

MSAC Application 1760

***DPYD* genotyping to predict
fluoropyrimidine-induced toxicity**

Application for MBS eligible service or health technology

ID:

HPP200060

Application title:

DPYD genotyping to predict fluoropyrimidine-induced toxicity

Submitting organisation:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Submitting organisation ABN:

52000173231

Application description

Succinct description of the medical condition/s:

Fluoropyrimidines (FP) are widely used for the treatment of solid tumours (colorectal, upper gastrointestinal, breast, head & neck, and pancreatic cancer). FP can be administered as an intravenous 5-Fluorouracil (5-FU) solution, orally as capecitabine (that is converted to 5-FU) or as a topical cream (not a safety risk in the context of this application). Dihydropyrimidine dehydrogenase (DPD) is the enzyme encoded by the DPYD gene that is involved in the metabolism of circulating 5-FU. Variants in the DPYD gene may result in decreased DPD production. Individuals with non or partially-functional DPYD variants cannot metabolise FP at normal rates, which results in a supratherapeutic exposure when patients are treated with a standard FP dose, potentially leading to life-threatening toxicity (Dean & Kane 2021 (Update); White et al 2022b). A complete absence of DPD function only occurs in ~0.2% of the population and exposure to FP chemotherapy can be fatal for such people

Succinct description of the service or health technology:

DPD deficiency is inherited in an autosomal recessive manner and has highly variable penetrance, with not all DPD deficiency being clinically or phenotypically identifiable. DPYD gene variant carriers are often unaware of their variant status until exposure to FP initiates the development of toxicity symptoms which can lead to hospitalisation, intensive care admission and even death (White et al 2022b). Four DPYD variants have been studied in-depth and have demonstrated a reproducibly significant association with an elevated risk of severe toxicity. Targeted testing for these four variants using polymerase chain reaction (PCR) prior to treatment with FP will identify carriers of variants associated with DPD deficiency in European populations (Diasio & Offer 2022; White et al 2022b). Identifying patients who are variant carriers prior to FP exposure allows for pre-emptive dose reduction, improving patient tolerance and safety and reducing hospital-related management incidents.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Applicant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Is the applicant organisation the organisation you are representing in the HPP today?

Yes

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prostheses List?

No

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

Please select any relevant MBS items.

MBS item number	Selected reason type

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology:

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:

Multigene/biomarker panel assay

Specify the number of genes/biomarkers in the panel assay:

at least 4

Is it possible to vary or select the genes/biomarkers requested within the panel?

Yes

PICO Sets

Application PICO sets

PICO set number	PICO set name
1	Adults undergoing fluoropyrimidine-based treatment for cancer

Adults undergoing fluoropyrimidine-based treatment for cancer

State the purpose(s) of the health technology for this PICO set and provide a rationale:

Purpose category:

Predisposition

Purpose description:

To identify a hereditary predisposition to disease(s) or condition(s) in affected or at risk but currently unaffected patients

