MSAC Application 1760

DPYD genotyping to predict fluoropyrimidine-induced toxicity

Population

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

Fluoropyrimidines (FP) are a standard chemotherapy agent prescribed to treat several solid organ tumours, including colorectal, upper gastrointestinal, breast and head and neck cancers. FP can be used alone or in combination with other treatment regimens, including radiotherapy. Fluorouracil, or 5-flourouracil (5-FU) administered intravenously is the most common FP cancer treatment; however, a precursor of fluorouracil, capecitabine, may be administered orally depending on patient indications or preference (Ontario Health 2021).

The therapeutic effect of 5-FU is mediated by only a small fraction (1-3%) of the administered dose, which is converted into cytotoxic metabolites, that exerts a chemotherapeutic effect on both tumour cells and normal tissues via the inhibition of DNA synthesis and repair, and RNA processing and function, resulting in cell death. Approximately 80% of an administered FP dose is metabolised in the liver into inactive metabolites by dihydropyrimidine dehydrogenase (DPD) before being excreted in the urine along with the remaining 5–20% of unprocessed 5-FU (Ontario Health 2021; Dean & Kane 2021 (Update); White et al 2021).

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 (White et al 2021). There are four well-characterised and prevalent *DPYD* variants that result in decreased function:

Non-functioning variants:

- c.1905+1G>A (also known as rs3918290, also known as *DPYD*2A*, DPYD:IVS14 1 1G>A)
- c.1679T>G (also known as rs55886062, *DPYD *13*, p.I560S)

Partially functioning variants (moderately reduced DPD activity):

- c.2846A>T (also known as rs67376798, p.D949V) and
- c.1129–5923C>G (also known as rs75017182, HapB3) The variant c.1236G>A is in complete linkage disequilibrium with this variant and can be used as suitable proxy (Dean & Kane 2021 (Update)).

DPD deficiency is inherited in an autosomal recessive manner and has highly variable disease penetrance:

- DPD normal metabolisers – two 'normal' genes resulting in fully functional, normal DPD enzyme activity;
- DPD intermediate metabolisers have reduced DPD activity as they carry either:
  - one normal gene plus one gene with a non-functional variant, or
  - two genes with partially functioning variants.
- DPD poor metabolisers carry either:
  - two non-functional genes or
  - one non-functional gene plus one partially functioning gene (Amstutz et al 2018).

The prevalence of partial or intermediate metabolisers varies with the ethnic makeup of the population and occurs in approximately 3-5% of individuals. Apart from susceptibility to fluoropyrimidine toxicity, there is no phenotype associated with partial DPD deficiency.

Complete absence of DPD function, which can be fatal on exposure to a fluoropyrimidine, occurs in only 1-2 per 1,000 of the general population (Dean & Kane 2021 (Update)). Complete deficiency can be associated with a severe neurological disorder in some children, but there usually no phenotypic manifestation until an individual is exposed to a fluoropyrimidine. The reason for this phenotypic variation is unknown.

Individuals who are intermediate or poor metabolisers cannot metabolise FPs at normal rates and are at risk of potentially life-threatening toxicity, which typically develops within the first 1–2 cycles of standard dose treatment. Toxicity may be evident as bone marrow suppression, haematologic reactions (leukopenia, neutropenia, anaemia, thrombocytopenia), gastrointestinal symptoms (mucositis, diarrhoea, nausea, and vomiting), neurotoxicity and palmar-plantar erythrodysaesthesia (hand-foot syndrome). These adverse events can lead to hospitalisation, dose reduction, treatment delay, or discontinuation of treatment (Ontario Health 2021). A complete absence of DPD function can often be fatal with exposure to FP chemotherapy. The remaining severe toxicity is likely explainable by other genes implicated in 5-FU metabolism or by up or down-stream enzyme regulators of the 5-FU metabolic pathway. The prevalence of DPD deficiency varies with factors other than the frequency of *DPYD* variants in the population. These other factors include the patient's age, sex, renal function, the type and stage of cancer, and concurrent exposure to other anticancer drugs such as platinum-based drugs (Ontario Health 2021; White et al 2021).

Although the prevalence of *DPYD* gene variant related DPD enzyme deficiency varies with ethnicity, the majority of data has been obtained in European populations and is estimated to range between 5-8%. 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. In addition, there is a lack of robust Australian data describing the overall incidence of severe toxicity related to the administration of FPs, and rates of toxicity associated morbidity and mortality (White et al 2021). The Database of Adverse Event Notifications hosted by the TGA is a voluntary reporting mechanism, which includes adverse reactions to fluoropyrimidines, but the record is incomplete and there is no estimate of the rate of such reactions. This database does not, however, allow for the inclusion of patient ethnicity.

Sharma et al (2021) conducted a systematic review and meta-analysis on treatment related mortality in patients treated with 5-FU. A total 35 studies were included, evaluating pathogenic *DPYD* variants in 13,929 patients receiving standard doses of fluoropyrimidine-based chemotherapy. A total of 27 treatment-related deaths were reported, equating to a crude treatment-related mortality rate of 0.2%, and at least one treatment-related death was reported in 13 of the 35 studies (Table 1). A total of 561 patients were intermediate metabolisers; 11 of whom died. The remaining five patients were poor metabolisers; two of whom died. (Sharma et al 2021).

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.

