HHS Public Access

Author manuscript

*Clin Colorectal Cancer*. Author manuscript; available in PMC 2023 September 12.

Published in final edited form as:

*Clin Colorectal Cancer*. 2022 September ; 21(3): e189–e195. doi:10.1016/j.clcc.2022.05.001.

# Cost-effectiveness of *DPYD* genotyping prior to fluoropyrimidine-based adjuvant chemotherapy for colon cancer

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## Abstract

**Background:** Adjuvant fluoropyrimidine-based chemotherapy substantially reduces recurrence and mortality after resection of stage 3 colon cancer. While standard doses of 5-fluorouracil and capecitabine are safe for most patients, the risk of severe toxicity is increased for the approximately 6% of patients with dihydropyimidine dehydrogenase (DPD) deficiency caused by pathogenic *DPYD* gene variants. Pre-treatment screening for pathogenic *DPYD* gene variants reduces severe toxicity but has not been widely adopted in the U.S.

**Methods:** We conducted a cost-effectiveness analysis of *DPYD* genotyping prior to fluoropyrimidine-based adjuvant chemotherapy for stage 3 colon cancer, covering the c.1129–5923C>G (HapB3), c.1679T>G (*13), c.1905+1G>A (*2A), and c.2846A>T gene variants. We used a Markov model with a 5-year horizon, taking a U.S. healthcare perspective. Simulated patients with pathogenic *DPYD* gene variants received reduced-dose fluoropyrimidine chemotherapy. The primary outcome was the incremental cost-effectiveness ratio (ICER) for *DPYD* genotyping.

**Results:** Compared with no screening for DPD deficiency, *DPYD* genotyping increased per-patient costs by $78 and improved survival by 0.0038 quality-adjusted life years (QALYs), leading to an ICER of $20,506/QALY. In one-way sensitivity analyses, The ICER exceeded $50,000 per QALY when the cost of the *DPYD* genotyping assay was greater than $286. In probabilistic sensitivity analysis using a willingness-to-pay threshold of $50,000/QALY *DPYD* genotyping was preferred to no screening in 96.2% of iterations.

**Conclusions:** Among patients receiving adjuvant chemotherapy for stage 3 colon cancer, screening for DPD deficiency with *DPYD* genotyping is a cost-effective strategy for preventing infrequent but severe and sometimes fatal toxicities of fluoropyrimidine chemotherapy.

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## Introduction

Adjuvant chemotherapy reduces risk for cancer recurrence and improves survival in patients with stage 3 (node-positive) colon cancer.[1] 5-fluoruracil and its oral prodrug, capecitabine, are the essential components of adjuvant chemotherapy for colon cancer, usually given in conjunction with oxaliplatin. 5-fluorouracil and capecitabine, both classified as fluoropyrimidine chemotherapy agents, are safe for most patients at standard treatment doses. However, their therapeutic index is narrow. Toxicities linked to fluoropyrimidine chemotherapy range from mild to life-threatening, and may include diarrhea, mucositis, enteritis, neutropenia, thrombocytopenia, and palmar-plantar erythrodysesthesia.[2] Fatal fluoropyrimidine toxicity is rare, occurring in less than 1% of treated patients.[2–4] However, severe and sometimes fatal toxicity is greatly increased in patients with the syndrome of dihydropyrimidine dehydrogenase (DPD) deficiency,[5–7] with risk of early treatment-related death among these patients estimated in the range of 2.3–10%.[8, 9]

DPD is the rate limiting enzyme in the metabolic clearance of 5-FU. DPD deficiency affects an estimated 3–8% of patient treated with fluoropyrimidine chemotherapy,[10–12] often leading to severe toxicity. The most well-described causes of DPD deficiency are genetic variants of the *DPYD* gene, which encodes the DPD enzyme. Patients who are carriers of consensus pathogenic variants of the *DPYD* gene can be readily identified through genotyping assays, using peripheral blood. In recent years, multiple prospective studies have shown that screening for pathogenic *DPYD* gene variants prior to treatment with fluoropyrimidine chemotherapy, coupled with reduction of chemotherapy doses in patients with identified variants, leads to substantial reductions in severe treatment-related toxicity.[8, 13, 14] On the basis of these findings, the European Medicines Agency (EMA) issued a recommendation in April of 2020 that all patients should be tested for DPD deficiency prior to starting a fluoropyrimidine-containing chemotherapy regimen.

