

# Medical Services Advisory Committee (MSAC) Public Summary Document

## ***Application No. 1760 – DPYD genotyping to predict fluoropyrimidine-induced toxicity***

**Applicant:** The Royal College of Pathologists of Australasia (RCPA)

**Date of MSAC consideration:** 29 November 2024

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

### **1. Purpose of application**

An application requesting Medicare Benefits Schedule (MBS) listing of *dihydropyrimidine dehydrogenase (DPYD)* genotyping to predict fluoropyrimidine (FP)-induced toxicity in patients with solid tumours who are about to commence a treatment protocol that includes oral or intravenous FP was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health and Aged Care.

### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the public funding of *dihydropyrimidine dehydrogenase (DPYD)* genotyping to predict or diagnose toxicity from fluoropyrimidine (FP) chemotherapy. MSAC considered there is a high clinical need for *DPYD* testing as it can identify patients who are highly likely to experience life-threatening toxicity from FP-chemotherapy and require a lower dose of FP chemotherapy. MSAC considered *DPYD* genotyping has superior clinical effectiveness and non-inferior safety compared with usual care (no testing), however there were limitations in the clinical evidence. MSAC considered *DPYD* genotyping is cost-effective as it is expected to be cost saving to Australian governments as it will reduce the likelihood of severe toxicity and therefore costs of treating severe toxicity from FP chemotherapy.

MSAC noted testing for the four *DPYD* variants identified in the application will not identify all patients who may develop toxicity from FP-based chemotherapy. MSAC considered that while the currently identified variants are mainly prevalent in Caucasian populations, ongoing Australian clinical trials may lead to the identification of variants in people of non-European ancestry, including First Nations people. Therefore, MSAC considered the MBS item should be futureproofed to enable testing of additional variants as they are identified.

**Table 1 MSAC's supported MBS item descriptor**

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
<p><b>MBS item AAAA</b></p> <p>Genetic testing in the <i>DPYD</i> gene to diagnose or predict fluoropyrimidine-induced toxicity in a patient, where:</p> <ol style="list-style-type: none"> <li>a) the service is requested by a specialist or consultant physician; and</li> <li>b) the service is conducted before, during or after systemic administration of chemotherapy or radio-sensitisation, with a fluoropyrimidine; and</li> <li>c) genotyping is conducted to detect <i>DPYD</i> variants linked to reduced or absent dihydropyrimidine dehydrogenase (DPD) activity.</li> </ol> <p>Once per lifetime.</p> <p>Fee: \$182.00 Benefit: 75% = \$136.50 85% = \$154.70</p>	
<p><b>Explanatory note PN.7. XX - DPYD genotyping to predict fluoropyrimidine-induced toxicity - Item AAAA</b></p> <p>The list of gene variants analysed should be selected in line with current clinical guidelines, such as the eviQ guidelines, and should include direct detection of at least the following variants:</p> <ul style="list-style-type: none"> <li>• NM_000110.4(<i>DPYD</i>):c.1905+1G&gt;A</li> <li>• NM_000110.4(<i>DPYD</i>):c.1679T&gt;G</li> <li>• NM_000110.4(<i>DPYD</i>):c.2846A&gt;T</li> <li>• NM_000110.4(<i>DPYD</i>):c.1129-5923C&gt;G</li> </ul>	

<b>Consumer summary</b>
<p>This application from the Royal College of Pathologists of Australasia (RCPA) requested Medicare Benefits Schedule (MBS) listing of <i>dihydropyrimidine dehydrogenase (DPYD)</i> genetic testing. This test may identify patients who are likely to have severe side effects (toxicity) with a type of cancer chemotherapy called fluoropyrimidines (FP). MSAC supported funding for this test in patients who are about to commence FP-based treatment. MSAC also supported expanding the proposed patient population to include patients who are currently undergoing or have previously received FP-based treatment, to predict or ascertain FP-induced toxicity.</p> <p>FPs are chemotherapy agents used to treat solid tumours such as breast, colorectal or pancreatic cancers. FPs can also be used as radio-sensitising agents for radiotherapy. Commonly used FPs are 5- fluorouracil (5-FU) (administered intravenously) and capecitabine (a precursor of 5-FU) (administered orally). The enzyme dihydropyrimidine dehydrogenase (DPD) is needed to break down 5-FU and removing it from the body. Decreased DPD enzyme activity can lead to higher levels of FP in the body, subsequently resulting in increased toxicity risk from FPs. Individuals with adverse events related to FP sensitivity require admission to hospital for management, and in some cases the FP toxicity can lead to death. The <i>DPYD</i> gene is responsible for DPD enzyme activity. <i>DPYD</i> genotyping is a genetic test (a type of medical test) that looks at a person's deoxyribonucleic acid (DNA) for differences in genes (called genetic variants) that could explain why a person has a certain condition or in this case severe adverse reaction to FP-treatment.</p> <p><i>DPYD</i> genotyping in patients who are about to receive or received FP-based treatment would enable clinicians to predict FP-induced toxicity in many individuals. Patients with positive test results will either have their FP treatment dose lowered, or an alternative treatment option may be selected.</p> <p>MSAC acknowledged that <i>DPYD</i> testing does not identify all people who may have FP toxicity. MSAC noted that approximately 25% of patients who test negative may still have toxicity from</p>

## Consumer summary

FP-based chemotherapy. This is because testing for the four common *DPYD* genetic variants proposed in the application will not identify all patients who may develop toxicity from FP-based chemotherapy.

MSAC noted that *DPYD* testing aligns with international and national guidelines recommending the test before patients start FP-based treatment. MSAC considered that although *DPYD* testing would be beneficial for a small number of patients, it has significant clinical impact and will improve health outcomes for these patients. MSAC noted that *DPYD* testing is not expected to reduce the effectiveness of FP-based chemotherapy in treating cancer. Additionally, MSAC anticipated that the testing to be cost saving to Australian government as it will reduce hospitalisations and the cost to treat severe toxicity from FP chemotherapy. However, MSAC considered there was uncertainty in the estimated financial impact as utilisation may have been underestimated and therefore advised that a review of utilisation should be conducted.

MSAC noted that as this test does not identify everyone who is sensitive to FP-based treatment, clinician and patient education about the test limitations is essential prior to undergoing *DPYD* genotyping.

### MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported the public funding of *dihydropyrimidine dehydrogenase (DPYD)* genotyping to predict or diagnose toxicity from fluoropyrimidine (FP) chemotherapy. MSAC considered there is a high clinical need for *DPYD* testing due to the life-threatening consequences associated with FP-induced toxicity. MSAC further considered *DPYD* testing is safe, cost-effective, improves health outcomes, and subsequently is expected to be cost saving to Australian government as it will reduce the cost of treating severe toxicity from FP chemotherapy.

## 3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from the Royal College of Pathologists of Australasia (RCPA) requested Medicare Benefits Schedule (MBS) listing of *dihydropyrimidine dehydrogenase (DPYD)* genotyping to predict fluoropyrimidine (FP)-induced toxicity in patients with solid tumours who are about to commence a treatment protocol that includes oral or intravenous FP-based treatment. MSAC supported expanding the proposed patient population to include patients who are currently undergoing FP-chemotherapy, and also to include patients who had previously experienced FP-chemotherapy related adverse reactions.

MSAC noted that FP chemotherapy and FP-based radio-sensitisation are widely used, especially in the treatment of colorectal, pancreatic and breast cancers. Commonly used FPs are fluorouracil (5-FU) and capecitabine, a precursor of 5-FU. The therapeutic effect of 5-FU is mediated by a small fraction (1–3%) of the administered dose that is anabolised into cytotoxic metabolites. The enzyme dihydropyrimidine dehydrogenase (DPD) is crucial for breaking down 5-FU, mediating about 85% of its catabolism in the liver<sup>1</sup>. Patients with reduced DPD enzyme activity due to *DPYD* genetic variations experience increased drug exposure and therefore 5-FU toxicity.

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<sup>1</sup> Mattison LK, et al. Implications of dihydropyrimidine dehydrogenase on 5-fluorouracil pharmacogenetics and pharmacogenomics. *Pharmacogenomics*. 2002 Jul 1;3(4):485-92.

MSAC noted that approximately 3–8% of the Caucasian population have low DPD enzyme activity<sup>2</sup>, and 0.3% have no DPD enzyme activity<sup>3</sup>. These patients accumulate the active drug metabolite, leading to FP related toxicity. MSAC noted that *DPYD* genotyping of the four most common genetic variants predicts 20–30% of early onset life-threatening 5-FU toxicities. MSAC considered that results from the *DPYD* genotyping can inform the development of personalised treatment strategies, including dose optimisation of FP, or use of an alternative non-FP-based treatment. However, MSAC noted that severe FP-related toxicity still occurs in approximately 25% of wildtype *DPYD* carriers, indicating the absence of the four *DPYD* variants does not eliminate risk of developing FP-related toxicity and additional factors such as other deleterious *DPYD* variants may contribute to toxicity.

MSAC further noted that *DPYD* genotyping is recommended by several international and national guidelines, including eviQ<sup>4</sup>. MSAC noted that *DPYD* genotyping is not yet widely available in Australia, and testing is offered mostly through private pathology laboratories. MSAC further noted a RCPA Quality Assurance Program (QAP) is planned for 2025.

MSAC noted that the consultation feedback was supportive for the listing of *DPYD* genotyping, including from Bowel Cancer Australia (BCA) which highlighted the impact of FP-induced toxicity on the quality of life of patients. MSAC further noted feedback from Australian Genomics highlighting the lack data from First Nations peoples in genetic databases, and that testing negative for a variant does not exclude risk of toxicity.

MSAC noted the population, intervention, comparator and outcome (PICO) that had been ratified by the PICO Advisory Subcommittee. MSAC noted that the proposed population had no specific age restrictions, which was considered appropriate as it included both adults and paediatric patients. MSAC noted the proposed clinical management algorithm.

MSAC agreed with Evaluation Subcommittee (ESC) that the clinical claim was non-inferior safety compared with no testing. However, MSAC noted that education about the test limitations is essential, since *DPYD* genotyping will not detect all *DPYD* variant-associated FP-induced toxicity. MSAC noted the concern that the turnaround time (TAT) for the test could delay the start of treatment, especially in rural or remote areas. However, MSAC noted a small study suggested that the TAT is within 5 days for most samples and typically FP treatment commenced about 1-2 weeks post-diagnosis. MSAC further noted that safety is not adversely affected by FP dose reductions.

MSAC noted that the clinical evidence for this application was informed by 4 direct comparative studies and 3 direct non-comparative studies (all single arm studies for the intervention). MSAC noted that although the studies all had serious or critical risk of bias as they were underpowered and used retrospective control cohorts, MSAC acknowledged that presence of *DPYD* variants had a significant clinical impact for a small number of patients receiving FP-based chemotherapy.

MSAC noted ESC's concern regarding the use of proposed *DPYD* proxy variant c.1236G>A which is not in complete linkage disequilibrium with causal variant c.1129-5923C>G (*HapB3* variant) according to a recent study<sup>5</sup>. MSAC noted that most direct evidence studies used the proxy variant. However, recent literature identified that c.1236G>A is not a suitable proxy for the c.1129-5923C>G variant. MSAC noted that this emphasised the importance of directly detecting the causal variant that is responsible for decreased DPD activity (i.e. the c.1129-5923C>G variant). MSAC therefore recommended *DPYD* genotyping should include the variant c.1129-

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<sup>2</sup> Amstutz U, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther.* 2018 Nov 20; 103(2):210–216.