Table 1 Risk of death by DPYD genotype in patients undergoing standard 5-FU chemotherapy (Sharma et al 2021)

***DPYD* variants**	**Patients tested, n**	**Variant carriers n (%)**	**Deaths in variant carriers, n**	**Risk of death in variant carriers, % [95% CI]**
Non-functioning variants				
c.1905+1G>A*	13,929	183 (1.3)	8	4.4 [2.2-8.5]
c.1679T>G*	8,799	17 (0.2)	1	5.9 [0.8-32.0]
Partially functioning variants				
c.2846A>T*	10,759	127 (1.2)	5	3.9 [1.7-9.1]
c.1129-5923C>G	6,242	241 (3.9)	1	0.4 [0.01-2.9]
Any of 3 variants*	13,929	325 (2.3)	12	3.7 [2.1-6.4]
Any of the 4 variants	13,929	566 (4.1)	13	2.3 [1.3-3.9]

It should be noted that uridine triacetate can be administered as a treatment for FP toxicity. The exogenous uridine competes with 5-FU for incorporation into RNA, diluting the toxic effects of high 5-FU levels (Dean & Kane 2021 (Update)).

It has become standard of care to conduct upfront evaluation of DPD enzyme activity and/or DPYD carrier status throughout Europe and the UK, following statements from NHS England and the European Medicines Agency recommending pharmacogenomic testing for *DPYD* polymorphisms which cause DPD deficiency test prior to the administration of FP therapies (EMA 2020; NHS England 2020).

Evidence-based guidelines such as the Dutch Pharmacogenetics Working Group (DPWG) recommend "*DPYD* genotyping prior to treatment must be performed for all patients initially being prescribed therapy with 5-FU, capecitabine or tegafur (a 5-FU pro-drug not available in Australia) with DPD inhibitors, to optimize the initial dose and to prevent potentially fatal toxicity" (Lunenburg et al 2020). In addition, the guideline produced by the Clinical Pharmacogenetics Implementation Consortium (CPIC) makes recommendations on FP dosing for normal/high, intermediate, and deficient DPD activity phenotypes based on *DPYD* genotypes (Amstutz et al 2018).

It should be noted that in September 2022, the Australian Therapeutic Goods Administration expanded its existing warning and information about DPD deficiency and that eviQ[1] is in the process of updating its guidelines recommending clinicians discuss *DPYD* testing with patients prior to starting FP chemo.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

The target population for genetic analysis of the DPYD gene would be patients with solid tumours who are about to commence a treatment protocol which includes oral or intravenous fluoropyrimidine. The medical oncologist would request the DPYD genetic testing to predict the patient's metaboliser status and thereby inform the starting dose of fluoropyrimidine.

Fluoropyrimidines are widely used in the treatment of patients with a variety of solid tumours. eviQ lists the following cancers for which protocols with a fluoropyrimidine (typically as combination chemotherapy) are currently recommended: breast, colorectal, anal, nasopharyngeal, head and neck, upper gastrointestinal, neuroendocrine, pancreatic, bladder and biliary. 5-FU and capecitabine are listed on the Pharmaceutical Benefits Scheme and would typically be prescribed by a medical oncologist. Approximately 10,000 cancer patients in Australia receive treatment with 5-FU or capecitabine each year (White et al 2022a).

It is important to note that a patient who is shown to be an intermediate metaboliser can still be managed with a fluoropyrimidine treatment protocol, albeit with a lower starting dose. Patients for whom a different treatment protocol may be required would be those uncommon patients who are shown to be poor metabolisers.

In the absence of genotyping, patients may experience FP toxicity with symptoms ranging from mild (e.g. diarrhoea) to severe, resulting in hospitalisation or intensive care admission, or in some cases death.

As noted above, complete absence of DPD activity can rarely present as a congenital neurodevelopmental disorder. Such children would be managed by specialist paediatricians. This group of patients lies outside the scope of this application

Provide a rationale for the specifics of the eligible population:

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.

Are there any prerequisite tests?

No

[1] https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-treatment/1744-dihydropyrimidine-dehydrogenase-dpd-enzyme#assessment

Are the prerequisite tests MBS funded?

N/A

Please provide details to fund the prerequisite tests:

N/A

Intervention

Name of the proposed 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 *DYPD* 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).

Describe the key components and clinical steps involved in delivering the proposed health technology:

Determination of expected DPD enzyme activity is based on the identification of variants in the *DPYD* gene. Genotyping of *DPYD* variants is typically conducted using polymerase chain reaction (PCR) on DNA extracted from peripheral blood cells (4ml EDTA sample). Clinical practice guidelines recommend the analysis of the *DPYD* gene to detect *at least* the following four variants: **13* (c.1679T>G), **2A* (c.1905+1G>A), c.2846A>T, HapB3 (c.[483+18G>A;1129-5923C>G;1236G>A]).

The turnaround time for *DPYD* genotyping is approximately 5-6 days, with testing conducted in a NATA accredited diagnostic laboratory in accordance with NPAAC guidelines.

Identify how the proposed technology achieves the intended patient outcomes:

As described in Figure 2, all patients who are scheduled to undergo chemotherapy with FP should be genotyped for *DPYD* variants prior to commencing therapy. Individuals who have no variant detected are assumed to have two copies of normal activity *DPYD* alleles and are therefore known as “normal metabolisers” with fully functional DPD enzyme activity. These patients can continue with standard FP chemotherapy as planned.

Individuals who have combinations of one normal function and one decreased function or non-functional *DPYD* allele are “intermediate metabolisers”, as well as those individuals with two decreased function alleles. Intermediate metabolisers have partial DPD deficiency and are at increased risk of toxicity. The starting chemotherapy dose should be reduced by 50% in these patients, followed by dose titration based on clinical judgement. Patients can receive further

dose reduction or dose increase pending clinical tolerance and should be monitored consistently throughout the entirety of their treatment.