Despite the growing evidence in favor of *DPYD* genotyping as a tool to prevent severe chemotherapy toxicity, there has been little uptake of this approach in the United States to date. The U.S. Food and Drug Administration (FDA) has yet to issue any updated recommendations regarding screening for DPD deficiency, and guidelines from the National Comprehensive Cancer Network [NCCN]) do not endorse or recommend any form of screening for DPD deficiency prior to fluoropyrimidine chemotherapy. Opponents of screening for DPD deficiency have argued that the benefits of this practice are too small to justify the costs, while proponents contend that screening is supported by the mounting evidence that this practice prevents severe toxicity and infrequent but avoidable deaths.[15] To better weigh the costs and benefits of *DPYD* genotyping as a screening test for DPD deficiency, we conducted a model-based cost-effectiveness analysis from the U.S. healthcare perspective. Our model estimates the cost-effectiveness of *DPYD* genotyping prior to adjuvant chemotherapy for stage 3 colon cancer, compared with no screening for DPD deficiency.

## Methods

We conducted a model-based cost-effectiveness analysis, using methods consistent with recommendations of the ISPOR CHEERS Task Force.[16] We constructed a Markov model to estimate quality adjusted life years (QALYs) and treatment-related costs in patients receiving fluoropyrimidine-based adjuvant chemotherapy for stage 3 colon cancer. We modeled strategies of chemotherapy treatment with or without pretreatment *DPYD* genotyping to screen for DPD deficiency; the model structure is shown in Figure 1. In the screening arm of the model, all patients undergo *DPYD* genotyping, and patients who screen positive for a pathogenic *DPYD* gene variant receive reduced-dose fluoropyrimidine chemotherapy. In the no screening arm of the model, all patients receive standard-dose fluoropyrimidine-based chemotherapy, without prospective *DPYD* genotyping. All model cycles are six months long. Patients receive adjuvant chemotherapy in the first model cycle; outcomes modeled in the first cycle include grade 3–4 chemotherapy-related toxicity, toxicity-related hospitalization, treatment-related death (grade 5 toxicity), and non-treatment mortality. The main outcome modeled in subsequent six-month cycles is death from any cause. Cancer recurrence is assumed to be equivalent in the screening and no screening arms and is not explicitly modeled, with one exception. In the subgroup of patients with a "false positive" *DPYD* variant result the model allows for an increased risk of death related to reduced effectiveness of adjuvant treatment (due to use of reduced-dose fluoropyrimidine chemotherapy in patients with wild-type *DPYD* genotype).

### Source of model estimates

A summary of model estimates and their sources is shown in Table 1. We based our estimate for the prevalence of pathogenic *DPYD* gene variants on the prevalence of variants reported in NCCTG N0147, a U.S.-based cooperative group study which identified subjects with the c.1129–5923C>G (HapB3), c.1679T>G (*13), c.1905+1G>A (*2A), and c.2846A>T gene variants.[5, 17] PCR-based tests represent the gold standard for genotype testing, and the analytic sensitivity and specificity of PCR-based genotyping tests is generally reported as ≥99%.[18] In the base case analysis we modeled the sensitivity and specificity of PCR-based genotyping for *DPYD* gene variants as 99%.

Estimates for the risk of treatment-related toxicity and hospitalization came from Henricks *et al*[13] (NCT02324452; a large, prospective study of dose-reduced chemotherapy for patients with pathogenic *DPYD* mutations, with a comparison group of patients with wild-type *DPYD* genotyping), Deenen *et al*[8] (which described grade ≥3 toxicities in a historical cohort of patients with the *DPYD* *2A variant who received standard-dose fluoropyrimidine chemotherapy), and Toffoli *et al*[19] (which reported on hospitalizations in a historical cohort of patients with *DPYD* *2A, *13, c.2846A>T, or HapB3 variants who received standard-dose chemotherapy.) The risk of treatment-related death, conditional on *DPYD* genotype and standard vs reduced-dose chemotherapy, was taken from the systematic review by Sharma et al.[20] There is scant evidence to estimate the risk of treatment-related death in patients with pathogenic *DPYD* variants receiving reduced-dose chemotherapy; however, two prospective studies suggest that this risk is similar to the risk of treatment-related death in patients with wild-type *DPYD* genotype receiving standard-dose chemotherapy,[8, 13] and

our analysis uses an estimate of 0.2% (two times the risk of a patient with wild-type *DPYD* genotype receiving standard-dose chemotherapy.)