Supporting documentation

Document type	File name(s)
Application PICO set documents	HPP200060_Adults undergoing fluoropyrimidine-based treatment for cancer(1).docx
Reference list	1869-dpyd-policy-statement(2).pdf; Abdullah.pdf; Amstutz-2018-Clinical Pharmacogenetics Impleme.pdf; Avila.pdf; Bank-2018-Comparison of the Guidelines of the.pdf; Boisdron.pdf; Brooks.pdf; CDiA-2022-Book-1a-Cancer-incidence-age-standa.xlsx; Clin Pharma and Therapeutics - 2022 - White -.pdf; Conti-2020-A genotyping_phenotyping approach w.pdf; Deenen.pdf; Diasio-2022-Testing for Dihydropyrimidine Dehy.pdf; DPYD genotypingv0.5.docx; Eccles.pdf; Etienne-Grimald-2017-New advances in DPYD geno.pdf; Fragoulakis-2019-Estimating the Effectiveness.pdf; Glewis-2022-A systematic review and meta-analy.pdf; Henricks 2019a.pdf; Henricks-2019-Effectiveness and safety of redu.pdf; Jolivet-2021-Implementing DPYD_2A Genotyping i.pdf; Kestenbaum.pdf; Lunenburg 2018.pdf; Lunenburg-2020-Dutch Pharmacogenetics Working.pdf; Meulendijks.pdf; Murphy-2018-Cost Implications of Reactive Vers.pdf; Ontario Health 2021_DPYD HTA.pdf; Prospective safety analysis for DPYD deficienc.pdf; Risk of treatment-related death in carr...als.pdf; Sharma-2021-Pathogenic DPYD Variants and Treat.pdf; Toffoli-2019-The genotype for DPYD risk varian.pdf; Tsiachristas-2022-Can upfront DPYD extended va.pdf; White-2021-Ethnic Diversity of DPD Activity an.pdf; White-2022-Pharmacogenomics-in-the-era-of-pers.pdf; Wörmann-2020-Dihydropyrimidine Dehydrogenase T.pdf

Population**Describe the population in which the proposed health technology is intended to be used:**

Patients with solid organ tumours, including colorectal, upper gastrointestinal, breast and head and neck cancers, who are undergoing standard chemotherapy treatment with fluoropyrimidines (FP). FP can be administered intravenously (5-Fluorouracil (5-FU) solution) or orally as capecitabine (a pro-drug converted to 5-FU). The conversion of 5-FU into inactive metabolites by DPD, encoded by the

DPYD gene, is the rate-limiting step in fluorouracil metabolism. Variants in the DPYD gene can lead to reduced or completely absent levels of DPD activity. The goal of testing for DPYD variants is to reduce the risk of severe toxicity by identifying patients with DPD deficiency, which, depending on the level of deficiency, may allow patients to receive either a reduced FP dose reduction or an alternative treatment. The aim of a lower FP dose in patients with partial DPD deficiency is to maintain plasma concentrations of 5-FU and its metabolites at the intended therapeutic level, in so doing decrease the risk of severe toxicity whilst maintaining treatment efficacy (Ontario Health 2021). Genotyping would ideally be conducted prior to first exposure to FP chemotherapy, to avoid severe toxicities in carriers of clinically significant DPYD variants.

Search and select the most applicable Medical condition terminology (SNOMED CT):

Malignant neoplastic disease

Intervention

Name of the proposed health technology:

DPYD genotyping to predict fluoropyrimidine-induced toxicity

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

The nominated comparator is no DPYD genotyping, where all patients receive standard-dose FP chemotherapy unless a previous episode of toxicity has been noted or a patient is deemed unfit to receive full dose chemotherapy following medical assessment by an oncologist.

Phenotypic testing may be conducted; however, these tests are not listed on the MBS, are not routinely available and issues around the interpretation of results makes their use for predictive purposes unclear. Phenotypic testing can be conducted by the measurement of DPD enzyme activity; however, assays are technically demanding and time consuming, and results are subject to much variation e.g. DPD activity displays a circadian rhythm with as much as a two-fold variation over a 24 h period (Diasio & Offer 2022). Analysis methods differ across testing facilities and are difficult to standardise. The average European DPD enzyme activity is 9.9 ± 0.95 nmol/h per mg protein (Lunenburg et al 2020). Indirect measurement of DPD activity can be conducted by either measurement of plasma uracil or the dihydrouracil to uracil ratio. If an individual is DPD-deficient, the catabolism of uracil to dihydrouracil is reduced, resulting in elevated uracil and a reduced dihydrouracil to uracil ratio (Diasio & Offer 2022). Regardless of the accuracy of such an assay, the result can only indicate in hindsight that a patient has been exposed to a potentially toxic level of FP. This assay does not predict whether a patient should be treated initially with a different dose or drug.