Individuals who have a combination of non-functional DPYD alleles, or decreased function DPYD alleles, or both, are known as “poor metabolisers”. These patients can be homozygote or compound heterozygote carriers. As these individuals have complete/ near complete DPD deficiency and are at high risk of toxicity, treatment with FP should either be avoided or administered at a markedly reduced dose population (Dean & Kane 2021 (Update)).

There are international consortia guidelines to assist with dose adjustment decisions and these should be readily available for consultation by clinicians to prescribing decision making (Amstutz et al 2018, Lunenburg et al 2020).

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

No

Provide details and explain:

Patients only require this test to be carried out once prior to commencing first FP treatment. Results remain applicable to subsequent FP cycles and future treatment regimens containing a FP. There is no benefit in cascade testing of relatives.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Testing would be requested by the treating clinician and provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Patients should be referred by an oncologist or consultant physician.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Testing would be delivered only by Approved Practising Pathologists with appropriate scope of practice in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☒ Laboratory
- ☐ Outpatient clinic
- ☐ Patient's home
- ☐ Point of care testing
- ☐ Residential aged care facility
- ☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:

N/A

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.

List any existing MBS item numbers that are relevant for the nominated comparators:

N/A

Please provide a rationale for why this is a comparator:

The nominated comparator is no *DPYD* genotyping.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases
☒ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:

The nominated comparator is no *DPYD* genotyping. There is no comparator

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☒ Resources
☐ Value of knowing

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

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

As described in Figure 2, all patients who are scheduled to undergo chemotherapy with FP should be genotyped for DPYD variants prior to commencing therapy. Individuals who have no variant detected are assumed to have two copies of normal activity DPYD alleles and are therefore known as “normal metabolisers” with fully functional DPD enzyme activity. These patients can continue with standard FP chemotherapy as planned.

Individuals who have combinations of one normal function and one decreased function or non-functional *DPYD* allele are “intermediate metabolisers”, as well as those individuals with two decreased function alleles. Intermediate metabolisers have partial DPD deficiency and are at increased risk of toxicity. The starting chemotherapy dose should be reduced by 50% in these patients, followed by dose titration based on clinical judgement. Patients can receive further dose reduction or dose increase pending clinical tolerance and should be monitored consistently throughout the entirety of their treatment.

Individuals who have a combination of non-functional DPYD alleles, or decreased function DPYD alleles, or both, are known as “poor metabolisers”. These patients can be homozygote or compound heterozygote carriers. As these individuals have complete/ near complete DPD

deficiency and are at high risk of toxicity, treatment with FP should either be avoided or administered at a markedly reduced dose population (Dean & Kane 2021 (Update)).

There are international consortia guidelines to assist with dose adjustment decisions and these should be readily available for consultation by clinicians to prescribing decision making (Amstutz et al 2018, Lunenburg et al 2020).

Proposed MBS items

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 funding

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention:

Proposed item details

MBS item number (where used as a template for the proposed item)	
Category number	Category 6
Category description	Pathology services Group P7 - Genetics
Proposed item descriptor	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
Indicate the overall cost per patient of providing the proposed health technology	$188
Please specify any anticipated out of pocket expenses	Nil
Provide any further details and explain	