<sup>3</sup> Detaillieur, S., E. Segelov, M. D. Re, et al. 2021. "Dihydropyrimidine dehydrogenase deficiency in patients with severe toxicity after 5-fluorouracil: a retrospective single-center study." *Ann Gastroenterol.* 2020 Oct 12; 34(1):68-72.

<sup>4</sup> <https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-treatment/1744-dihydropyrimidine-dehydrogenase-dpd-enzyme>

<sup>5</sup> Turner AJ, et al. Updated *DPYD* HapB3 haplotype structure and implications for pharmacogenomic testing. *Clin Transl Sci.* 2024 Jan;17(1):e13699. doi: 10.1111/cts.13699. PMID: 38129972; PMCID: PMC10777430.

5923C>G, and not the c.1236G>A proxy. Although MSAC supported the use of direct testing of the causal variant for *DPYD* genotyping; however, it also considered that if laboratories choose to use the proxy variant for *DPYD* testing, it would be good clinical practice to include a limitation in their report acknowledging the incomplete LD, as well as information pertaining to c.1129-5923C>G as the underlying causal variant.

MSAC noted that there were no Australian studies or international studies that accurately reflected the ethnic diversity of Australia's population, limiting the available evidence on the effectiveness of *DPYD* genotyping in the Australian context. However, MSAC noted, 4 Australian trials on *DPYD* genotyping were being conducted with some preliminary results available from the Nalder et al, 2021 study and the GENESCREEN pilot study.<sup>6, 7</sup> MSAC noted that preliminary findings from the Nalder et al, 2021 study indicated a modest reduction in the risk of FP related severe toxicity and hospital admission when dosing was guided by *DPYD* genotyping in comparison to the untested cohort. MSAC highlighted the need for further Australian-specific studies to better understand the prevalence of the 4 common variants across the diverse ancestry groups in Australia, and to identify and determine the prevalence of other rare *DPYD* variants and their impact on DPD activity. MSAC also noted the evolving evidence base for *DPYD* variants, with more than 1,600 variants described so far, although the functional significance of many of these remains unclear. As a result, MSAC considered that the MBS item descriptor of *DPYD* genotyping should remain dynamic and adaptable to accommodate future developments in this space.

MSAC noted the applicant's pre-MSAC response which acknowledged that factors beyond the four listed *DPYD* variants may contribute to FP related toxicity. However, it emphasized that it would be more pragmatic to support *DPYD* testing based on existing evidence to mitigate the severe effects for the small number of affected patients. MSAC also noted the applicant agreed to the revised fee proposed by ESC. Subsequently, MSAC agreed with ESC that a revised fee of \$182 was appropriate for *DPYD* genotyping. To futureproof the item, MSAC agreed with the department's proposal of removing specific reference to the number of variants to be tested. Additionally, MSAC considered the department's proposed amendment to the explanatory note to refer to 'current clinical guidelines, such as the eviQ guidelines' was reasonable.

MSAC noted that the economic evaluation included a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). MSAC further noted that the incremental cost-effectiveness ratio (ICER) was \$67,910 per patient to avoid severe FP-related toxicity, and the test was considered a dominant strategy in the cost-utility analysis. However, MSAC acknowledged the uncertainty in the economic model, as it largely relied on assumptions such as reduced length of stay in hospital due to FP-related adverse events (AEs) and the predicted uptake of testing.

MSAC noted the estimated financial impact on the MBS using the supported fee of \$182 would be \$1.5 million in Year 1, increasing to \$3.4 million by Year 6 as the uptake of genotyping increases over time with greater patient awareness of testing. MSAC considered *DPYD* genotyping to be cost-effective as it is expected to result in cost savings to Australian government by reducing the likelihood of severe toxicity and the associated costs of treating severe toxicity from FP chemotherapy. However, MSAC noted ESC's concerns regarding the clinical uncertainty around the effectiveness of *DPYD* genotyping and the large impacts uptake rate had on the financials. MSAC noted that these uncertainties may have led to an overestimation of the savings attributed to the listing of *DPYD* genotyping. Subsequently, MSAC advised that a review of utilisation of *DPYD* testing should be conducted following implementation. Overall, MSAC supported listing *DPYD* genotyping on the MBS, as it has significant clinical benefits to some patients who may otherwise have life-threatening AEs due to FP-induced toxicity. MSAC further noted that as *DPYD* genotyping is standard clinical practice and is recommended in international

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<sup>6</sup> Nalder, M et al. [Routine, prospective DPYD genotyping guided dose-individualisation for patients receiving fluoropyrimidines: Implementation, prevalence and patient safety outcomes from a multi-institutional clinical trial](#). *JCO*. 2024; 42(16), 12121-12121.

<sup>7</sup> White, C et al. (2023). Feasibility of DPYD genotyping in Australian cancer patients. doi.org/10.21203/rs.3.rs-2838793/v1

and national guidelines, it is important that the MBS aligns with these guidelines. MSAC further noted the GENESCREEN trial, which is investigating *DPYD* genotyping, is funded by the Medical Research Future Fund (MRFF), and advised the department that the funding body be informed about MSAC's decision.

## 4. Background

MSAC has not previously considered *DPYD* genotyping to predict FP-induced toxicity in patients with solid tumours who are about to commence a treatment protocol that includes oral or intravenous FP-based therapy.

## 5. Prerequisites to implementation of any funding advice

There are no prerequisites to be met.

## 6. Proposal for public funding

The intervention proposed is *DPYD* genotyping targeting at least four *DPYD* gene variants before the commencement of FP-based chemotherapy (to identify patients at risk of severe FP-related toxicity). The proposal intends to create a new MBS item (Table 2).

**Table 2 Presentation of an existing, amended or newly proposed MBS item**

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
<p>MBS item AAAA            Genetic testing for four or more variants in the <i>DPYD</i> gene to predict fluoropyrimidine-induced toxicity in a patient, where:</p> <ol style="list-style-type: none"> <li>the service is requested by a specialist or consultant physician; and</li> <li>the service is conducted prior to the initiation of chemotherapy, or radio-sensitisation, with a fluoropyrimidine, administered systemically; and</li> <li>genotyping is conducted to detect at least four <i>DPYD</i> variants that can lead to reduced or completely absent dihydropyrimidine dehydrogenase (DPD) activity.</li> </ol> <p>Once per lifetime.</p>	
<p>Fee: \$188.00 Benefit: 75%=\$141.00    85%=\$159.80</p>	
<p>Explanatory note:            The variants analysed should be selected in line with current guidelines, and must include at least:</p> <ul style="list-style-type: none"> <li>NM_000110.4(<i>DPYD</i>):c.1905+1G&gt;A</li> <li>NM_000110.4(<i>DPYD</i>):c.1679T&gt;G</li> <li>NM_000110.4(<i>DPYD</i>):c.2846A&gt;T</li> <li>NM_000110.4(<i>DPYD</i>):c.1129-5923C&gt;G</li> </ul> <p>Published evidence for the association of presence of these four variants with severe fluoropyrimidine-related toxicity, is based on people with Caucasian ancestry only.</p>	

Source: p30 of the [PICO confirmation](#).

DPD=Dihydropyrimidine dehydrogenase enzyme; *DPYD*=*Dihydropyrimidine dehydrogenase* gene; MBS=Medicare Benefits Schedule.

PASC considered that the variants recommended for testing may change over time and that the inclusion of the four proposed variants (based on current guidelines) in the testing will be ensured through the external quality assessment (EQA) process. PASC considered that the item descriptor be phrased adequately to allow testing for newly identified gene variants in the future as evidence emerge on new genetic variants associated with severe FP-related toxicity and in population groups with ancestry other than Caucasian. PASC considered that specifying the

variants in the item descriptor was therefore not necessary, and the four currently specified variants should be moved to an explanatory note. PASC considered the explanatory note should further state that these variants are based on studies in Caucasian populations only, to convey to laboratories that additional variants may also be appropriate in patients of ancestries with other relevant variants.

The proposed MBS fee for *DPYD* genotyping is \$188. The applicant advised that the proposed fee included a commercially available kit, specimen collection and transportation, sample processing and consumables, technician labour, genomic analysis, interpretation and report generation, and pre-analytical steps required such as DNA extraction ([PICO confirmation](#)). PASC considered that this fee was similar to the range of current fees for this testing in private laboratories in Australia (\$95-\$160, as described by *eviQ*). PASC noted the fee was also similar to that for MBS item 73397 (Fee \$200) for characterisation of variants in the *CALR* and *MPL* genes, although much higher than MBS item 73317 (\$36) for detecting genetic mutations for haemochromatosis. On balance, PASC considered the proposed fee of \$188 appeared reasonable.

## 7. Population

There was one PICO set provided, defining the population as all patients with solid tumours who are about to commence a treatment protocol that includes oral or intravenous FP. Systemic FPs are used to treat solid tumours of (but not limited to) colorectal, upper gastrointestinal, head and neck, breast, and pancreatic cancers. The population also includes all patients requiring FPs as radiosensitising agents for radiotherapy.

FPs are chemotherapy agents used to treat solid tumours. Commonly used FPs are:

- fluorouracil, or 5-fluorouracil (5-FU), administered intravenously, and
- capecitabine, a precursor of 5-FU, administered orally.

The enzyme DPD is crucial for breaking down 5-FU, handling about 80% of its liver catabolism. Catabolism is a key factor in the elimination of 5-FU from the body and any decrease in DPD enzyme activity can lead to prolonged exposure to the cytotoxic metabolites of FPs with consequent increased toxicity risk from FPs. *DPYD* variant carriers are at increased risk of diminished DPD enzyme activity and hence increased risk of toxicity to 5-FU.

*DPYD* genotyping to predict FP-induced toxicity in patients with solid tumours would be in addition to FP-based chemotherapy and take place before the commencement of the FP-based chemotherapy.

## 8. Comparator

The comparator is no pre-treatment *DPYD* genotyping.

Currently (in the absence of *DPYD* genotyping) all patients receive standard-dose systemic FP-based chemotherapy unless they experienced a previous episode of toxicity or are deemed unfit to receive full-dose chemotherapy following medical assessment by an oncologist.

## 9. Summary of public consultation input

The MSAC welcomed consultation input received for this application and noted the period for public consultation closed on 11 October 2024. Consultation input was welcomed from ten professional organisations, one consumer organisation and three individuals, two of whom were medical specialists and one consumer.

The organisations that submitted input were:

- Therapeutic Goods Administration (TGA)
- National Pathology Accreditation Advisory Council (NPAAC)
- The Royal College of Pathologists of Australasia (RCPA)
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
- Australian Pathology
- PathWest Laboratory Medicine, QEII Medical Centre, Nedlands
- The Society of Hospital Pharmacists of Australia (SHPA)
- Consumer Representatives from Melbourne Genomics Health Alliance
- Australian Genomics
- Bowel Cancer Australia (BCA)
- Australasian Gastro-Intestinal Trials Group (AGITG)

### Benefits

- *Dihydropyrimidine dehydrogenase gene (DPYD)* testing may identify at-risk patients allowing to tailor their treatments to avoid potential significant/catastrophic toxicity.
- Public funding of *DPYD* genotyping will promote equity of access for all Australians, particularly benefitting rural patients who face geographical barriers. In addition, it would remove any financial barriers to patient access for this vulnerable patient group.