Outcomes

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Safety Outcomes:

Test adverse events

Adverse events (or avoidance of AE) from treatment e.g. severe toxicity (haematological, gastrointestinal, or dermatological)

Adverse events (or avoidance of AE) from change in patient management (treatment modifications)

Clinical Effectiveness Outcomes:

Direct evidence:

Change in patient health outcomes: mortality, morbidity, quality of life - comparing patients who receive a genotype-guided reduced fluoropyrimidine dose to patients treated with a standard dose.

Indirect evidence

Clinical utility: change in patient management/treatment resulting in change in patient outcomes: mortality, morbidity, quality of life

Health system resources:

Cost of DPYD variant genotyping

Cost of toxicity-related hospitalisation, morbidity, mortality

Cost per quality-adjusted life years

Total Australian Government healthcare costs

Proposed MBS items

Proposed Item AAAAA

MBS item number:

Please search and select the proposed category:

PATHOLOGY SERVICES

Please search and select the proposed group:

GENETICS

Please search and select the proposed item descriptor or draft a proposed item descriptor to define the population and health technology usage characteristics that would define eligibility for funding:

Genotyping of a patient for at least four DPYD variants prior to the initiation of chemotherapy with a fluoropyrimidine, administered either orally or intravenously, by or at the request of a medical specialist or consultant physician.

The variants analysed must include:

- c.1905+1G>A
- c.1679T>G
- c.2846A>T
- 1129-5923C>G or c.1236G>A

Once per lifetime

Proposed MBS fee:

\$188.00

Indicate the overall cost per patient of providing the proposed health technology:

\$188.00

Please specify any anticipated out of pocket costs:

\$0.00

Provide details and explain:

Nil

How is the technology/service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):

Self-funded, state-based funding (minimal) – no public funding

Please provide a cost break down attachment:

Document type	File name(s)
Cost breakdown attachment	Costs.jpg

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

FP chemotherapy is the backbone of many solid organ malignancy treatments, in both curative and palliative contexts; however, an increased risk of severe and potentially fatal toxicity is strongly linked to complete or partial deficiency of DPD, the enzyme required to breakdown 5-FU. Toxicity to FP may result in severe haematological, mucosal, cutaneous, and/or digestive toxic side effects, including death, and management of this toxicity incurs financial burden on both patients and the health system.

Identifying DPD variant carriers via genotyping before FP chemotherapy can identify patients who are at high risk of toxicity, allowing for the administration of chemotherapy at an adjusted dose or the cessation of treatment. Pre-treatment genotyping is safe, has been demonstrated to reduce patient morbidity and mortality, reduce hospitalisations and cost-effective.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

There is a paucity of data describing the prevalence of DPD deficiency and DPYD variant carriers in Australia, and no data describing DPYD variants in Aboriginal and Torres Strait Islander peoples (White et al 2021). Most DPYD genotyping studies have been carried out in European populations, where it has been estimated that of heterozygous DPYD variants have a prevalence of 3-5% (Kestenbaum & Hill 2019).

The 2021 systematic review conducted by Ontario Health included 29 observational studies, 25 of which compared the risk of severe toxicity in carriers of a DPYD variant treated with a standard 5-FU

dose with the risk in wild-type patients. Table 2 summarises the prevalence of DPYD variants in the included studies. Heterozygous carriers of c.1905+1G>A and c.1679T>G variants result in 50% and 60-68% reductions in DPD enzyme activity, respectively. Homozygous carriers of c.1905+1G>A and c.1679T>G variants result in DPD reductions in DPD enzyme activity of 100% and 75%, respectively. Heterozygous carriers of c.2846A>T and c.1236G>A variants have 20-30% and 20-35% reductions in enzyme activity, respectively, whereas homozygous carriers of c.2846A>T and c.1236G>A have reported reductions of 50% and 20-70%, respectively (Ontario Health 2021).