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

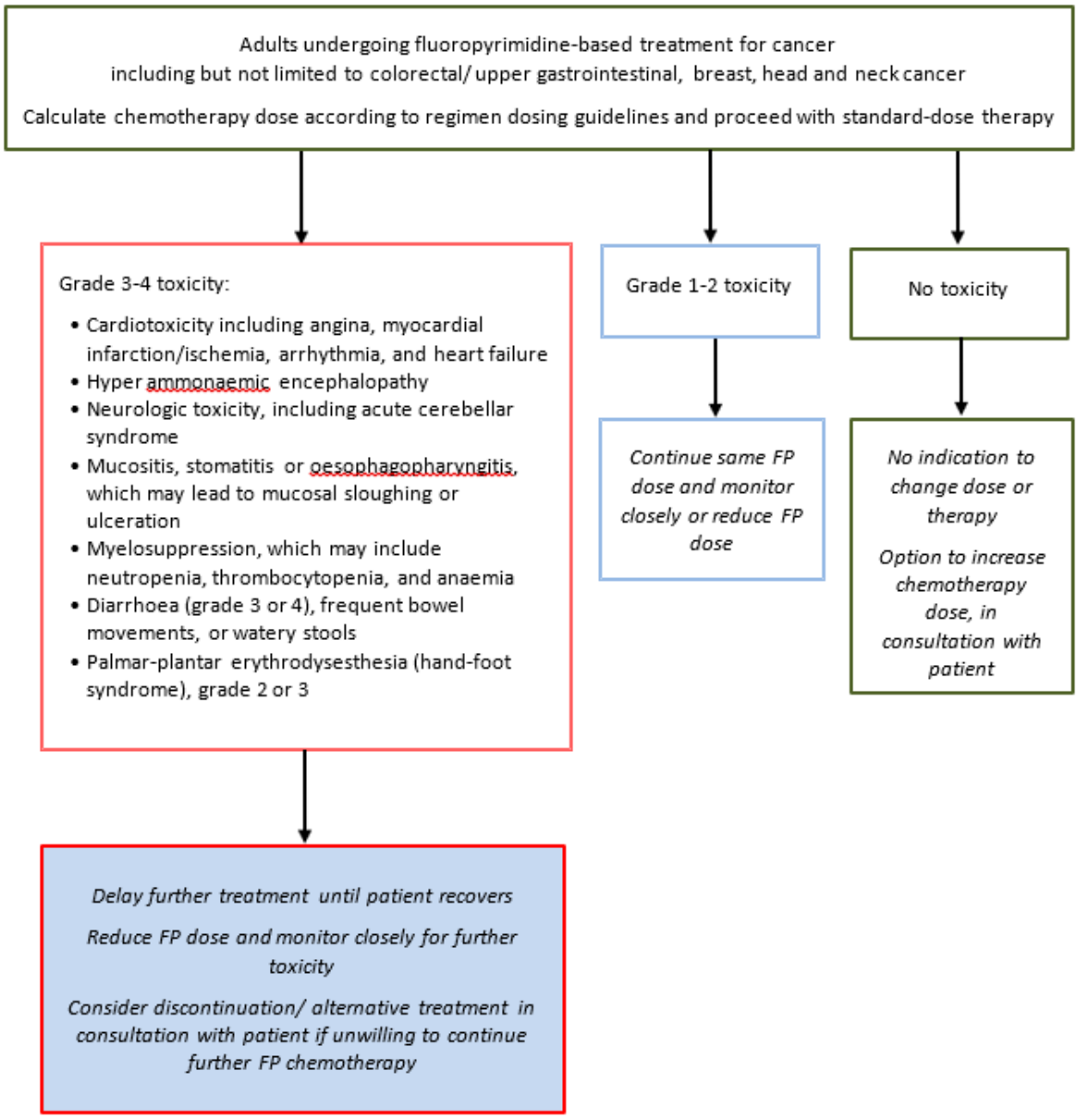

Figure 1 Current clinical algorithm in the absence of DPYD genotyping

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?

Yes

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

There is no difference in the clinical management of patients prior to testing with the proposed intervention as there is no comparator (the comparator is no genetic testing).

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Nil – the intervention is a genetic test. No other resources are required other than the test itself.

Explain what other healthcare resources are used in conjunction with the comparator health technology:

Nil – there is no comparator.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

No healthcare resources are used in conjunction with the proposed health technology vs. the comparator health technology.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

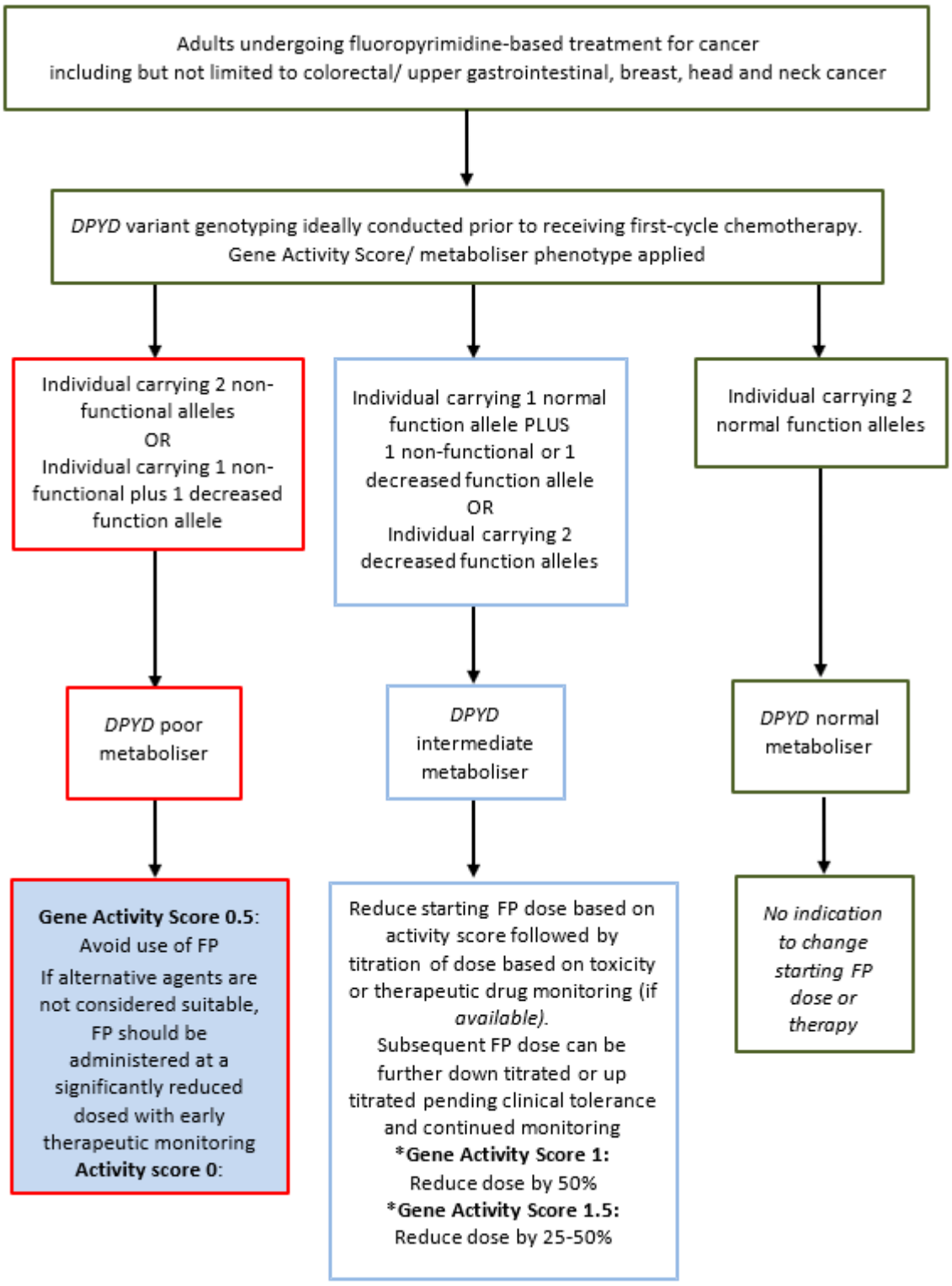

Figure 2 *Proposed clinical management algorithm with the use of DPYD genotyping*