### Disadvantages

- There may be delays in treatment commencement due to the turnaround time for the test results to the clinician.
- Targeted *DPYD* genotyping as a standalone test to prospectively screen for DPD deficiency has poor sensitivity. Furthermore, testing negative for a *DPYD* variant does not eliminate the possibility of experiencing FP-related toxicity.

### Additional Comments

The RCPA noted the test is in line with the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines from 2017 for Fluoropyrimidine Dosing in cancer patients and the ASCEPT noted that screening for a panel of *DPYD* gene variants is recommended by the European Medicines Agency and the National Health Service (NHS) and is considered safe practice by eviQ.

ASCEPT further noted that currently no other screening procedures have the high-quality evidence-base that has been reported for *DPYD* single nucleotide polymorphism (SNP) panel testing. The economic costs of severe adverse events following 5-fluorouracil and capecitabine treatment to the Australian health system are likely substantial.

### Feedback following ESC consideration

ESC requested further information on the current usage of *DPYD* testing in Australian clinical practice, as this test is currently available to some patients in Australia. ESC also sought information on therapeutic drug monitoring (TDM) and its utilisation. The department sought feedback from Medical Oncology Group of Australia (MOGA) and Clinical Oncology Society of Australia (COSA).

Three expert members identified by MOGA provided input. Overall, routine *DPYD* testing for all patients anticipated to receive FP anticancer treatment is not currently considered standard practice in Australia as protocols vary between organisations. *DPYD* testing is not funded on the MBS and is thus either self-funded by patients or funded by the treatment centre. While some organizations routinely conduct *DPYD* testing before administering FP anticancer treatment, others may selectively test based on treatment regimen risk or patient willingness to cover costs. Although the current eviQ guidelines does not mandate the test, it is recommended, and with the



increasing trend in usage of *DPYD* testing prior to FP-based anticancer treatment, it is anticipated that the guidelines will evolve to recommend the testing. Currently, TDM is not routinely performed for patients receiving pre-treatment *DPYD* genotyping for FP-based anticancer treatment. TDM can be achieved by using commercial kits on standard biochemical analysers, however it is not currently funded and is primarily used as part of clinical trials. Since TDM is not funded, its usage would remain unchanged with *DPYD* testing.

## 10. Characteristics of the evidence base

Seven studies<sup>8,9,10,11,12,13,14</sup> provided direct test to health outcomes evidence of *DPYD* genotyping before the commencement of systemic FP-based chemotherapy to identify patients at risk of severe FP-related toxicity. Four studies provided direct comparative evidence (comparing the intervention with the comparator), and an additional 3 studies provided evidence for the intervention only. A summary of the key features of the studies providing direct from test to health outcome evidence is provided in Table 3.

Given that the intervention described in the PICO only has clinical utility when treatment management decisions are made using the results, the “intervention” group in direct evidence studies are considered to be *DPYD* variant carriers with pre-treatment *DPYD* genotyping who receive an initial reduced dose of FP-based chemotherapy.

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<sup>8</sup> Kleinjan, JP *et al.* Tolerance-based capecitabine dose escalation after *DPYD* genotype-guided dosing in heterozygote *DPYD* variant carriers: a single-center observational study. *Anticancer Drugs*. 2019;30(4):410-5.

<sup>9</sup> Knikman, JE *et al.* Survival of patients with cancer with *DPYD* variant alleles and dose-individualized fluoropyrimidine therapy-a matched-pair analysis. *J Clin Oncol*. 2023;41(35):5411-21.

<sup>10</sup> Lunenburg, C *et al.* Standard fluoropyrimidine dosages in chemoradiation therapy result in an increased risk of severe toxicity in *DPYD* variant allele carriers. *Eur J Cancer*. 2018;104:210-8.

<sup>11</sup> Paulsen, NH *et al.* Implementation and clinical benefit of *DPYD* genotyping in a Danish cancer population. *ESMO Open*. 2023;8(1):100782.

<sup>12</sup> Wang L, Howlett S, Essapen S. Treating patients with dihydropyrimidine dehydrogenase (DPD) deficiency with fluoropyrimidine chemotherapy since the onset of routine prospective testing-The experience of a large oncology center in the United Kingdom. *Semin Oncol*. 2022;49(2):170-7.

<sup>13</sup> Wigle, TJ *et al.* Impact of pretreatment dihydropyrimidine dehydrogenase genotype-guided fluoropyrimidine dosing on chemotherapy associated adverse events. *Clin Transl Sci*. 2021;14(4):1338-48.

<sup>14</sup> Henricks, LM *et al.* A cost analysis of upfront *DPYD* genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. *Eur J Cancer* 2018;107: 60-67.

**Table 3 Key features of the direct evidence**

Trial/Study	Country	Study design	Number of Participants <sup>^</sup>	c.1129-5923C>G proxy?	Risk of bias	Key outcome(s)
<b>Direct comparative evidence</b>						
Henricks et al. (2018) <sup>14</sup> NCT02324452	Netherlands	Prospective, multicentre	Intervention=85 Comparator=333	Yes	Critical	Grade ≥3 FP-related toxicity Hospitalisation Treatment stopping
Lunenburg et al. (2018) <sup>8</sup>	Netherlands, Italy	Retrospective, multicentre	Intervention=23 Comparator=34	Yes	Critical	Grade ≥3 FP-related toxicity Hospitalisation
Paulsen et al. (2023) <sup>9</sup> NCT05266300	Denmark	Prospective, single centre	Intervention=22 Comparator=42	No	Critical	Survival outcomes (OS, PFS) Grade ≥3 FP-related toxicity Treatment discontinuation
Wigle et al. (2021) <sup>11</sup>	Canada	Retrospective, single centre	Intervention=47 Comparator=333	Yes	Serious	Grade ≥3 FP-related toxicity Treatment discontinuation
<b>Direct non-comparative evidence</b>						
Kleinjan et al. (2019) <sup>6</sup>	Netherlands	Retrospective, single centre	Intervention=11	Yes	Serious	Grade ≥3 FP-related toxicity Hospitalisation
Knikman et al. (2023) <sup>7</sup> NCT02324452	Netherlands	Retrospective matched-pair survival analysis, multicentre	Intervention=93	Yes	Serious	Grade ≥3 FP-related toxicity Survival outcomes (OS, PFS) Treatment discontinuation
Wang et al. (2022) <sup>10</sup>	United Kingdom	Retrospective, single centre	Intervention=23	Yes	Critical	Grade ≥3 FP-related toxicity Hospitalisation Treatment response

FP=Fluoropyrimidine; OS=Overall survival; PFS=Progression-free survival;

<sup>^</sup>Where the intervention group are *DPYD* variant carriers with pre-treatment *DPYD* genotyping who receive an initial reduced dose of FP-based chemotherapy, and the comparator group are *DPYD* variant carriers with no pre-treatment *DPYD* genotyping and receipt of standard dosing.

Findings for outcomes of interest were summarised and assessed using GRADE. All included studies were non-randomised studies of interventions (NSRI), assessed as having critical or serious risk of bias using ROBINS-I. The main issues contributing to risk of bias resulted from a combination of the limitations inherent to NSRIs and poor study design in some studies, as well as underpowered sample sizes and use of retrospective control cohorts.

Overall, the department contracted assessment report (DCAR) considered there were significant issues with transitivity and applicability of the direct from test to health outcomes evidence found in the literature. Primarily:

- There were no Australian studies or studies representative of the ethnic make-up of the Australian population. Of note, four Australian trials are currently underway, and one has

recently presented interim results<sup>15,16,17,18</sup> (White et al., 2023, Michael, 2020, Alexander, 2024, Nalder, 2021). The Australian trial (GENESCREEN) is currently underway following a pilot feasibility study (White et al., 2023). This aims to recruit 5,000 patients including all ethnic groups, and specifically target all eligible cases with Aboriginal and Torres Strait Islander ancestry<sup>18</sup>. The study will evaluate key outcomes of toxicity at 60-day post initiation of FP-based chemotherapy and long-term cancer outcomes. The interim trial results Michael (2020) (n=493) examined the feasibility of the implementation *DPYD* pre-emptive screening. Secondary endpoints included safety outcomes and Quality of Life (QoL). Exploratory examination of cancer outcomes was also conducted. The interim results demonstrated that:

- 4% of patients were *DPYD* intermediate metabolisers requiring upfront dose reduction
- 8% of patients were UGT1A1\*28 poor metabolisers requiring upfront dose reduction
- 96% of gene test results (for *DPYD* and UGT1A1\*28) reported prior to cycle 1, allowing us to dose adjust prior to patients commencing fluoropyrimidines or irinotecan to prevent severe toxicities.
- Average days from sample collection to reporting of gene test results:
  - Approx. 5 days for *DPYD* genotyping
  - 7 days for UGT1A1\*28 genotyping that are available do not influence the overall findings of this report.
- Key direct clinical evidence studies excluded poor *DPYD* metabolisers. These patients are at the highest risk of FP-associated toxicity, though estimated population prevalences are low (0.1%).
- Most direct evidence studies used *DPYD* proxy variant c.1236G>A which is not in complete linkage disequilibrium with c.1129-5923C>G. In these studies, there is a risk of false negative results (though there is no documented case of this in the literature)<sup>1</sup>.

## 11. Comparative safety

There was no direct evidence for safety related to *DPYD* genotyping, though adverse events of the genotyping test itself are expected to be minimal. Genotyping is not invasive and while psychosocial harms of genetic information are reported in other clinical contexts, given that *DPYD* genotyping does not have other clinical utilities or applications, these are not expected to be significant.

Adverse events from change in patient management (e.g., treatment modifications, monitoring) from *DPYD* genotyping are also expected to be minimal because treatment modification protocols recommend dose reductions only, which would reduce toxicity. However, there are concerns that dose reductions could compromise therapeutic effectiveness. This was assessed in two direct non-comparative studies reporting treatment response and survival outcomes for *DPYD* variant carriers receiving the intervention; results, interpretation, key uncertainties and GRADE assessments are presented in Table 4 under comparative effectiveness.

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<sup>15</sup> White, C et al. (2023). Feasibility of *DPYD* genotyping in Australian cancer patients. doi.org/10.21203/rs.3.rs-2838793/v1

<sup>16</sup> Alexander, M. 2024. Pharmacogenomic medicines optimisation for people with cancer – a multicentre teletrial enabled Interrupted Time Series trial (PRECISION-ITS): Medication safety outcomes in the Pharmacogenomics primary study and discovery program [Online]. The Australian New Zealand Clinical Trials Registry (ANZCTR). Available: <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=386668&isReview=true>.

<sup>17</sup> Nalder, M. 2021. Pre-treatment dihydropyrimidine dehydrogenase (*DPYD*) genotyping to individualise fluoropyrimidine-based chemotherapy: An evaluation of clinical implementation and treatment-related toxicity. [Online]. The Australian New Zealand Clinical Trials Registry (ANZCTR). Available: <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=381432&isReview=true>.