Estimates for mortality in the five years after completing adjuvant chemotherapy were based on our analysis of data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program for patients with stage 3 colorectal cancer (see Table 2).[21] For patients receiving reduced-dose chemotherapy after a "false positive" *DPYD* genotype test, we modeled a 32% increase in the hazard of death. This estimate is the inverse of the 24% reduction in the hazard of death associated with receipt of fluoropyrimidine chemotherapy in the IMPACT meta-analysis,[22] reflecting a conservative assumption that the fluoropyrimidine component of adjuvant chemotherapy is ineffective in patients with a normal (wild-type) *DPYD* genotype who receive reduced-dose therapy.

Utility values for specific health states were derived from published studies of patients with colorectal cancer.[23, 24] The model incorporated monetary costs for *DPYD* genotyping, derived from the Clinical Laboratory Fee Schedule of the Centers for Medicare and Medicaid Services.[25] The estimated cost of hospitalization for chemotherapy toxicity was derived from a U.S. study of inpatient hospitalization costs in patients with chemotherapy-induced nausea and vomiting.[26] For patients with "false positive" *DPYD* genotyping results, we modeled additional costs associated with cancer recurrence and death.[27] We assumed that other costs would accrue equally across both arms of the model. All costs were adjusted to 2020 U.S. dollars, using the Personal Health Care price index and the Personal Consumption Expenditure health component price index.[28] Future costs were discounted at 3% per year.

### Sensitivity analysis

We performed one-way sensitivity analyses of key model estimates including prevalence of patients with *DPYD* gene variants, sensitivity and specificity of *DPYD* genotyping, health utility values before, during and after adjuvant chemotherapy, cost of *DPYD* genotyping, cost of hospitalization related to chemotherapy toxicity, and increased mortality risk and cost in patients with "false positive" *DPYD* genotyping. The range of parameter values tested in the sensitivity analyses is shown in Table 1. We also conducted probabilistic sensitivity analysis to demonstrate parameter uncertainty by sampling each parameter's value from a distribution. We used a uniform distribution for each parameter, constraining minimum and maximum values to correspond with the parameter's upper and lower bounds.

## Results

Compared with no screening for DPD deficiency, *DPYD* genotyping was associated with an incremental cost of $78 and an incremental effectiveness of 0.0038 QALYs. The ICER for *DPYD* genotyping was $20,506/QALY. In one-way sensitivity analyses, the cost-effectiveness of *DPYD* genotyping was sensitive to the input parameters for test cost and the cost of hospitalization for chemotherapy-related toxicity. The ICER exceeded $50,000 per QALY when the cost of the *DPYD* genotyping assay was greater than $286. The strategy of *DPYD* genotyping became dominant to the "no screening" strategy (with lower cost and

greater quality-adjusted survival) when the cost of *DPYD* genotyping was less than $96 or when the cost of hospitalization related to chemotherapy toxicity was greater than $27,778.

In the probabilistic sensitivity analysis, we conducted a Monte Carlo simulation of 100,000 iterations. At the willingness-to-pay threshold of $50,000 per QALY *DPYD* genotyping was preferred to no screening in 96.2% of iterations, and *DPYD* genotyping dominated no screening (with lower cost and higher QALYs) in 47.5% of iterations. Figure 2 depicts a plot of incremental costs and QALYs for each of the 100,000 Monte Carlo iterations.

## Discussion

DPD deficiency is an uncommon condition that predisposes patients to severe, potentially fatal toxicity from treatment with fluoropyrimidine chemotherapies (5-fluorouracil or capecitabine).[2] A large proportion of patients with DPD deficiency can be detected through genotyping for pathogenic variants of the *DPYD* gene, and two high-quality prospective clinical trials have demonstrated that *DPYD* genotyping, linked with chemotherapy dose reductions for variant carriers, leads to substantial reductions in severe chemotherapy toxicities.[8, 13] In this analysis, we evaluated the cost-effectiveness of *DPYD* genotyping prior to adjuvant chemotherapy for stage 3 colon cancer from the perspective of the U.S. healthcare system. In the base-case analysis, we found that *DPYD* genotyping improved quality-adjusted survival, with an ICER of $20,506 per QALY. Probabilistic sensitivity analysis showed that the ICER was less than $50,000/QALY in 96% of the model simulations—with 47.5% of showing that *DPYD* genotyping dominated the no screening strategy. We conclude that *DPYD* genotyping is highly likely to be cost-effective from a U.S. healthcare perspective, whether that is measured in reference to the widely-cited threshold of $100,000/QALY, or in reference to the cost-effectiveness of colon cancer treatments that are widely used in the U.S.[29–31]