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:

The comparator technology is no genetic testing.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

As described in Figure 2, all patients who are scheduled to undergo chemotherapy with FP should be genotyped for *DPYD* variants prior to commencing therapy. Individuals who have no variant detected are assumed to have two copies of normal activity *DPYD* alleles and are therefore known as "normal metabolisers" with fully functional DPD enzyme activity. These patients can continue with standard FP chemotherapy as planned.

Individuals who have combinations of one normal function and one decreased function or non-functional *DPYD* allele are "intermediate metabolisers", as well as those individuals with two decreased function alleles. Intermediate metabolisers have partial DPD deficiency and are at increased risk of toxicity. The starting chemotherapy dose should be reduced by 50% in these patients, followed by dose titration based on clinical judgement. Patients can receive further dose reduction or dose increase pending clinical tolerance and should be monitored consistently throughout the entirety of their treatment.

Individuals who have a combination of non-functional DPYD alleles, or decreased function DPYD alleles, or both, are known as "poor metabolisers". These patients can be homozygote or compound heterozygote carriers. As these individuals have complete/ near complete DPD deficiency and are at high risk of toxicity, treatment with FP should either be avoided or administered at a markedly reduced dose population (Dean & Kane 2021 (Update)).

It is therefore likely that more health resources will be used using the 'comparator' technology (no genetic testing), as there will be a number of patients who will experience the toxic effects of FP treatment. This may involve toxicity-related hospitalisation, morbidity, and mortality.

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Provided above.

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
☐ Non-inferior
☐ Inferior

Comparator is no *DPYD* testing, therefore *DPYD* testing will result in superior health outcomes.

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.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

Comparator is no *DPYD* testing. Without *DPYD* testing, patients will be at risk of

Identify how the proposed technology achieves the intended patient outcomes:

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.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?	Yes
A change in health outcome?	Yes
Other benefits?	Yes

Please provide a rationale, and information on other benefits if relevant:

Pre-treatment genotyping is safe, has been demonstrated to reduce patient morbidity and mortality, reduce hospitalisations and cost-effective.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

As there is currently no comparative test, then the addition of testing will increase costs. However, the associated reductions in patient morbidity and mortality, and hospitalisations will ensure that *DPYD* testing is cost-effective.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

Do not attach full text articles; this is just a summary (repeat columns as required).

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research
Review – comparison of guidelines (Abdullah-Koolmees et al 2020) Netherlands	Pharmacogenetics Guidelines: Overview and Comparison of the DPWG, CPIC, CPNDS, and RNPGx Guidelines	A literature review of guidelines with recommendations published in English. The Dutch Pharmacogenetics Working Group (DPWG), the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and the French National Network (Réseau) of Pharmacogenetics (RNPGx) were selected. Guidelines were compared with regard to the methodology of development, translation of genotypes to predicted phenotypes, pharmacotherapeutic recommendations and recommendations on genotyping.	https://pubmed.ncbi.nlm.nih.gov/33568995/
Review – comparison of guidelines (Bank et al 2018) Multicentre	Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group	The Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group provide therapeutic recommendations for well-known gene-drug pairs. Published recommendations show a high rate of concordance. However, as a result of different guideline development methods used by these two consortia, differences between the published guidelines exist. This paper aims to compare both initiatives and explore these differences, with the objective to achieve harmonization.	https://pubmed.ncbi.nlm.nih.gov/28994452/

Type of study design*	**Title of journal article or research project**	**Short description of research (max 50 words)****	**Website link to journal article or research**
Guideline (Amstutz et al 2018) Multicentre - Clinical Pharmaco-genetics Implementation Consortium	Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update	This guideline provides information for the interpretation of clinical dihydropyrimidine dehydrogenase (*DPYD*) genotype tests so that the results can be used to guide dosing of fluoropyrimidines (5-fluorouracil and capecitabine).	https://pubmed.ncbi.nlm.nih.gov/29152729/
Guideline (Lunenburg et al 2020)	Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines	The Dutch Pharmacogenetics Working Group (DPWG) aims to facilitate pharmacogenetics (PGx) implementation by developing evidence-based guidelines to optimize pharmacotherapy. This guideline describes the starting dose optimization of three anti-cancer drugs (fluoropyrimidines: 5-fluorouracil, capecitabine and tegafur) to decrease the risk of severe, potentially fatal, toxicity. The *DPYD*-gene activity score, determined by four *DPYD* variants, predicts DPD allele activity and can be used to optimize an individual's starting fluoropyrimidine dose. The gene activity score ranges from 0 (no DPD activity) to 2 (normal DPD activity). Based on the DPWG gene activity score, *DPYD* genotyping is considered "essential" prior to initiating fluoropyrimidines.	https://pubmed.ncbi.nlm.nih.gov/31745289/
Consensus paper (Wörmann et al 2020)	Dihydropyrimidine Dehydrogenase Testing prior to Treatment with 5-Fluorouracil, Capecitabine, and Tegafur: A Consensus Paper	The statement was developed as a consensus statement organized by the German Society for Hematology and Medical Oncology in cooperation with 13 medical associations from Austria, Germany, and Switzerland. Key Messages: (i) Patients should be tested for the 4 most common genetic *DPYD* variants before treatment with drugs containing FU. (ii) Testing forms the basis for a differentiated, risk-adapted algorithm with recommendations for treatment with FU-containing drugs. (iii) Testing may optionally be supplemented by therapeutic drug monitoring.	https://pubmed.ncbi.nlm.nih.gov/33099551/