<sup>18</sup> Scott, R. 2021. GeneScreen 5-FU: *DPYD* Genotype-guided dose Personalisation for Fluoropyrimidine prescribing in Solid Organ Cancer Patients. [Online]. The Australian New Zealand Clinical Trials Registry (ANZCTR). Available: <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384319>.

There is the potential for test turnaround time (5-10 days) to result in delay to treatment commencement, which has been expressed as a concern by oncology clinicians qualitatively<sup>2,19</sup>, though no evidence was identified to support whether this has clinically relevant impacts. This may be a particular concern in regional, rural and remote areas, where there are additional access delays. In addition, improved procedures for blood collection, transportation and laboratory handling of samples may reduce TATs<sup>14</sup>.

## 12. Comparative effectiveness

Seven studies reported direct evidence of clinical effectiveness outcomes; results, interpretation, key uncertainties, and GRADE assessments are presented in Table 4. For all toxicity outcomes, pooled results were not possible due to differences in study design and measurement of outcomes, particularly dose reduction algorithms. Due to very small sample sizes, statistical comparison was generally not appropriate<sup>20</sup>. Narrative interpretation of results is therefore required which has significant limitations, and it is not possible to rule out confounders for all reported effects<sup>20</sup>.

Overall, the DCAR considered there was insufficient evidence to support conclusions about clinically meaningful efficacy of the intervention. The DCAR considered the true effect size would require appropriately powered, randomised controlled trials. However, it is noted that given the level of evidence for the association of *DPYD* variants and increased toxicity, prospective RCTs would be considered unethical and impractical.

**Table 4 Summary of findings table – clinical effectiveness outcomes**

Outcomes	Participants and studies	Results, interpretation and key uncertainties	Certainty of the evidence (GRADE) Evidence statement
Incidence of Grade ≥3 FP-related toxicity	Comparative evidence (4 studies)  Intervention: N=177 Comparator: N=859*	<ul style="list-style-type: none"> <li>The proportion of patients with Grade ≥3 toxicity was generally lower in the intervention cohorts, though studies were not powered to detect significant differences. Due to very small sample sizes and lack of adjustment, results could be confounded or mediated.</li> <li>One key concern is that distribution of specific alleles across intervention and control cohorts in multiple studies was not comparable. For example, Paulsen et al. (2023) reported 23% (5/22) patients experienced toxicity in the intervention group, versus 29% (11/42) in the control group. However, there were less c.1905+1G&gt;A carriers in the intervention group (4.6% (1/22)) than the control group (16.7% (7/42)), and most (6/9) c.1905+1G&gt;A carriers experienced severe toxicity. This limits capacity to draw conclusions about the efficacy of <i>DPYD</i> genotyping for 4 variants on a population level.</li> </ul>	<p>⊕⊕⊕⊕ VERY LOW<sup>a</sup> The evidence is very uncertain about the effect of <i>DPYD</i> genotyping before the commencement of systemic FP-based chemotherapy compared to no <i>DPYD</i> genotyping on incidence of Grade ≥3 FP-related toxicity.</p>
	Non-comparative evidence (7 studies)	<ul style="list-style-type: none"> <li>Comparing <i>DPYD</i> variant carriers receiving reduced dose to wildtypes, studies generally reported no significant difference in severe FP-related toxicity. This may suggest that <i>DPYD</i> variant carriers receiving dose reduction do not experience increased risk of severe FP-related AEs compared with non-carriers receiving the standard of care.</li> </ul>	

<sup>19</sup> Lau-Min, KS et al. Preemptive pharmacogenetic testing to guide chemotherapy dosing in patients with gastrointestinal malignancies: a qualitative study of barriers to implementation. *BMC Cancer* 2022;22(1):47.

<sup>20</sup> Kim H, Gurrin L, Ademi Z, Liew D. Overview of methods for comparing the efficacies of drugs in the absence of head-to-head clinical trial data. *Br J Clin Pharmacol.* 2014;77(1):116-21.

Outcomes	Participants and studies	Results, interpretation and key uncertainties	Certainty of the evidence (GRADE) Evidence statement
	Intervention: N=304	However, small sample sizes, key differences in study characteristics (such as carrier frequencies of alleles and dose reduction protocols) and serious to critical risk of bias concerns for all studies limits reliability of conclusions.	
FP-related hospitalisations	Comparative evidence (2 studies)  Intervention: N=55 Comparator: N=76	<ul style="list-style-type: none"> <li>Results were conflicting; one study suggested lower rates of hospitalisation for the intervention group Paulsen et al. (2023), where the other suggested no difference Lunenburg et al. (2018). For the former, as with toxicity, there were less c.1905+1G&gt;A carriers in the intervention group (4.6% (1/22)) than the control group (16.7% (7/42)), and most (6/9) c.1905+1G&gt;A carrier's experienced hospitalisation. Both studies were assessed as having critical risk of bias. Together, this suggests results are not reliable.</li> </ul>	<p>⊕⊕⊕⊕ VERY LOW<sup>a</sup></p> <p>The evidence is very uncertain about the effect of <i>DPYD</i> genotyping before the commencement of systemic FP-based chemotherapy compared to no <i>DPYD</i> genotyping on FP-related hospitalisations.</p>
	Non-comparative evidence (4 studies)  Intervention: N=164	<ul style="list-style-type: none"> <li>There were marked differences in reported proportions of patients hospitalised; hospital admission for <i>DPYD</i> variant carriers receiving a reduced dose ranged from 0% (0/22; 95% CI 0% - 15.4%) to 43.5% (10/23; 95% CI 23.2% - 65.5%). Extremely small sample sizes are likely key drivers of differences in results and directions of effect, and most studies were assessed at critical risk of bias.</li> </ul>	
FP-related treatment intervention (stopping, delay or dose reduction)	Comparative evidence (2 studies)  Intervention: N=55 Comparator: N=76	<ul style="list-style-type: none"> <li>Results of two studies suggested minimal, if any, differences in toxicity related treatment stopping and dose reduction between the intervention and comparator. However, small sample sizes and critical risk of bias make results unreliable.</li> </ul>	<p>⊕⊕⊕⊕ VERY LOW<sup>a</sup></p> <p>The evidence is very uncertain about the effect of <i>DPYD</i> genotyping before the commencement of systemic FP-based chemotherapy compared to no <i>DPYD</i> genotyping on FP-related hospitalisations.</p>
	Non-comparative evidence (6 studies)  Intervention: N=252	<ul style="list-style-type: none"> <li>Four studies reported no significant difference in the proportion of patients with treatment stopping for <i>DPYD</i> variant carriers with reduced FP-dose compared to wildtypes; two studies reported no difference in further dose reduction. This may suggest that <i>DPYD</i> variant carriers receiving dose reduction do not experience increased risk of treatment non-completion compared with non-carriers receiving the standard of care. However, small sample sizes, key differences in study characteristics (such as carrier frequencies and dose reduction protocols) and serious to critical risk of bias concerns for all studies should be considered.</li> </ul>	
Survival outcomes (OS, PFS)	Non-comparative evidence (1 study)  Intervention: N=93	<ul style="list-style-type: none"> <li>One study conducted a retrospective matched-pair survival analysis, reporting no significant differences in overall survival (OS) or progression-free survival (PFS) for <i>DPYD</i> variant carriers receiving reduced doses compared to wildtypes. This would suggest that, overall, dose reduction based on <i>DPYD</i> genotyping may not compromise treatment effectiveness. However, PFS outcomes were borderline significant and trending towards shorter PFS for <i>DPYD</i> variant carriers. Secondary analyses suggested that this was likely driven by survival results in the c.1236G&gt;A subgroup. In this group, over 75% of c.1236G&gt;A carriers were kept on a consistent 75% dose over all treatment cycles. As dose escalation was not completed according to the protocol, this may have impacted treatment</li> </ul>	<p>⊕⊕⊕⊕ VERY LOW<sup>a</sup></p> <p>The evidence is very uncertain about the effect of <i>DPYD</i> genotyping before the commencement of systemic FP-based chemotherapy compared on survival outcomes.</p>

Outcomes	Participants and studies	Results, interpretation and key uncertainties	Certainty of the evidence (GRADE) Evidence statement
		effectiveness. Overall, the study was judged as having a critical risk of bias with post-hoc power analysis showing the study was significantly underpowered for PFS events (and likely for OS).	
Treatment response	Non-comparative evidence (1 study)  Intervention: N=23	<ul style="list-style-type: none"> <li>Treatment response outcomes were reported in one small retrospective study. Most patients (N=11/15) with measurable disease had at least a partial response to treatment despite dose reductions. This may suggest reduced dosing in <i>DPYD</i> does not impair antitumor efficacy of FP, supporting conclusions from Knikman et al. (2023). However, this was a small, retrospective study assessed at critical risk of bias. Further research is needed on treatment response of reduced FP doses.</li> </ul>	⊕⊕⊕⊕ VERY LOW <sup>a</sup> The evidence is very uncertain about the effect of <i>DPYD</i> genotyping before the commencement of systemic FP-based chemotherapy on treatment response.

AE=Adverse event; *DPYD*=Dihydropyrimidine dehydrogenase gene; FP=Fluoropyrimidine; OS=Overall survival; PFS=Progression-free survival; Critical/serious risk of bias in all studies (downgraded one for risk of bias). Not enough participant characteristics reported to assess applicability to Australian context, dose reduction protocols not aligned with current CPIC guidelines (downgrade one for indirectness). Not appropriately powered to detect significant differences in effect sizes (downgraded one for imprecision).

As part of the systematic review procedure, linked evidence was also identified and was presented as supporting information. Key results for PICO-specified outcomes are summarised in Table 5 below.

**Table 5 Summary of findings table – test performance and change in management outcomes.**

Outcomes Studies, N	Results, interpretation and key uncertainties
Test performance outcomes  10 studies (observational) N=15037	<ul style="list-style-type: none"> <li>The pooled total carrier rate across 10 studies of any <i>DPYD</i> variant was 5.5% (823/15037). Naive comparison of results with two reviews found in the literature (but did not fit the PICO) suggests results are reasonable.</li> <li>One study contributed over half of the sample to the pooled carrier rate and reported a lower c.1905+1G&gt;A carrier rate when compared to one of the reviews (0.9% versus 1.9%). Given c.1905+1G&gt;A is a no function variant which potentially drove key clinical outcomes (e.g., toxicity and hospitalisation in Paulsen et al. (2023) in the direct evidence, this variance may have important implications for clinical and cost-effectiveness outcomes. There were some potential risk of bias concerns as assessed using QUADAS 2<sup>21</sup>, primarily related to non-consecutive or random sampling and inappropriate exclusions.</li> <li>Only 4 of 10 included studies reported patient ethnicity, which were between 90.4% and 99% Caucasian. This precluded analysis of any differences in diagnostic yield across race or ancestry. Without any studies conducted in an Australian setting, and in absence of reported ethnicity, applicability of the calculated variant frequencies may therefore be different in an Australian setting.</li> <li>Published evidence suggests <i>DPYD</i> genotyping has very low sensitivity but high specificity to predict FP-related toxicity<sup>22</sup>, which was supported by one study identified in the systematic literature search<sup>23</sup>. Low sensitivity would result in a high number of false negative results, potentially missing patients at high risk of developing FP-related toxicity. On developing FP-related toxicity these patients will require treatment, and thereafter dose titration or therapy switching based on the type of cancer.</li> </ul>

<sup>21</sup> Whiting, PF et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-36.

