriers[c]: 0.97 (0.30–3.05)	NR	Carriers: 4 (18.2) Wild-type: 60 (7.8) Carriers[c]: 6 (17.6) RR (95% CI) vs. wild-type: 2.24 (0.69–5.14) RR (95% CI) vs. carriers[c]: 1.03 (0.27—4.03) *Days in hospital, median (range)* Carriers: 4 (2–5) Carriers[c]: 23 (6–36) Wild-type: 13 (1–76) *P* = .01 (carriers vs. carriers[c]) *P* = NR (carriers vs. wild-type)

Abbreviations: CI, confidence interval; NA, not applicable; NR, not reported; RR, risk ratio.

[a]Calculated by study authors based on the Wilcoxon–Mann–Whitney *test.*[71]

[b]One patient was excluded from the analyses.

[c]*DPYD* carriers who received a standard dose.

Table A19: Fluoropyrimidine Treatment Effectiveness Study Results—Treatment Response and Survival

Author, Year N (Carriers/Wild-Type)	Treatment Response, n (%)	Disease Progression, n (%)	Overall Survival, n (%)	Progression-Free Survival, n (%)
Henricks et al, 2019[11] 74 (37/37) *DPYD**2A	*Disease controlled* Carriers: 12 (60) Wild-type: 10 (48) *Complete response* Carriers: 0 Wild-type: 1 (5) *Partial response* Carriers: 4 (20) Wild-type: 6 (29) *Stable disease* Carriers: 8 (40) Wild-type: 3 (14) *P* > .99 (overall for treatment response and progressive disease)	Carriers: 8 (40) Wild-type: 11 (30) *P* > .99 (overall for treatment response and progressive disease)	*Median (range), months* Carriers: 27 (1—83) Wild-type: 24 (0.7—97) HR: 0.82 (95% CI 0.47—1.43) *P* = .47	*Median (range), months* Carriers: 14 (0.7—83) Wild-type: 10 (0.2—97) HR: 0.83 (95% CI 0.47—1.50) *P* = .54

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; NR, not reported.

Appendix 6: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary Reason for Exclusion
Systematic Reviews	
Leung HW, Chan AL. Association and prediction of severe 5-fluorouracil toxicity with dihydropyrimidine dehydrogenase gene polymorphisms: A meta-analysis. Biomed Rep. 2015;3(6):879-83	Focused on a subpopulation of Asian patients
Rosmarin D, Palles C, Church D, Domingo E, Jones A, Johnstone E, et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. J Clin Oncol. 2014;32(10):1031-9	Evaluated the association between severe and non-severe toxicity and did not provide information on fluoropyrimidine-related toxicity in *DPYD* carriers vs. wild-type patients
Primary Studies	
Amstutz U, Farese S, Aebi S, Largiadèr CR. Dihydropyrimidine dehydrogenase gene variation and severe 5-fluorouracil toxicity: a haplotype assessment. Pharmacogenomics. 2009;10(6):931-44	Results of this study were part of a more recent and more complete publication included in this report
Boisdron-Celle M, Capitain O, Faroux R, Borg C, Metges JP, Galais MP, et al. Prevention of 5-fluorouracil-induced early severe toxicity by pre-therapeutic dihydropyrimidine dehydrogenase deficiency screening: Assessment of a multiparametric approach. Semin Oncol. 2017 Feb;44(1):13-23	Results for *DPYD* genotyping alone could not be separated
Deenen MJ, Meulendijks D, Cats A, Sechterberger MK, Severens JL, Boot H, et al. Upfront genotyping of *DPYD**2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol. 2016;34(3):227-34	Results of this study were part of a more recent and more complete publication included in this report

Appendix 7: Applicability of Studies Included in the Economic Literature Review

Table A20: Assessment of the Applicability of Studies Included in the Economic Literature Review

Author, Year, Country of Publication	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Deenen et al, 2016[79] Netherlands	Yes	Yes	Yes	Yes, health care payer	No[b]	NA	No	No	Partially
Henricks et al, 2019[80] Netherlands	Yes	Yes	Yes	Yes, health care payer	No[b]	NA	No	No	Partially

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

[b]Effects on patient's survival and quality of life were not included.