Type of study design*	**Title of journal article or research project**	**Short description of research (max 50 words)****	**Website link to journal article or research**
HTA (Ontario Health 2021)	DPYD genotyping in patients who have planned cancer treatment with fluoropyrimidines: a health technology assessment	A systematic literature search of the clinical evidence, a systematic economic literature review and cost-effectiveness and cost-utility analyses were conducted, as well as the budget impact of publicly funding pre-treatment *DPYD* genotyping in patients with planned FP treatment. 29 observational studies in the clinical evidence review, 25 of which compared the risk of severe toxicity in carriers of a *DPYD* variant treated with a standard fluoropyrimidine dose with the risk in wild-type patients.	https://pubmed.ncbi.nlm.nih.gov/34484488/
Meta-analysis (Glewis et al 2022)	A systematic review and meta-analysis of toxicity and treatment outcomes with pharmacogenetic-guided dosing compared to standard of care BSA-based fluoropyrimidine dosing	17publications met predefined eligibility criteria. The meta-analysis observed reduced incidence of grade 3/4 overall toxicity (RR= 0.32 [95% CI 0.27-0.39], p < 0.00001) and grade 3/4 diarrhoea (RR 0.38 [95% CI 0.24-0.61], p < 0.0001) among PGD versus non-PGD cohorts. Within PGD cohorts, there was no statistical differences for overall response rates (complete/partial) (RR 1.31 [95% CI 0.93-1.85], p = 0.12). Similar results were found with stable disease (RR 1.27 [95% CI 0.66-2.44], p = 0.47). PGD improves patient outcomes in terms of grade 3/4 toxicity, in particular overall toxicity and diarrhoea, without impacting on treatment response.	https://pubmed.ncbi.nlm.nih.gov/35306539/
Meta-analysis (Meulendijks et al 2015)	Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data	7,365 patients from 8 studies were included in the meta-analysis. *DPYD* c.1679T>G was significantly associated with fluoropyrimidine-associated toxicity (adjusted RR 4·40, p<0·0001), as was c.1236G>A/HapB3 (1·59, p<0·0001). The association between c.1601G>A and FP-associated toxicity was not significant (adjusted RR 1·52, p=0·15). Analysis of individual types of toxicity showed consistent associations of c.1679T>G and c.1236G>A/HapB3 with gastrointestinal toxicity (adjusted RR 5·72, p=0·015; and 2·04, p<0·0001, respectively) and haematological toxicity (adjusted RR 9·76, p=0·00014; and 2·07, p=0·013, respectively), but not with hand-foot syndrome. *DPYD**2A and c.2846A>T were also significantly associated with severe FP-associated toxicity (adjusted RR 2·85, 95% CI 1·75-4·62, p<0·0001; and 3·02, 2·22-4·10, p<0·0001, respectively). *DPYD* variants c.1679T>G and c.1236G>A/HapB3 are clinically relevant predictors of FP-associated toxicity. Upfront screening for these variants, in addition to the established variants *DPYD*2A* and c.2846A>T, is recommended to improve the safety of patients with cancer treated with fluoropyrimidines.	https://pubmed.ncbi.nlm.nih.gov/26603945/

Type of study design*	**Title of journal article or research project**	**Short description of research (max 50 words)****	**Website link to journal article or research**
Systematic review (Rai et al 2019)	Risk of treatment-related death in carriers of pathogenic DPYD polymorphisms treated with fluoropyrimidine chemotherapy: A systematic review and patient-level analysis	Of the 1,290 references screened, 37 publications were included in the final analysis. Patient-level data identified 485 of 14,377 patients (3.4%) with pathogenic *DPYD* polymorphisms. There were 12 deaths among polymorphism carriers, resulting in a 2.5% risk of treatment-related mortality (95% CI 1.3-4.4%). Only 2 treatment-related deaths were reported in 13,892 patients without identified polymorphisms. Patients with pathogenic *DPYD* polymorphisms who are treated with standard-dose FP chemotherapy are at significant risk of death and can be prospectively identified through pharmacogenetic testing.	https://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.e15132
Prospective case series and systematic review (Conti et al 2020)	A genotyping/phenotyping approach with careful clinical monitoring to manage the fluoropyrimidines-based therapy: Clinical cases and systematic review of the literature	A case series of patients in whom we performed *DPYD*-PGx (by real-time PCR), 5-FU clearance and a dihydrouracil/uracil ratio (as the phenotyping analysis) and a continuous clinical monitoring. Patients who had already experienced severe toxicity were then identified as carriers of *DPYD* variants. A systematic review on genotyping/phenotyping combinations used as predictive factors of FP safety was conducted. Measuring plasma 5-FU clearance and/or dihydrouracil/uracil (UH2/U) ratio could improve the predictive potential of *DPYD*-PGx. The upfront *DPYD*-PGx combined with clinical monitoring and feasible phenotyping method is essential to optimising FP-based chemotherapy.	https://pubmed.ncbi.nlm.nih.gov/32899374/
Prospective cohort – matched pair analysis (Henricks et al 2019b)	Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the *DPYD**2A variant: A matched pair analysis	A cohort of 40 prospectively identified heterozygous *DPYD**2A carriers, treated with a ~50% reduced fluoropyrimidine dose, was identified. For effectiveness analysis, a matched pair-analysis was performed in which for each *DPYD**2A carrier a matched *DPYD**2A wild-type patient was identified. The frequency of severe (grade ≥ 3) treatment-related toxicity was compared to 1] a cohort of 1606 wild-type patients treated with full dose and 2] a cohort of historical controls derived from literature, i.e. 86 *DPYD*2A* variant carriers who received a full fluoropyrimidine dose. For 37 out of 40 *DPYD*2A* carriers, a matched control could be identified. Compared to matched controls, reduced doses did not negatively affect overall survival (median 27 months versus 24 months, p = 0.47) nor progression-free survival (median 14 months versus 10 months, p = 0.54). Risk of severe fluoropyrimidine-related toxicity in *DPYD**2A carriers treated with reduced dose was 18%, comparable to wild-type patients (23%, p = 0.57) and significantly lower than the risk of 77% in *DPYD**2A carriers treated with full dose (p < 0.001). *DPYD**2A genotype-guided dosing appears to have no negative effect on effectiveness of fluoropyrimidine-based chemotherapy, while resulting in significantly improved patient safety.	https://pubmed.ncbi.nlm.nih.gov/30485432/