<sup>22</sup> Lee, AM et al. *DPYD* Variants as Predictors of 5-fluorouracil Toxicity in Adjuvant Colon Cancer Treatment (NCCTG N0147). JNCI: *Journal of the National Cancer Institute*. 2014;106(12):dju298.

<sup>23</sup> Froehlich TK, Amstutz U, Aebi S, Joergler M, Largiadèr CR. Clinical importance of risk variants in the dihydropyrimidine dehydrogenase gene for the prediction of early-onset fluoropyrimidine toxicity. *Int J Cancer*. 2015;136(3):730-9.

<p>Change in management outcomes</p> <p>7 studies (observational) N=304</p>	<ul style="list-style-type: none"> <li>• There was variation in initial dose reduction protocols across studies, likely aligning with the CPIC guidelines, other jurisdiction-based guidelines and best available evidence at the time of each study.</li> <li>• According to CPIC guidelines, only poor metabolisers (GAS score 0 or 0.5) are recommended to avoid use of FP-based treatment regimens. Based on calculated estimates from Section 2B.2.4 (linked evidence of diagnostic yield), the frequency of poor metabolisers in the population is 0.1% (ranging from 0% to 0.2%). Initial changes in intended treatment as a result of <i>DPYD</i> testing will therefore be limited. As this outcome is descriptive, risk of bias concerns are minimal.</li> <li>• Dose escalation protocols differed slightly (possibly due to reporting omissions in study papers). The number of patients receiving dose escalation (or cumulative dose escalation) varied widely. This is expected given escalation protocols are personalised, based on multiple individual factors, and ultimately at the clinician's discretion<sup>24</sup>.</li> <li>• Knikman et al. (2023)s' publication attributed reduced treatment effectiveness to <i>DPYD</i> c.1236G&gt;A carriers (who received dosing reduced by 25%) not receiving titration (i.e., most patients remaining at 75%). CPIC has since published an update based on these results<sup>25</sup><a href="#">Error! Bookmark not defined.</a>, citing that "particular emphasis should be placed on dose titration after the initial dosing in this patient group", and that the guideline is in the process of being updated. The role of dose escalation following initial dose reduction as a result of the intervention may play an important moderating role in health outcomes. However, further evidence is needed to evaluate this.</li> <li>• Adherence to <i>DPYD</i> genotype-guided dosing in practice was reported narratively in two studies (Wigle et al. 2021, Wang et al. 2022). While one study reported that carriers were treated according to the dose recommendations provided to the clinician (verified by mean initial dose intensities; Wigle 2021), the other study reported that their protocol was not adhered to in most (19/23) cases; Wang 2022). Treatment and dosing of FP-based therapies are ultimately based on clinician judgement and discretion, and while guidelines may be available and advocated, they may not be used in practice.</li> </ul>
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CPIC=Clinical Pharmacogenetics Implementation Consortium; *DPYD*=Dihydropyrimidine dehydrogenase gene; FP=Fluoropyrimidine; GAS=gene activity score; PICO=Population, Intervention, Comparator, Outcome

### Conclusion of the clinical claim

The use of *DPYD* genotyping before the commencement of systemic FP-based chemotherapy results in superior effectiveness in terms of predicting fluoropyrimidine-induced toxicity compared with no pre-treatment *DPYD* genotyping.

The use of *DPYD* genotyping before the commencement of systemic FP-based chemotherapy results in noninferior safety compared with no pre-treatment *DPYD* genotyping.

The DCAR considered that the evidence base is not strong enough to determine the effectiveness of pre-treatment *DPYD* genotyping compared to no pre-treatment *DPYD* genotyping in terms of:

- preventing fluoropyrimidine-induced toxicity (because of reduced FP dosing) though the evidence tends towards superior effectiveness (without statistical confirmation),
- cancer response rates, and
- overall survival.

<sup>24</sup> Ragia, G et al. Implementing pharmacogenetic testing in fluoropyrimidine-treated cancer patients: *DPYD* genotyping to guide chemotherapy dosing in Greece. *Front Pharmacol.* 2023;14:1248898.

<sup>25</sup> CPIC. CPIC® Guideline for Fluoropyrimidines and *DPYD*, January 2024 update (edited March 2024) 2024 [Available from: <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>].

### 13. Economic evaluation

Based on the clinical claim of superiority in clinical effectiveness, the economic evaluation conducted was a cost-effectiveness analysis (CEA) (cost per patient with a *DPYD* variant identified and cost per patient avoiding severe ( $\geq$ grade 3) FP-related toxicity), and a cost-utility analysis (CUA) (cost per quality-adjusted life years (QALY) gained). Table 6 provides a brief overview of the model parameters.

**Table 6 Summary of the economic evaluation**

Component	Description
Perspective	Health care system perspective
Population	All patients including adults and children who are about to commence FP-based chemotherapy for the treatment of solid tumours
Prior testing	N/A
Comparator	No testing
Type(s) of analysis	CEA and CUA
Outcomes	Number of patients with a <i>DPYD</i> variant identified Number of patients avoiding severe ( $\geq$ grade 3) FP-related toxicity QALYs gained
Time horizon	6 months
Computational method	Decision tree model
Generation of the base case	Modelled
Health states	N/A
Cycle length	N/A
Transition probabilities	All transition probabilities were from the clinical evidence (Section 2), published literature and assumptions: <ul style="list-style-type: none"> <li>• Prevalence of normal/intermediate/poor metabolisers</li> <li>• Probabilities of hospitalisation for normal/intermediate/poor metabolisers with standard/reduced doses of FP-related treatments or alternative treatment</li> <li>• Probabilities of severe toxicities for normal/intermediate/poor metabolisers with standard/reduced doses of FP-related treatments or alternative treatment</li> <li>• Probabilities of death due to toxicities for normal/intermediate/poor metabolisers with standard/reduced doses of FP-related treatments or alternative treatment</li> </ul>
Discount rate	N/A
Software	Excel and TreeAge Pro

CEA=cost-effectiveness analysis; CUA=cost-utility analysis; *DPYD*=Dihydropyrimidine dehydrogenase gene; FP=fluoropyrimidine; N/A=Not applicable; QALY=Quality-adjusted life year

The model was conducted using a stepped approach considering the absence of robust evidence. Step 1 considered the cost of *DPYD* genotyping and the prevalence of normal, intermediate, and poor metabolisers. Step 2 considered the probabilities of severe toxicities for normal, intermediate, and poor metabolisers with various doses or alternative treatments. The stepped results are presented in Table 7. The overall results of the economic evaluation considered the additional costs associated with hospitalisations due to toxicities, and the probabilities of hospitalisation and death due to toxicities for normal, intermediate, and poor metabolisers with various doses or alternative treatments. QALYs was used as health outcomes. The results are presented in Table 8.



**Table 7 Results of the stepped economic analysis**

Step	DPYD genotyping	No testing	Increment	ICER
Step 1 – Cost per patient with a DPYD variant identified				
Costs	\$188	0	\$188	
Outcome 1 (proportion of patients with a DPYD variant identified)	0.0705	0	0.0705	\$2,666.67
Step 2 – Cost per patient avoiding severe (≥grade 3) FP-related toxicity				
Costs	\$188	0	\$188	
Outcome 2 (proportion of patients with severe (≥grade 3) FP-related toxicity; the difference in patients avoiding severe (≥grade 3) FP-related toxicity)	0.21336	0.21604	0.00268	\$70,148.99

DPYD=Dihydropyrimidine dehydrogenase gene; ICER=Incremental cost-effectiveness ratio; QALY=quality-adjusted life year; FP=Fluoropyrimidine

Note: Multiple outcomes may be informative for MSAC decision making-within each step.

**Table 8 Results of the economic evaluation**

Parameter	DPYD genotyping	No testing	Increment
Costs	\$3,395.28	\$3,931.09	-\$535.81
QALYS	0.3679	0.3665	0.0014
<b>Incremental cost per QALY gained</b>			<i>DPYD genotyping is a dominant strategy</i>

DPYD=Dihydropyrimidine dehydrogenase gene; QALY=quality-adjusted life year.

The key drivers (top five parameters) from the one-way sensitivity analysis are presented in Table 9.

**Table 9 Key drivers of the model**

Description	Method/Value	Impact Base case: <i>DPYD</i> genotyping is a dominant strategy: less costly and more effective
Number of days of hospitalisation for intermediate metabolisers, standard dose	This value for the model taken from Lunenburg et al. (2018). <sup>8</sup>	High, favours <i>DPYD</i> genotyping when this value increased.
Probability of hospitalisation for intermediate metabolisers having severe toxicities, standard dose	This value was pooled estimate from Lunenburg et al. (2018) and Paulsen et al. (2023). <sup>9</sup>	High, favours <i>DPYD</i> genotyping when this value increased.
Cost of hospitalisation per day per severe toxicity	This value was calculated based on the AR-DRG used in Australia <sup>26</sup> and proportions of severe toxicities published in Paulsen et al. (2023), <sup>9</sup> which was a weighted cost.	High, favours <i>DPYD</i> genotyping when this value increased.
Number of severe toxicities for intermediate metabolisers, standard dose	This value for the model taken from Lunenburg et al. (2018). <sup>8</sup>	High, favours <i>DPYD</i> genotyping when this value increased.
Probability of death for intermediate metabolisers having severe toxicities, standard dose	This value was pooled estimate from Paulsen et al. (2023). <sup>9</sup>	High, favours no testing when this probability increased.

AR-DRG=Australain-refined-Diagnostic Related Groups; *DPYD*=Dihydropyrimidine dehydrogenase gene.

The results of key univariate sensitivity analysis (one-way sensitivity analysis) are summarised below (Table 10), using the top driver (i.e., number of days of hospitalisation for intermediate metabolisers, standard dose) as an example.

**Table 10 Sensitivity analyses**

Analyses	Incremental cost	Incremental QALY	ICER
Base case	-\$535.81	0.0014	<i>DPYD</i> genotyping is a dominant strategy
Number of days of hospitalisation for intermediate metabolisers, standard dose (base case 23 days; ±20%)			
27.6 days	-\$690.88	0.0014	<i>DPYD</i> genotyping is a dominant strategy, with a greater absolute value of incremental cost compared to base case analysis
18.4 days	-\$390.13	0.0014	<i>DPYD</i> genotyping is a dominant strategy, with a smaller absolute value of incremental cost compared to base case analysis

*DPYD*=Dihydropyrimidine dehydrogenase gene; ICER=Incremental cost-effectiveness ratio; QALY=quality adjusted life year.

## 14. Financial/budgetary impacts

An incidence-based epidemiological approach was used to estimate the financial implications of the introduction of *DPYD* genotyping. Information on data sources and their application in the budget impact assessment are provided in Table 11.

<sup>26</sup> Independent Health and Aged Care Pricing Authority. National Hospital Cost Data Collection (NHCDC) Public Sector Report 2020-21. 2021.