Appendix 8: Alternative Model Parameters Used in the Economic Scenario Analysis

For this scenario analysis, we used alternative clinical studies (Henricks et al, 2018[80,81]) to inform some of the clinical and resource use model parameters. Other parameters and/or assumptions not shown in the table remain the same as in the reference case analysis.

Table A21: Alternative Model Parameters Used in the Economic Scenario Analysis

Model Parameter	Scenario Analysis (Henricks et al 2018[80,81])	Reference Case Analysis (Lunenburg et al 2018[7])
Probability of Severe Toxicity		
DPYD wild-type	22.69%	13.62%
DPYD intermediate, reduced dose	38.82%	22.73%
DPYD intermediate, standard dose	50.15%	23.53%
Probability of Hospitalization[a]		
DPYD wild-type	13.56% (ward); 0.88% (ICU)	7.8%
DPYD intermediate, reduced dose	16.47% (ward); 2.35% (ICU)	18.2%
DPYD intermediate, standard dose	23.5% (ward); 3.10% (ICU)	17.6%
Hospital Length of Stay (days)		
DPYD wild-type	7.99 (ward); 3.11 (ICU)	13
DPYD intermediate, reduced dose	5.79 (ward); 1 (ICU)	4
DPYD intermediate, standard dose	13.1 (ward); 7 (ICU)	23
Cost of Hospitalization		
ICU per day[b]	$3,899	NA

Abbreviations: ICU, intensive care unit; NA, not applicable.

[a]For all patients.

[b]Source for ICU cost per day: Canadian Institute for Health Information, 2016.[96]

Appendix 9: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **DPYD testing** for people who will be treated with chemotherapy drugs called fluoropyramidines such as 5-Fluorouracil (5-FU) and capecitabine. The purpose is to understand whether this test should be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers with experience using chemotherapy drugs called fluoropyramidines that may or may not have used DPYD testing and people who could be considering it in the future.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30 minutes of your time for a phone
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 30 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US BEFORE AUGUST 3:

Appendix 10: Interview Guide

Interview Guide

I would like your permission to have an audio recording of this conversation so I can use your direct quotes and other information from this conversation to make a case for the decision makers. Your name or any other identifiers will not be placed in the report or the presentation and your privacy and your confidentiality will be protected. So do I have your permission to audio record this conversation?

Intro

History of cancer – type, diagnosis and background (general only)
How did you feel when diagnosed

Care and Treatment Journey

What treatment options were you offered?
Enough information going into treatment?
Anxiety about going to treatment
How was the treatment process? Were there any issues with accessibility?
Did you experience any side effects from chemotherapy? Were you told about the side effects?
-was chemo stopped or dosage altered after side effects?
-were you hospitalized because of the side effects?

Lived- Experience

Day-to-day routine
What is the impact on your quality of life? (Loss of independence?)
Impact on loved-ones/caregivers, work, etc?
Mental health

Therapies

Were you aware of the possibility of toxicity from fluoropyrimidines (chemo drug)? Source?
Were you aware/offered of DPYD testing? Source? When?
Do you believe that this test should be offered to patients who are candidates for fluoropyrimidine treatment, knowing that about 1% of individuals will have a positive result for this test?
Accessing DPYD testing
Would you want this test before? why

DPYD

Opinion on storage of genetic data
Sharing results with family
Opinion on PGx
Limiting medications?
Information surrounding DPYD testing
Decision-making
Testing process
Impact of test results on care
Overall result, impact, change in quality of life (if applicable)- side effects

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ISSN 1915-7398 (online)
ISBN 978-1-4868-5438-7 (PDF)