As previously discussed, there are a number of factors that affect the prevalence of DPYD variants including ethnicity. The allele frequency of DPYD variants in different ethnic populations are summarised in Table 3. Partial DPD deficiency affects 3-5% of the European population, with 0.01% to 0.2% estimated to have complete DPD deficiency. Approximately 5-8% of individuals with African ancestry have partial DPD deficiency. In Europeans, the c.1236G>A variant is the most common, affecting 2.6% to 6.3% of the population; with an estimated prevalence of c.2846A>T, c.1905+1G>A and c.1679T>G in Europeans of 1.1%, 0.7%, and 0.1%, respectively. The estimated prevalence of homozygous c.1905+1G>A carriers is 0.1% in Europeans (Ontario Health 2021)

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake(%):

25

Year 2 estimated uptake(%):

25

Year 3 estimated uptake(%):

25

Year 3 estimated uptake(%):

25

Estimate the number of patients who will utilise the proposed technology for the first full year:

Estimated utilisation in the first year will range between 18,000 to 67,000 patients

Optionally, provide details:

Testing for DPYD variants is proposed for all patients under the care of a medical oncologist and is being considered for treatment with an oral or intravenous fluoropyrimidine. At present, there are 57 protocols listed on the eviQ website which include fluorouracil; there are a further 34 protocols which include capecitabine. Protocols are frequently added, superseded and discontinued, making it difficult to predict the number of patients who would be eligible for testing of the DPYD gene. It is worth noting that retrospective testing of patients would not be required as patients who have had FP treatment have already survived or succumbed to that exposure. Testing is only of value when applied prospectively to treatment naive patients who are about to be exposed to FP.

As previously mentioned, it has been estimated that approximately 10,000 cancer patients in Australia would be eligible to receive treatment with 5-FU or capecitabine each year (White et al 2022a). This figure is likely to be an under-estimation of the true figure. Recent clinical opinion has estimated that the lower limit may be as high as 16,776 of patients with colorectal, breast, upper gastrointestinal (including oesophageal, stomach and pancreatic), and head and neck cancer based

on incidence rates in 2019 (AIHW 2019). This estimate is based on the stage of each cancer and the number of patients who refuse FP then relapse and progress to FP chemotherapy. Figures are available on request.

The 2022 projected incidence of cancers represent the potential upper limit of patients likely to be treated with FP for all ages combined are summarised in Table 4. This number is likely to be an over estimation of patients who may require DPYD genotyping, with the true figure lying somewhere between 16,776 and 65,851.

Will the technology be needed more than once per patient?

No, once only

Provide references to support these calculations.

Document type	File name(s)
Estimated utilisation references	DPYD Genotyping estimates.xls; Estimated utilisation.docx

Consultation

List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the health technology/service:

Professional body name:

Pathology Australia

Professional body name:

Public Pathology Australia

Professional body name:

The Royal College of Pathologists of Australasia

List all appropriate professional bodies / organisations representing the group(s) of health professionals who request the health technology/service:

Professional body name:

Australian and New Zealand Head & Neck Cancer Society (ANZHNCS)

Professional body name:

Clinical Oncology Society of Australia (COSA)

Professional body name:

Medical Oncology Group of Australia Incorporated (MOGA)

Professional body name:

Private Cancer Physicians of Australia (PCPA)

List all appropriate professional bodies / organisations representing the group(s) of health professionals that may be impacted by the health technology/service:

Professional body name:

Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)

Professional body name:

Pharmaceutical Society of Australia

Professional body name:

Society of Hospital Pharmacists of Australia (SHPA)

List the patient and consumer advocacy organisations or individuals relevant to the proposed health technology:

Number of organisations listed: 3

Professional body name:

Bowel Cancer Australia

Number of organisations listed: 3

Professional body name:

Consumer Health Forum

Number of organisations listed: 3

Professional body name:

GI Cancer Institute

List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed service or health technology:

Professional body name:

N/A

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?

Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

No

Is the therapeutic good classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III

Is the therapeutic good to be used in the service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?

No

Is the therapeutic good classified by the TGA as for Research Use Only (RUO)?

No