Type of study design*	**Title of journal article or research project**	**Short description of research (max 50 words)****	**Website link to journal article or research**
Retrospective cohort – matched pair analysis (Tsiachristas et al 2022)	Can upfront *DPYD* extended variant testing reduce toxicity and associated hospital costs of fluoropyrimidine chemotherapy? A propensity score matched analysis of 2022 UK patients	Propensity score matching (PSM) was used to match 466 patients tested with an extended *DPYD* variant panel (ToxNav®) with 1,556 patients from a historical cohort. ToxNav® appeared to reduce the likelihood of experiencing moderate (OR: 0.59) and severe anaemia (OR: 0.55), and experience of pain for more than 4 days a week (OR: 0.50), while it increased the likelihood of mild neutropenia (OR: 1.73). It also reduced the cost of chemotherapy by 12% or £9765, the cost of non-elective hospitalisation by 23% or £2331, and the cost of critical care by 21% or £1219 per patient. Upfront testing of *DPYD* variants appears to reduce the toxicity burden of Capecitabine and 5-FU in cancer patients and can lead to substantial hospital cost savings.	https://pubmed.ncbi.nlm.nih.gov/35473510/
Comparative study (Boisdron-Celle et al 2017)	Prevention of 5-fluorouracil-induced early severe toxicity by pre-therapeutic dihydropyrimidine dehydrogenase deficiency screening: Assessment of a multiparametric approach	Two parallel cohorts of patients treated with FP-based chemotherapy for colorectal carcinoma were compared in a prospective nonrandomized study. In arm A, patients had DPD deficiency screening before treatment. Arm B no pre-therapy screening was performed. At total of 1,142 patients (n = 1,116 evaluable) were enrolled. In arm A, out of 718 evaluable patients, nine grade 4 early toxicities potentially related to 5-FU were reported in nine patients (1.2%) with no toxic death despite one complete DPD deficiency and 24 partial deficiencies. The 24 patients with partial deficiency had safe pharmacokinetics (PK)-monitored 5-FU. In arm B, among 398 evaluable patients, 17 grade 4-5 toxic early events potentially related to FP were reported in 12 patients (4.2%). The incidence of early severe toxicity was significantly higher in arm B (P = .0019). The percent of patients with a toxicity grade 3 or higher observed in arm A was 10.8% (n = 78) compared to 17.55% (n = 69) in arm B (P = .0497). The percentage of death was reduced from 2.5/1,000 in arm B to 0 in arm A. Overall, one patient with complete DPD deficiency confirmed retrospectively died within 13 days from grade 5 multivisceral toxicity.	https://pubmed.ncbi.nlm.nih.gov/28395758/