A number of prior studies have evaluated the cost and outcomes of *DPYD* genotyping from European and Canadian perspectives. Henricks and colleagues performed a cost analysis[32] of *DPYD* genotyping from a Dutch perspective, using data from their pivotal prospective trial (NCT02324452).[13] Their analysis did not formally assess the effectiveness of *DPYD* genotyping (did not estimate incremental QALYs), but concluded that *DPYD* genotyping was likely cost-saving due to reduced costs of toxicity management in the context of the trial's patient population.[32] Murphy and colleagues retrospectively estimated savings from *DPYD* genotyping in a cohort of 134 patients from a single center in Ireland.[33] They found that the cost of *DPYD* genotyping for these 134 patients would have been considerably less than the cost of toxicity-related hospitalizations incurred in 5 patients with retrospectively identified pathogenic *DPYD* gene variants. In 2021 Ontario Health (the Canadian provincial health authority) conducted a Health Technology Assessment of *DPYD* genotyping; this assessment focused on short-term costs and benefits of *DPYD* genotyping occurring within a six-month time horizon.[34] The assessment found that *DPYD* genotyping dominated no screening for DPD deficiency, with incremental savings of $145 and a gain of 0.0011 QALYs. Additional studies have concluded that management costs for chemotherapy-related toxicity are higher in patients who are carriers of pathogenic *DPYD* gene variants.[19, 35]

Our study adds to prior research by using formal cost-effectiveness methods and incorporating evidence-based parameter estimates relevant to the U.S. healthcare setting. Our model uses conservative assumptions regarding the clinical utility of *DPYD* genotyping for improving quality-adjusted survival. For example, our model incorporates the hypothetical risk that *DPYD* genotyping could produce false-positive results in 1% of patients (specificity = 99%), leading to unwarranted chemotherapy dose-reductions and potential loss of therapeutic benefit from adjuvant chemotherapy. Even with this conservative approach, we found that the clinical benefits of *DPYD* genotyping outweighed harms, leading to an incremental improvement in QALYs.

The cost of *DPYD* genotyping is an important parameter in our model. We modeled the cost of genotyping at $174—the allowable amount listed in the Medicare Clinical Laboratory Fee Schedule. Alternatively, sensitivity analysis showed that *DPYD* genotyping dominates the no screening approach when the test cost is less than $96. These cost estimates assume that *DPYD* genotyping has not been previously completed and must be ordered *a la carte* prior to chemotherapy treatment. As the cost of germline genomic testing continues to decrease (with some vendors offering whole genome sequencing at less than $1000), it is increasingly feasible to imagine that many patients will have panel testing for actionable germline genetic variants as part of their initial oncologic evaluation.[36] In this case the marginal cost of assessing a patient's *DPYD* genotype could fall essentially to zero.

One notable aspect of our results is that the average benefit of *DPYD* genotyping is small, as reflected by the incremental survival benefit of 0.0038 QALYs. However, this small average benefit masks large effects in the tails of the probability distribution. Most patients in our model (>96.8%) experience neither benefit nor harm from *DPYD* genotyping, while all of the benefits of testing occur in the 6.3% of patients with detectable, pathogenic *DPYD* gene variants. A small proportion of patients is spared from treatment-related death (1 in 764 patients), and a larger proportion avoid grade 3–4 toxicity (1 in 48 patients).

Our analysis has limitations. Literature-based estimates are unavailable for some of the parameters in our model, including estimates for the precise sensitivity and specificity of *DPYD* genotyping and the effectiveness of reduced-dose adjuvant chemotherapy in patients with or without *DPYD* gene variants. As described above, we used conservative estimates for these model parameters so that our analysis would have a tendency to underestimate the cost-effectiveness of *DPYD* genotyping. We only modeled one strategy of screening for DPD deficiency, with *DPYD* genotyping. While *DPYD* genotyping is the only clinical test for DPD deficiency that is widely available in the U.S., alternative tests are used in Europe and other countries, including the plasma uracil concentration and a "multi-parametric" approach.[12, 14, 37] We did not model the clinical utility of *DPYD* genotyping in patients from distinct ancestral populations, and it is likely that *DPYD* genotyping is less sensitive for DPD deficiency in non-white patients, who are less likely to carry the canonical *DPYD* gene variants described in early studies of white patients of European ancestry.[38]