**Table 11 Data sources and parameter values applied in the utilisation and financial estimates.**

Data source	Justification
Cancer Data in Australia 2022 – Book 8 – Cancer incidence and survival by stage <sup>27</sup>	Projected counts of incident cases are required as genotyping is performed prior to commencement of FP-based treatment. The type and stage at diagnosis are important as the proportion of patients who receive FP-based treatment varies significantly across these cancer characteristics. For example, chemotherapy of any type is not indicated for patients with stage I colorectal carcinoma whereas FPs are the backbone of locally advanced and metastatic CRC (high risk stage II and beyond). Values for estimated numbers of eligible patients are presented in Table 51
Expert opinion ratified PICO for 1760	Estimates of stage at diagnosis. The applicant reported that the proportions of incident cancer patients at each stage at diagnosis were based on expert opinion. No information about the collection and collation of these opinions was reported. During assessment summation of incident cases of each cancer type by stage using data from Cancer in Australia confirmed these estimates were close to proportions obtained from the most recent collection of observed cases reported by stage at diagnosis (Table S8.1: Incidence of selected cancers diagnosed in 2011, by sex, age group and RD-stage) <sup>27</sup> Estimates of the proportion of incident cancer patients likely to receive FP-based chemotherapy. These estimates are based on expert opinion. No information about the methods of collecting and collating these opinions was provided. A scoping review of the literature confirmed that these proportions are comparable to current clinical practice in Australia. However, due to the paucity of Australian studies for certain cancers, international studies were required to supplant data about treatment in the Australian context. Whilst these estimates are reasonably representative of practice in Australia and there are widely accepted first line regimes for some cancers e.g., metastatic CRC the treatment of other cancers continues to change based on a constant stream of studies investigating regimes that uses different FP doses alone or in combination with established chemotherapeutic agents such as cisplatin and irinotecan and often newer targeted therapies including anti-angiogenic agents, immunotherapeutic agents and checkpoint inhibitors. Thus, there are variations in accepted treatments for some cancers based of factors other than cancer and patient characteristics such as regionality and the preference of each oncologist.
Requested PBS and RPBS items processed from July 2022 to 2023 <sup>28</sup>	Proportion of prescriptions dispensed for either capecitabine or 5-FU FP drug costs Alternate chemotherapy costs
Australian refined diagnosis-related groups (AR-DRG) data cubes <sup>29</sup>	Costs associated with severe FP-related toxicities were based on weighted averages of the three severe toxicities identified in Section 2 (GIT, haematological and cardiac)
Published literature including reports by: Henricks et al. (2018) <sup>12</sup> Lunenburg et al. (2018) <sup>8</sup> Paulsen et al. (2023) <sup>9</sup> Wigle et al. (2021) <sup>11</sup> Kleinjan et al. (2019) <sup>6</sup> Knikman et al. (2023) <sup>7</sup> Wang et al. (2022) <sup>10</sup>	Prevalence of normal, intermediate and poor <i>DPYD</i> metabolisers Probability of severe (Grade ≥3) FP-related toxicity LOS for hospitalisations due severe toxicities Number of treatment cycles Rates of uptake of genotype testing

*DPYD*=Dihydropyrimidine dehydrogenase gene; MBS=Medical Benefits Scheme; FP=fluoropyrimidine; RPBS=Repatriation pharmaceutical Benefits Scheme; LOS=length of stay; AR-DRG=Australian-refined Diagnostic Related Groups; GIT=gastrointestinal tract.

<sup>27</sup> Australian Institute of Health and Welfare. (2023). 'Data tables: CDIA 2023: Book 8 – Cancer incidence and survival by stage' [data set]. <https://www.aihw.gov.au/getmedia/9b861a57-82b2-455b-8228-7cfbcf4bd057/AIHW-CAN-122-CDiA-2021-Book-8-Cancer-incidence-and-survival-by-stage.xlsx.aspx>

<sup>28</sup> Pharmaceutical Benefits Schedule Item Reports [Internet] Canberra: Australian Government; [cited 2024 July 9]. Available from: [http://medicarestatistics.humanservices.gov.au/statistics/pbs\\_item.jsp](http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp)

<sup>29</sup> Australian refined diagnosis-related groups (AR-DRG) data from the National Hospital Cost Data Collection Report version 11

A table summarising the net financial implications for the MBS from the proposed listing of *DPYD* genotyping over 6 years is presented in Table 12, accounting for the estimated cost of the proposed health technology. There were no implications identified to other health technologies funded under the MBS.

**Table 12 Net financial implications of *DPYD* genotyping to MBS**

Parameter	2025	2026	2027	2028	2029	2030
<b>Estimated use and cost of the proposed health technology</b>						
Number of people eligible for <i>DPYD</i> genotyping	22,449	22,916	23,377	23,880	24,381	24,869
Estimated uptake of <i>DPYD</i> genotyping	50%	60%	70%	80%	90%	100%
Number of people who receive <i>DPYD</i> genotyping	11,224	13,749	16,364	19,104	21,943	24,869
Cost to the MBS (with appropriate copayments excluded)	\$1,582,584	\$1,938,609	\$2,307,324	\$2,693,664	\$3,093,963	\$3,506,529
<b>Revised cost to the MBS (with 85% rebate)</b>	<b>\$1,532,076</b>	<b>\$1,876,739</b>	<b>\$2,233,686</b>	<b>\$2,607,696</b>	<b>\$2,995,220</b>	<b>\$3,394,619</b>
<b>Change in use and cost of other health technologies</b>						
Change in use of no testing	0	0	0	0	0	0
Change in use of other MBS affected health technologies	0	0	0	0	0	0
Net change in costs to the MBS (with appropriate copayments excluded)	0	0	0	0	0	0
Net financial impact to the MBS	\$1,582,584	\$1,938,609	\$2,307,324	\$2,693,664	\$3,093,963	\$3,506,529
<b>Revised net financial impact to the MBS</b>	<b>\$1,532,076</b>	<b>\$1,876,739</b>	<b>\$2,233,686</b>	<b>\$2,607,696</b>	<b>\$2,995,220</b>	<b>\$3,394,619</b>

Source: Excel sheet '4. Net cost to Government' of Utilisation and Cost Model\_updated workbook. Bold text indicates updated calculation based on the MSAC's supported revised MBS item fee of \$182.00

Abbreviations: *DPYD*=*Dihydropyrimidine dehydrogenase* gene; MBS = Medical Benefits Scheme; PICO=Population, Intervention, Comparator, Outcome; MSAC=Medical Services Advisory Committee; CRC=Colorectal carcinoma; PBS=Pharmaceutical Benefits Scheme.

It was estimated that in the first year of listing the new MBS item would have a net financial implication of \$1.6 million, rising to \$3.5 million in Year 6. This equates to a net six-year financial implication of approximately \$15.1 million.

- The average cost of the proposed technology per patient per once in a lifetime is \$188.
- The average frequency of use of the proposed technology is once per lifetime.
- The average out-of-pocket cost per patient per course is: \$47.

Table 13 summarises the total cost to state/territory and commonwealth government health budgets. With the listing of *DPYD* genotyping, there should be a decrease in the demand for hospital admissions and extended hospitalisations due to grade 3 FP related toxicities leading to

a saving to the government health budgets of \$17.7 million in year one, rising to \$39.1 million by year six. The total saving over the first six years of listing is approximately \$168.7 million.

**Table 13 Total cost to government health budgets**

	2025	2026	2027	2028	2029	2030
Total cost to state governments	-\$19,102,689	-\$23,400,113	-\$27,850,712	-\$32,514,056	-\$37,345,892	-\$42,325,798
Total cost to Commonwealth government	\$1,443,486	\$1,768,219	\$2,104,526	\$2,456,910	\$2,822,025	\$3,198,329
<b>Net cost to government</b>	<b>-\$17,659,203</b>	<b>-\$21,631,894</b>	<b>-\$25,746,186</b>	<b>-\$30,057,146</b>	<b>-\$34,523,867</b>	<b>-\$39,127,469</b>
<b><i>Revised net cost to government*</i></b>	<b><i>-\$17,709,694</i></b>	<b><i>-\$21,694,353</i></b>	<b><i>-\$25,819,310</i></b>	<b><i>-\$30,143,333</i></b>	<b><i>-\$34,622,457</i></b>	<b><i>-\$39,239,005</i></b>

Source: Excel sheet '4. Net cost to Government' of Utilisation and Cost Model workbook.

\*Bold italics text indicates revised net cost to government using MSAC's supported MBS item fee of \$182.00

A sensitivity analysis was conducted due to some uncertainties and is presented in Table 14 below. Sensitivity analysis demonstrated that the budget impact is most sensitive to the difference in the severity of the adverse events, which can change the estimates from cost saving to having a budget impact of costing up to \$1.5 million in year six.

**Table 14 Results of sensitivity analysis for net budget impact of making *DPYD* genotyping available for patients about to receive FP chemotherapy.**

	2025	2026	2027	2028	2029	2030
<b>Base case</b>	-\$17,659,203	-\$21,631,894	-\$25,746,186	-\$30,057,146	-\$34,523,867	-\$39,127,469
<b><i>DPYD</i> genotyping uptake (base case = 50% in 2025 rising to 100% in 2030)</b>						
100% uptake all years	-\$35,319,979	-\$36,054,730	-\$36,780,041	-\$37,571,433	-\$38,359,678	-\$39,127,469
<b>Number of 5-FU chemotherapy cycles (base case = 5)</b>						
7	-\$17,741,621	-\$21,732,853	-\$25,866,348	-\$30,197,428	-\$34,684,995	-\$39,310,083
<b>Addition of a consultant oncologist for reduced metabolisers (base case = 0)</b>						
1 x MBS item 108 per reduced metaboliser	-\$17,604,663	-\$21,565,085	-\$25,666,670	-\$29,964,316	-\$34,417,241	-\$39,006,625
<b>Length of hospitalisation for toxic events (base case = variable)</b>						
Length of hospitalisation for toxic events and number of toxic events are the same for intervention and control.	\$664,968	\$814,562	\$969,488	\$1,131,819	\$1,300,016	\$1,473,368
<b>Mean Benefit (base case = 75%)</b>						
<b>Mean Benefit a mix of hospital inpatients and outpatients based on Item 73332 (82%)</b>	-\$17,508,909	-\$21,447,790	-\$25,527,066	-\$29,801,337	-\$34,230,043	-\$38,794,464

Source: Excel workbook "Utilisation and Cost Model\_basecase"

Abbreviations: *DPYD*=Dihydropyrimidine dehydrogenase gene; 5-FU= 5-fluorouracil.

The clinical uncertainty around the efficacy of *DPYD* genotyping and the ability of reduced dosing being able to reduce toxicity has the biggest impact on the financial implications and is likely to overestimate the savings attributed to listing *DPYD* genotyping.