In summary, we found that *DPYD* genotyping improves quality-adjusted survival and is highly likely to be cost-effective among patients receiving adjuvant chemotherapy for stage 3 colon cancer. Our analysis uses parameter estimates that are relevant to the U.S. health

care setting, and we conclude that U.S. health authorities should include *DPYD* genotyping in clinical care guidelines for patients who will receive fluoropyrimidine chemotherapy, consistent with the EMA's recent recommendation in favor of universal screening for DPD deficiency.[37] Further study is warranted to evaluate how the clinical utility, cost-effectiveness, and equity of *DPYD* genotyping compare with other modalities of screening for DPD deficiency.

## Acknowledgments

Research reported in this manuscript was supported by The Dartmouth-Hitchcock Cancer Research Fellows Program and by the National Cancer Institute Cancer Center Support Grant 5P30CA023108 to the Dartmouth-Hitchcock Norris Cotton Cancer Center, as well as by The Dartmouth Clinical and Translational Science Institute, under award number UL1TR001086 from the National Center for Advancing Translational Sciences of the National Institutes of Health. This research was presented in abstract form as part of the 2021 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (January 15, 2021 [virtual meeting]).

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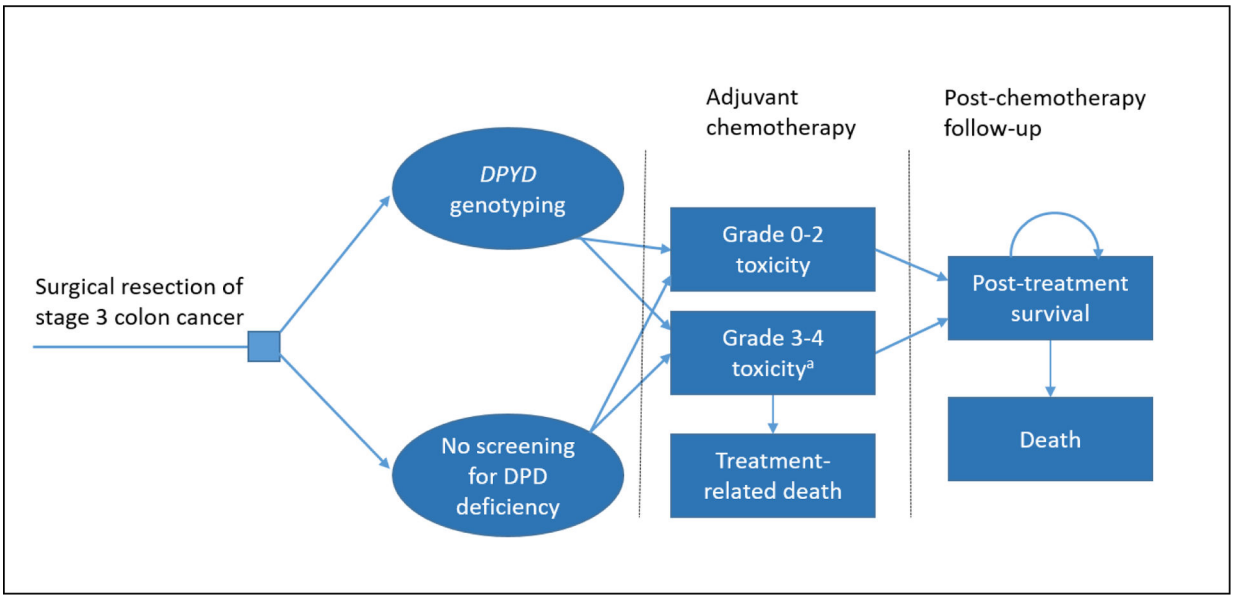


**Figure 1.**

Structure of Markov model simulating adjuvant chemotherapy for stage 3 colon cancer

[a]A subset of patients with grade 3–4 toxicity experience toxicity-related hospitalizations.

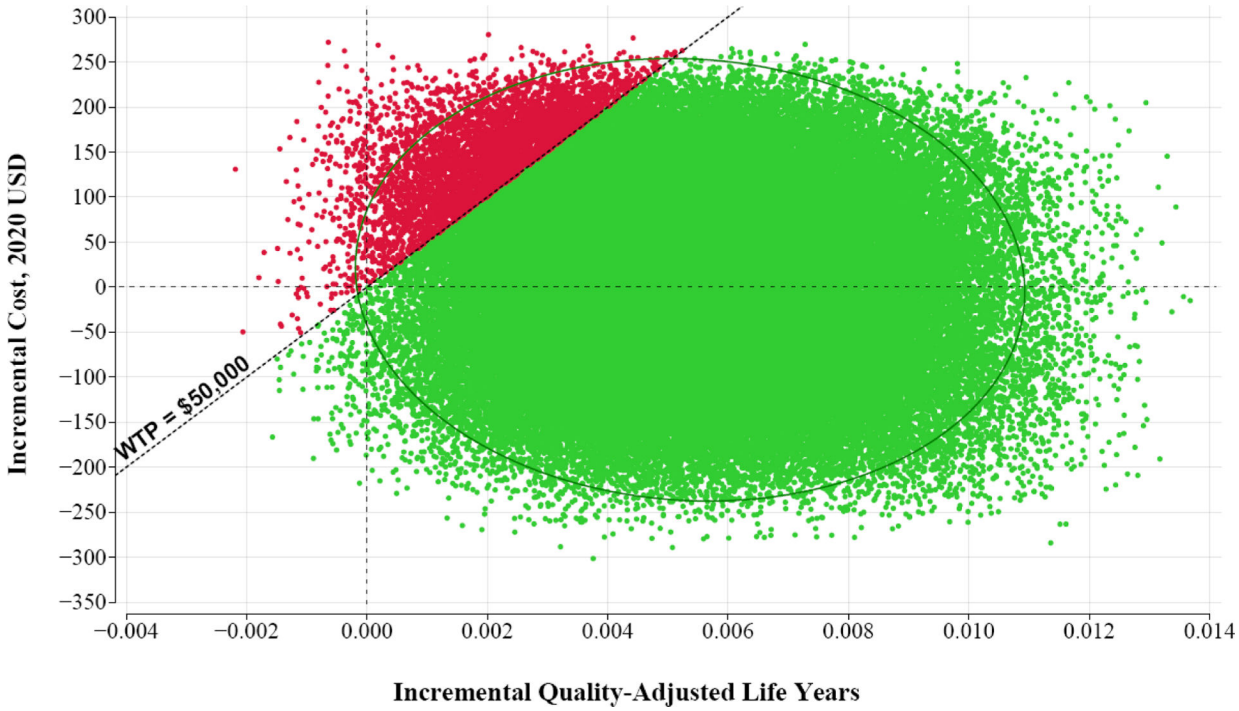


**Figure 2.**

Monte Carlo plot of 100,000 model iterations from probabilistic sensitivity analysis

Each plotted point represents an iteration of the probabilistic sensitivity analysis. The diagonal line indicates a willingness-to-pay (WTP) threshold of $50,000 and the ellipse represents the 95% confidence interval. *DPYD* genotyping is preferred to the no screening strategy for green points below the WTP threshold.