## 15. Other relevant information

Other considerations include:

- Equity related to access: *DPYD* genotype testing is currently not widely available, therefore, specimens may need to be sent interregional or interstate.<sup>19</sup> This may have implications for equity of access for those in rural, regional or remote areas. There is also the potential that *DPYD* testing may delay treatment commencement; availability and access of the test – particularly for those outside metro areas – may result in further delays.
- Equity related to non-Caucasian populations: There is currently a lack of evidence for all outcomes in non-Caucasian populations. As there were no published studies identified which were conducted in an Australian sample, the applicability of the reported results for the Australian population may be limited. PASC also considered that more research may be required to determine relevant alleles in non-Caucasian populations, such as Aboriginal and Torres Strait Islander people. In the PICO, PASC considered that including the option to test for “four or more variants” would allow additional variants with relevant clinical utility (including those in non-Caucasian populations, and those discovered in the future) to be included as required.
- Ethical considerations: *DPYD* genotyping does not have the same ethical considerations as other types of genetic testing. This test only provides useful information for an individual about their ability to breakdown a specific type of cancer drug. As such, findings with any other clinical utility or meaning are highly unlikely. In addition, it provides little information for family or relatives, and cascade testing is not recommended.
- Uptake: In public consultation, Australian Genomics noted that the intervention risks low uptake due to a lack of awareness and suitable educational programs. These issues were also identified in qualitative studies of barriers and enablers to genetic testing implementation.<sup>1319</sup> Effective education campaigns for oncologists and other treating clinicians will be important to ensure pre-treatment *DPYD* testing is used in practice.

### Additional analyses

A sensitivity analysis using a market share approach was used to estimate the financial implications of the introduction of *DPYD* genotyping. Information on data sources and their application in the budget impact assessment are provided in Table 15.

**Table 15 Data sources and parameter values applied in the utilisation and financial estimates.**

Data source	Justification
PBS	PBS patient quarterly data who received their first script (only patients that initiated treatment) for systemic treatment of drugs Capecitabine or Fluorouracil from 2016-17 to 2022-23. Patients were only counted once (the first time they initiated a systemic fluoropyrimidine treatment) for the period 1 July 2016 to 30 June 2023 and were not counted if they had received treatment prior to 1 July 2016. Attached data to inform the DCAR – 1760: “Updated Quarterly PBS data: patient counts by quarter”.
PBS and RPBS items processed from July 2022 to 2023 <sup>30</sup>	Proportion of prescriptions dispensed for either capecitabine or 5-FU FP drug costs Alternate chemotherapy costs
Australian refined diagnosis-related groups (AR-DRG) data cubes <sup>31</sup>	Costs associated with severe FP-related toxicities were based on weighted averages of the three severe toxicities identified in Section 2 (GIT, haematological and cardiac)
Published literature including reports by: Henricks et al. (2018) Lunenburg et al. (2018) Paulsen et al. (2023) Wigle et al. (2021) Kleinjan et al. (2019) Knikman et al. (2023) Wang et al. (2022)	Prevalence of normal, intermediate and poor <i>DPYD</i> metabolisers Probability of severe (Grade $\geq 3$ ) FP-related toxicity LOS for hospitalisations due severe toxicities Number of treatment cycles Rates of uptake of genotype testing

AR-DRG=Australian-refined Diagnostic Related Groups; *DPYD*=*Dihydropyrimidine dehydrogenase* gene; FP=fluoropyrimidine; GIT=gastrointestinal tract; LOS=length of stay; MBS=Medical Benefits Scheme; PBS= Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme.

A table summarising the net financial implications for the MBS from the proposed listing of *DPYD* genotyping over 6 years is presented in Table 16, accounting for the estimated cost of the proposed health technology. There were no implications identified to other health technologies funded under the MBS.

<sup>30</sup> Pharmaceutical Benefits Schedule Item Reports [Internet] Canberra: Australian Government; [cited 2024 July 9]. Available from: [http://medicarestatistics.humanservices.gov.au/statistics/pbs\\_item.jsp](http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp)

<sup>31</sup> Australian refined diagnosis-related groups (AR-DRG) data from the National Hospital Cost Data Collection Report version 1.1

**Table 16 Net financial implications of *DPYD* genotyping to MBS**

Parameter	2025	2026	2027	2028	2029	2030
Estimated use and cost of the proposed health technology						
Number of people eligible for <i>DPYD</i> genotyping	12,264	12,263	12,262	12,261	12,260	12,258
Estimated uptake of <i>DPYD</i> genotyping	50%	60%	70%	80%	90%	100%
Number of people who receive <i>DPYD</i> genotyping	6,132	7,358	8,583	9,809	11,034	12,258
Cost to the MBS (with appropriate copayments excluded)	\$864,612	\$1,037,478	\$1,210,203	\$1,383,069	\$1,555,794	\$1,728,378
Change in use and cost of other health technologies						
Change in use of no testing	0	0	0	0	0	0
Change in use of other MBS affected health technologies	0	0	0	0	0	0
Net change in costs to the MBS (with appropriate copayments excluded)	0	0	0	0	0	0
Net financial impact to the MBS	\$864,612	\$1,037,478	\$1,210,203	\$1,383,069	\$1,555,794	\$1,728,378

Source: Excel sheet '4. Net cost to Government' of Utilisation and Cost Model workbook and Excel Workbook "R2024-057 Patient counts for drugs Capecitabine or Fluorouracil by quarter", provided by the Department.

Abbreviations: *DPYD*=*Dihydropyrimidine dehydrogenase* gene; MBS = Medical Benefits Scheme; PICO=Population, Intervention, Comparator, Outcome; MSAC=Medical Services Advisory Committee; CRC=Colorectal carcinoma; PBS=Pharmaceutical Benefits Scheme.

It was estimated that in the first year of listing the new MBS item would have a net financial implication of \$865K, rising to \$1.7 million in year 6. This equates to a net six-year financial implication of approximately \$7.8 million.

- The average cost of the proposed technology per patient per once in a lifetime is \$188.
- The average frequency of use of the proposed technology is once per lifetime.
- The average out-of-pocket cost per patient per course is: \$47.

Table 17 summarises the total cost to state/territory and commonwealth government health budgets. The listing of *DPYD* genotyping will lead to a saving to the government health budgets of \$9.7 million in year one, rising to \$19.3 million by year six. total saving over the first six years of listing is approximately \$86.8 million.

**Table 17 Total cost to government health budgets**

	2025	2026	2027	2028	2029	2030
Total cost to state governments	-\$10,436,358	-\$12,522,949	-\$14,607,838	-\$16,694,429	-\$18,779,318	-\$20,862,505
Total cost to Commonwealth government	\$788,619	\$946,291	\$1,103,835	\$1,261,507	\$1,419,050	\$1,576,466
<b>Net cost to government</b>	<b>-\$9,647,740</b>	<b>-\$11,576,658</b>	<b>-\$13,504,004</b>	<b>-\$15,432,922</b>	<b>-\$17,360,268</b>	<b>-\$19,286,039</b>

Source: Excel sheet '4. Net cost to Government' of Utilisation and Cost Model workbook.



The clinical uncertainty around the efficacy of *DPYD* genotyping and the ability of reduced dosing being able to reduce toxicity has the biggest impact on the financial implications and is likely to overestimate the savings attributed to listing *DPYD* genotyping.

## 16. Key issues from ESC to MSAC

### Main issues for MSAC consideration

#### Clinical issues:

- The included studies have a serious to critical risk of bias due to issues including small sample sizes and retrospective toxicity scoring in some studies. There are significant evidence gaps, transitivity & applicability issues due to exclusion of highest risk patients who are poor *DPYD* metabolisers and use of imperfect proxy variant. Overall, ESC considered the evidence showed that the claim for superior effectiveness was uncertain. New prospective studies (including Australian studies) with contemporary controls are underway, which could address the issues of confounding and selection bias through applying causal inference methods to observational data.
- There are no Australian studies evaluating the intervention, nor representative international evidence for the Australian population (primarily ancestry differences). ESC advised information from the current ongoing Australian trials would be useful for MSAC decision-making. Subsequently, the assessment group produced an Addendum which included further information on additional studies and the ongoing clinical trials.

#### Economic issues:

- Based on the economic evaluation, pre-treatment *DPYD* genotyping is slightly more effective (considered negligible) and less costly compared to usual care (no testing). *DPYD* genotyping is a dominant strategy when quality adjusted life years (QALY) is used as a health outcome. However, the cost-effectiveness is highly uncertain due to weak supporting clinical evidence.
- Some key model parameters are highly uncertain and impact the incremental cost-effectiveness ratio (ICER). The assumption of hospitalisation days avoided from reduced fluoropyrimidine (FP)-related toxicity has a large impact on the ICER and the financial impact, and cost inputs from these are driving the ICER.
- The impact of test performance (sensitivity or specificity) has not been considered in the economic model. Subsequently, the assessment group produced an Addendum (see **Attachment 1**) which addresses the issue raised by ESC.

#### Financial issues:

- Utilisation of pre-treatment *DPYD* genotyping in current routine Australian clinical practice remains unclear. The uptake rate of *DPYD* genotyping has a major impact on the financials. Thus, this gives rise to uncertainty in the financial impact and will become problematic if clinical acceptance and use is slow. The number of patients receiving FPs as radiosensitisers is also unknown.

#### Other relevant issues:

- The justification for the proposed fee of \$188 remains unclear.
- ESC noted equity issues arising from slower access for patients in rural and remote areas potentially delaying treatment commencement. In addition, ESC noted that interim results from an ongoing Australian trial demonstrated that genotyping results were available prior to commencing treatment 96% of the time. ESC considered this potential issue arises for most genetic based testing as genetic testing generally takes place in tertiary laboratories based in the larger cities, and samples are transported via couriers.

- There is limited evidence on the safety and effectiveness of *DPYD* genotype testing for non-Caucasian populations, including First Nations people.

## ESC discussion

ESC noted that this application from the Royal College of Pathologists of Australasia (RCPA) sought Medicare Benefits Schedule (MBS) listing of *dihydropyrimidine dehydrogenase (DPYD)* genotyping to predict fluoropyrimidine (FP)-induced toxicity in patients with solid tumours who are about to commence a treatment protocol that includes oral or intravenous FP.

ESC noted and welcomed public consultation feedback from 10 professional organisations, 1 consumer organisation and 3 individuals of whom 2 were medical specialists and 1 a consumer.

ESC noted feedback from Bowel Cancer Australia (BCA) highlighting that patients who have a reaction or experience FP related cardiotoxicity have a decreased quality of life and prior testing can help in planning and monitoring these patients or utilising other treatment options to avoid serious side effects and death. BCA considered the proposed population and pre-emptive testing to be appropriate. ESC noted, the feedback from the consumer organisation was supportive. It highlighted experience of a patient with breast cancer who had received 5-FP as part of a 6 dose chemotherapy regime acknowledging that without the test, not understanding the cause of their reaction to the therapy would likely have contributed to the mental anguish associated with chemotherapy itself. ESC noted the consumer organisation further highlighted that the availability of the test would mean a more comfortable journey through chemotherapy for carers and patients who are identified with *DPYD* variants. It also outlined that disadvantages could potentially include short delays in treatment commencement and any additional costs for the patient as a result of testing. Additionally, ESC noted the consumer organisation expressed concerns about the lack of reliable Australian data, especially for First Nations people, who may carry *DPYD* variants of uncertain risk for conferring FP toxicity, highlighting health inequity. ESC noted that it was argued that public funding of the test would help improve knowledge among broader populations than exists currently and enable personalised treatment. ESC noted feedback from Australian Genomics that emphasized the inequity issue of representativeness in genomic databases and highlighted that testing negative for a *DPYD* variant does not eliminate the possibility of experiencing FP-related toxicity. ESC noted that the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) supported the test as it would reduce toxicity and guide dose adjustment of 5-FU and capecitabine resulting in decreased hospitalisations and intensive care unit admissions. ESC noted that ASCEPT emphasized that several guidelines, including eviQ<sup>32</sup> (Australia), the National Health Service (UK) and the European Medicines Agency (European Union) recommend *DPYD* genotyping before administering FP-based chemotherapy.