**Table 1.**

Model parameters and sources

| Parameter name | Parameter estimate | Range for sensitivity analysis | Source |
|---|---|---|---|
| Probability of carrying a deleterious *DPYD* gene variant | 0.063 | 0.05, 0.08 | Lee et al., J Natl Cancer Inst, 2014[5], Lee et al., Pharmacogenet Genomics 2016[17] |
| Sensitivity of *DPYD* genotyping | 0.99 | - | Vendor website18 |
| Specificity of *DPYD* genotyping | 0.99 | 0.985, 0.999 | Vendor website |
| Probability of grade 3–4 toxicity | | | |
| - *DPYD* variant, standard-dose chemotherapy | 0.73 | 0.65, 0.90 | Deenen et al., J Clin Oncol 2016[8] |
| - *DPYD* variant, reduced-dose chemotherapy | 0.39 | 0.34, 0.44 | Henricks et al., Lancet Oncol, 2018[13] |
| - *DPYD* wild-type, standard-dose chemotherapy | 0.23 | 0.18, 0.28 | Henricks et al., Lancet Oncol, 2018 |
| - *DPYD* wild-type, reduced dose chemotherapy | 0.23 | 0.18, 0.28 | Henricks et al., Lancet Oncol, 2018[a] |
| Probability of hospitalization | | | |
| - *DPYD* variant, standard-dose chemotherapy | 0.297 | 0.25, 0.40 | Toffoli et al., Clin Pharm Ther, 2019[19] |
| - *DPYD* variant, reduced-dose chemotherapy | 0.188 | 0.15, 0.20 | Henricks et al., Lancet Oncol, 2018 |
| - *DPYD* wild-type, standard-dose chemotherapy | 0.144 | 0.12, 0.16 | Henricks et al., Lancet Oncol, 2018 |
| - *DPYD* wild-type, reduced dose chemotherapy | 0.144 | 0.12, 0.16 | Henricks et al., Lancet Oncol, 2018[a] |
| Health utility values | | | |
| Baseline, prior to chemotherapy | 0.61 | 0.5, 0.9 | Best et al., Qual Life Res 2010[23] |
| −6 to 24 months after chemotherapy | 0.82 | 0.7, 1 | Ramsey et al., Cancer 2000[24] |
| -Year 3 after chemotherapy | 0.95 | 0.7, 1 | Ramsey et al., Cancer 2000 |
| - Years 4 to 5 after chemotherapy | 0.79 | 0.7, 1 | Ramsey et al., Cancer 2000 |
| - Utility during toxicity-related hospitalization (applied for 1 week) | 0.20 | 0, 0.48 | Author estimate |
| - Utility during grade 3–4 toxicity (applied for 3 months during chemotherapy treatment) | 0.48 | 0.40, 0.55 | Best et al., Qual Life Res 2010 |
| Probability of early treatment-related death | | | |
| - *DPYD* variant, standard-dose chemotherapy | 0.023 | 0.013, 0.039 | Sharma et al, Oncologist 2021[20] |
| - *DPYD* variant, reduced-dose chemotherapy | 0.002 | 0.001, 0.005 | Derived from Sharma et al, Oncologist 2021 |
| - *DPYD* wild-type, standard-dose chemotherapy | 0.001 | 0.001, 0.002 | Sharma et al, Oncologist 2021 |

| Parameter name | Parameter estimate | Range for sensitivity analysis | Source |
|---|---|---|---|
| - *DPYD* wild-type, reduced dose chemotherapy | 0.001 | 0.001, 0.002 | Sharma et al, Oncologist 2021[a] |
| Mortality after completion of adjuvant treatment period | | | |
| - Until year 5 | Supplementary data table | | Derived from SEER data (author analysis) |
| - Until year 5, patients with “false positive” *DPYD* genotyping and reduced-dose chemotherapy | Hazard ratio (HR) of 1.32[b] | HR 1.00, 1.50 | Derived from[22]IMPACT investigators, Lancet ’95. |
| Costs[c] | | | |
| - *DPYD* genotyping | $174.42 | $0, $300 | [25]Clinical Laboratory Fee Schedule, CMS.gov |
| - Hospitalization for chemotherapy toxicity | $15,524.04 | $0, $30,000 | [26]Roeland et al. J Clin Oncol ’18 (suppl, 112) |
| - Cancer recurrence after reduced-dose chemotherapy (*DPYD* wild-type) | $97,064.91 | $0, $120,000 | [27]Mariotto et al. J Natl Cancer Inst ’11. |

[a]Toxicities and adverse events extrapolated from observations in patients receiving standard-dose 5-FU chemotherapy.

[b]Increased hazard of death is expressed as compared to SEER-derived survival data described in the row above.

[c]Costs expressed in 2020 US dollars.

**Table 2.**

Six month interval probability of death following adjuvant chemotherapy for stage 3 colon cancer

| Model stage | Time from treatment | Probability of death |
|---|---|---|
| 1 | 0 to <6 months | 0.017 |
| 2 | 6 to <12 months | 0.034 |
| 3 | 12 to <18 months | 0.041 |
| 4 | 18 to <24 months | 0.042 |
| 5 | 24 to <30 months | 0.044 |
| 6 | 30 to <36 months | 0.041 |
| 7 | 36 to <42 months | 0.04 |
| 8 | 42 to <48 months | 0.035 |
| 9 | 48 to <54 months | 0.039 |
| 10 | 54 to <60 months | 0.038 |

Probability of death in six month intervals derived from the authors' analysis of SEER data for patients with stage 3 colon cancer receiving adjuvant chemotherapy.