ESC noted the population, intervention, comparator and outcomes (PICO) that had been ratified by the PICO Advisory Subcommittee. ESC noted the target population for this application is all patients with solid tumours who are about to start an FP-based chemotherapy regime or about to start systemic FPs as radiosensitising agents for radiotherapy. ESC noted that in rare instances, FP-based therapy could be used in patients with haematological malignancies, such as chronic myeloid leukemia. ESC noted the onset of toxicity often occurs during or within four days of FP dosing. ESC noted that the test itself requires minimal expertise to perform and that although the test specificity is high, sensitivity is low. ESC noted uridine triacetate, the antidote for severe FP toxicity, is difficult to source and delays increase risk of death for patients. ESC further noted that the antidote is expensive and is not currently listed on the Pharmaceutical Benefits Scheme (PBS).

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<sup>32</sup> <https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-treatment/1744-dihydropyrimidine-dehydrogenase-dpd-enzyme>

ESC noted the clinical management algorithms and considered it was appropriate.

ESC noted that the proposed genotyping targeted at least four *DPYD* gene variants before starting FP-based chemotherapy. ESC acknowledged that other genes, such as *microRNA 27a* (*MIR27A*), *thymidylate synthetase* (*TYMS*), *enolase superfamily member 1* (*ENOSF1*) and *methylenetetrahydrofolate reductase* (*MTHFR*), may be important in predisposing to FP-related toxicity. However, ESC considered that these genes would require separate applications, as the current evidence was limited to *DPYD* genotyping. ESC also foreshadowed future applications using next-generation sequencing to identify more variants and genes, which may be more expensive but will be able to identify more people at risk as pathogenicity of variants and genes of uncertain significance (VUS) are validated.

ESC noted the proposed MBS item descriptor and fee. ESC noted that collection and transport costs are already reimbursed under patient episode initiation (PEI) items. Therefore, ESC agreed to revise the original proposed fee of \$188 to \$182 that had also accounted for these costs. ESC further queried the rationale behind the fee of \$182, although it acknowledged that PASC deemed the justification of the fee to be reasonable. Noting the varied fees for similar items on the MBS, ESC advised that the applicant provide a clear justification for the requested fee.

ESC agreed with the department's proposed removal of the Explanatory Note (EN) statement about ancestry, as other similar MBS item ENs do not include this level of detail. ESC noted the department's preference for the removal of the requirement in the descriptor to test "at least four" variants and that the *DPYD* variants are selected based on a recognised test directory. ESC further noted that the Australian Genomics test directory is currently underway and will become available in the future. Therefore, ESC considered that the eviQ guidelines may be the most appropriate reference for this MBS item until availability of Australian Genomics test directory.

ESC noted the clinical claims of superior effectiveness and non-inferior safety compared to no testing. ESC noted the evidence base for these claims comprised of four direct comparative studies (comparing the intervention with the comparator), and three direct non-comparative studies (single arm studies for the intervention). ESC noted that the non-randomised studies of intervention all had serious or critical risk of bias because they were underpowered and included retrospective control cohorts. ESC noted these studies also had transitivity and applicability issues due to lack of Australian studies and limited representation of ethnicities. ESC noted patients with poor *DPYD* expression (equating to the highest risk of FP toxicity) were excluded from key direct clinical evidence and that studies used an imperfect proxy variant. ESC noted the Clinical Pharmacogenetics Implementation Consortium (CPIC)<sup>33</sup> guidelines were updated to recommend not using the proxy variant. ESC noted the applicant pre-ESC response acknowledged the inherent issues with the direct evidence studies.

Regarding toxicity, ESC noted that the proportion of patients with at least grade 3 toxicity in the intervention group was generally lower than the group that did not receive genotyping. However, the studies were not powered to detect significant differences in toxicity and the alleles tested across the studies were not comparable limiting the capacity to draw conclusions about the efficacy of *DPYD* genotyping for four variants on a population level. ESC considered the results of FP-related hospitalisations to be uncertain as the evidence had conflicting results (demonstrating fewer hospitalisations vs no difference) and were assessed as having critical risk of bias.

Regarding FP-related treatment management changes, ESC noted that the studies had serious risk of bias. ESC noted that performing the test and acting on the results through a change in management did not affect safety because the likelihood of false positives is low. ESC noted in the instance of a false positive result where a patient is (incorrectly) started at a lower dose, this could be adjusted upwards through treatment drug monitoring (TDM) and/or based on patient response. Despite a negative result, clinical vigilance is still required, as ESC noted that the

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<sup>33</sup> <https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/>

genotyping proposed would not completely remove the possibility of *DPYD* variant-associated toxicity. Thus, ESC considered that physician and patient education about the test limitations is essential. ESC considered that longer-term follow-up is therefore required, as there is insufficient evidence to determine the impact on progression free survival (PFS) or overall survival (OS).

ESC noted that the test turnaround time (TAT) could potentially introduce delay in commencing treatment. However, ESC noted most FP treatments start about 1–2 weeks post-diagnosis. The TAT for the genotyping results was less than this (around 5 days), although TAT may be extended for patients in rural and remote areas. Additionally, ESC noted that one small study indicated that 96% of test results were available before the first cycle of treatment commenced.<sup>34</sup> ESC considered genetic testing generally takes place in tertiary pathology laboratories located in the capital cities, and samples are shipped via internal or external couriers.

Overall, ESC considered the evidence showed that the claim for superior effectiveness was uncertain but agreed with the claim of non-inferior safety.

ESC noted that the economic evaluation was a cost-utility analysis and a cost-effectiveness analysis with a time horizon of 6 months. ESC considered the time horizon to be appropriate given that toxicities from treatment generally manifest quickly. ESC noted the outcomes were based on several factors: the number of patients with a *DPYD* variant identified, number of patients avoiding severe ( $\geq$ grade 3) FP-related toxicity, and the patient days in hospital for severe toxicities. ESC noted the economic model inputs were derived from studies with a small number of patients. ESC noted the model did not take into account the sensitivity and specificity of the test. Given the model was only partially validated, ESC queried whether clinicians were consulted to ensure the validity of the model structure.

ESC noted the economic model included length of stay in hospital (LOS) and linked LOS to genotype. ESC noted there were small differences in the probabilities, of experiencing a severe AE when receiving a reduced dose of chemotherapy between the “genotyping” and “no genotyping” groups but large differences in LOS when a severe AE occurred. ESC noted the main economic determinant of the model was LOS. ESC noted LOS was lower for genotyped patients with AEs vs non-genotyped patients based on a small study. However, ESC considered it was unclear how LOS, reflecting recovery time from an AE, is impacted by genotype of patients.

ESC noted that the cost per patient to avoid severe FP-related toxicity was \$67,910 based on the revised MBS fee of \$182. When considering the incremental cost per QALY gained, ESC noted *DPYD* genotyping was a dominant strategy. Overall, while ESC deemed the model appropriate, it noted the uncertainty in the evidence underpinning the model and that the results needed to be interpreted with caution. ESC also noted that the differences in QALYs gained were negligible and similar across the two strategies.

ESC noted the financial implications were based on an incidence-based epidemiological approach. However, ESC noted several limitations, including reliance on overseas data sources and the unclear relevance to the Australian population, and the uncertainty in cancer staging. Cancer staging data for the patients are not routinely collected by Australian registries so estimating the eligible population is uncertain. ESC noted that the estimated financial impact to the MBS in Year 1 was \$1.6 million, increasing to \$3.5 million by Year 6 as uptake of the genotyping increases. However, ESC noted that the intervention could be cost-saving to the healthcare system and PBS when considering reduced hospitalisations, shorter LOS, reduced use of PBS-listed chemotherapy medications. ESC noted the pre-ESC response, which re-iterated that genotyping was cost-effective and cost-saving. ESC considered the cost savings rising up to nearly \$39.1 million by Year 6 could be overestimated as they largely depended on the shortened LOS, which was highly uncertain and may not result in any cost savings if the reduction in LOS is

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<sup>34</sup> Michael, M. 2020. [A multisite prospective study to implement and evaluate the feasibility of a Pharmacogenetics Screening Program for 5-fluorouracil, capecitabine and irinotecan chemotherapies in patients with cancer](#). [Online]. The Australian New Zealand Clinical Trials Registry (ANZCTR).

not realised. ESC also considered that the clinical uncertainty around the efficacy of *DPYD* genotyping and the use of reduced dosing to reduce toxicity had the biggest impact on the financial implications and was likely to overestimate the savings from listing *DPYD* genotyping. Further, ESC considered the uptake of genotyping to be uncertain, as no data were presented to support the numbers in the application. ESC noted the number of patients who receive FPs as radiosensitisers is also unknown.

ESC noted that the department contracted assessment report (DCAR) did not consider the additional costs of TDM and dose escalation if required, which would impact the economic evaluation and financials.

ESC noted the ongoing Australian clinical trials and considered that the additional information from these trials would be helpful for MSAC decision-making; specifically, any information on any other variants identified other than the four included in this application, as well as additional details that is more relevant to the Australian population. ESC also noted two recent publications that included genome-wide association studies (GWAS) and non-Caucasian population cohorts.<sup>35,36</sup>

ESC also requested more information on the current usage of *DPYD* testing in clinical practice, as this test is currently available to some patients in Australia.

ESC noted equity issues arising from slower access for patients in rural and remote areas potentially delaying commencement of treatment. ESC also noted limited genomic variant data availability for non-Caucasian populations, including First Nations people.

Overall, ESC considered that the evidence base is not strong enough to determine the effectiveness of pre-treatment *DPYD* genotyping compared to no testing in terms of preventing FP-induced toxicity. The evidence did not demonstrate superior effectiveness (i.e. was without statistical confirmation), but showed comparable cancer response rates and OS between populations with a FP dose-reduction in relation to reduced *DPYD* metaboliser status and those without a need for dose-reduction. ESC noted significant gaps in how well current studies represented the risks associated with FP-associated toxicity for different genetic profiles, particularly concerning the high-risk group of poor *DPYD* metabolisers. ESC noted that these uncertainties flowed onto the economic evaluation and budget impact. In addition, ESC noted the uncertainty in the calculated ICER and financial impact as they heavily relied on reduced LOS and the predicted uptake of the testing, both which are uncertain.

## 17. Applicant comments on MSAC's Public Summary Document

The College and Fellows have nil comments to make on the PSD for Application 1760. The College's Working Party would, however, like to express their delight in MSAC approving public funding for *DPYD* genotyping, and would like to take this opportunity to thank the Department for its assistance throughout the assessment process.

## 18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)

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<sup>35</sup> Knikman, JE et al. [Discovering novel germline genetic variants linked to severe fluoropyrimidine-related toxicity in- and outside \*DPYD\*](#). *Genome Med.* 2024; 16(1), 101.

<sup>36</sup> Chan, TH et al. [DPYD genetic polymorphisms in non-European patients with severe fluoropyrimidine-related toxicity: a systematic review](#). *Br J Cancer.* 2024;131(3), 498-514.