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Prospective cohort cost analysis (Henricks et al 2019a)	A cost analysis of upfront *DPYD* genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy	A cost-minimisation analysis from a health-care payer perspective was performed as part of the prospective clinical trial (NCT02324452) in which patients prior to start of fluoropyrimidine-based therapy were screened for the *DPYD* variants *DPYD**2A, c.2846A>T, c.1679T>G and c.1236G>A and received an initial dose reduction of 25% (c.2846A>T, c.1236G>A) or 50% (*DPYD**2A, c.1679T>G). Data on treatment, toxicity, hospitalisation and other toxicity-related interventions were collected. The model compared prospective screening for these *DPYD* variants with no *DPYD* screening. One-way and probabilistic sensitivity analyses were also performed. Expected total costs of the screening strategy were €2599 per patient compared with €2650 for non-screening, resulting in a net cost saving of €51 per patient. Results of the probabilistic sensitivity and one-way sensitivity analysis demonstrated that the screening strategy was very likely to be cost saving or worst-case cost-neutral.	https://pubmed.ncbi.nlm.nih.gov/30544060/
Prospective cohort and cost analysis (Deenen et al 2016)	Upfront Genotyping of *DPYD**2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis	A total of 2,038 patients were prospectively screened for *DPYD**2A, of whom 22 (1.1%) were heterozygous polymorphic. *DPYD**2A variant allele carriers were treated with a median dose-intensity of 48% (range, 17% to 91%). The risk of grade ≥ 3 toxicity was thereby significantly reduced from 73% (95% CI, 58% to 85%) in historical controls (n = 48) to 28% (95% CI, 10% to 53%) by genotype-guided dosing (P < .001); drug-induced death was reduced from 10% to 0%. Adequate treatment of genotype-guided dosing was further demonstrated by a similar incidence of grade ≥ 3 toxicity compared with wild-type patients receiving the standard dose (23%; P = .64) and by similar systemic fluorouracil (active drug) exposure. Furthermore, average total treatment cost per patient was lower for screening (€2,772 [$3,767]) than for non-screening (€2,817 [$3,828]), outweighing screening costs.	https://pubmed.ncbi.nlm.nih.gov/26573078/
Cost effectiveness (Brooks et al 2022)	Cost-effectiveness of *DPYD* Genotyping Prior to Fluoropyrimidine-based Adjuvant Chemotherapy for Colon Cancer	A cost-effectiveness analysis of *DPYD* genotyping prior to fluoropyrimidine-based adjuvant chemotherapy for stage 3 colon cancer, covering the c.1129-5923C>G (HapB3), c.1679T>G (*13), c.1905+1G>A (*2A), and c.2846A>T gene variants, taking a United States healthcare perspective. Compared with no screening, *DPYD* genotyping increased per-patient costs by $78 and improved survival by 0.0038 quality-adjusted life years (QALYs), leading to an ICER of $20,506/QALY. In 1-way sensitivity analyses, the ICER exceeded $50,000 per QALY when the cost of the *DPYD* genotyping assay was greater than $286. In probabilistic sensitivity analysis using a willingness-to-pay threshold of $50,000/QALY *DPYD* genotyping was preferred to no screening in 96.2% of iterations. *DPYD* genotyping is a cost-effective strategy for preventing rare but severe and sometimes fatal toxicities of fluoropyrimidine chemotherapy.	https://pubmed.ncbi.nlm.nih.gov/35668003/

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Retrospective cohort (Murphy et al 2018)	Cost Implications of Reactive Versus Prospective Testing for Dihydropyrimidine Dehydrogenase Deficiency in Patients With Colorectal Cancer: A Single-Institution Experience	All patients experiencing severe toxicity from FP-based chemotherapy for CRC over a 3-year period were tested for 4 *DPYD* polymorphisms previously associated with toxicity. The costs associated with an index admission for toxicity in DPD-deficient patients were examined. A cost analysis was undertaken comparing the anticipated cost of implementing screening for *DPYD* mutations versus current usual care. Of 134 patients commencing first-line FP chemotherapy over 3 years, 30 (23%) patients developed grade 3/4 toxicity. Of these, 17% revealed heterozygote *DPYD* mutations. The cost of hospitalisation for the *DPYD*-mutated patients was €232 061, while prospectively testing all 134 patients would have cost €23 718. Prospective testing would result in cost savings across all scenarios.	https://pubmed.ncbi.nlm.nih.gov/30288154/
Prospective case series (Eccles et al 2018)	Prospective *DPYD* testing in colorectal cancer patients in a real-world UK population	Consecutive colorectal cancer (CRC) patients in a UK cancer centre due to receive FP chemotherapy were genotyped by real time PCR for known clinically relevant *DPYD* mutations: c.1905+G>A 2*, c.2846A>T, c.1679T>G and c.1605 G>A and from March 2017, c.1236G>A/HapB. 230 patients were tested. 72% had capecitabine, 24% 5-FU, and 4% raltitrexed combinations. After dose reduction or alternative therapy, grade 3/4 diarrhoea was similar in wildtype and mutations (10 vs 13%) and any toxicity admissions were not significantly different (p=0.284). There were no treatment deaths.	https://www.annalsofoncology.org/article/S0923-7534(19)49024-8/fulltext
Prospective, multi-centre case series (Henricks et al 2018)	*DPYD* genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis	Prospective screening for the four most relevant *DPYD* variants (*DPYD**2A [rs3918290, c.1905+1G>A, IVS14+1G>A], c.2846A>T [rs67376798, D949V], c.1679T>G [rs55886062, *DPYD**13, I560S], and c.1236G>A [rs56038477, E412E, in haplotype B3]) across 17 sites. Of 1,103 evaluable patients, 85 (8%) were heterozygous *DPYD* variant allele carriers, and 1,018 (92%) were *DPYD* wild-type patients. Overall, fluoropyrimidine-related severe toxicity was higher in *DPYD* variant carriers (33 [39%] of 85 patients) than in wild-type patients (231 [23%] of 1,018 patients; p=0·0013). The RR for severe fluoropyrimidine-related toxicity was 1·31 (95% CI 0·63-2·73) for genotype-guided dosing compared with 2·87 (2·14-3·86) in the historical cohort for *DPYD**2A carriers, no toxicity compared with 4·30 (2·10-8·80) in c.1679T>G carriers, 2·00 (1·19-3·34) compared with 3·11 (2·25-4·28) for c.2846A>T carriers, and 1·69 (1·18-2·42) compared with 1·72 (1·22-2·42) for c.1236G>A carriers.	https://pubmed.ncbi.nlm.nih.gov/30348537/

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Prospective case series (Avila Andrade et al 2018)	Determination of *DPYD* polymorphisms before treatment with chemotherapy with a pyrimidine: Should we continue doing it?	374 patients, with colorectal cancer (85%), gastroesophageal cancer (12%) or cancer in the head and neck (3%). 97% were adenocarcinomas and 3% squamous carcinoma. The intention of adjuvant treatment in 46%, neoadjuvant 17%, a first line of metastatic disease 33%, the second line of metastatic disease 3%. Schemes used: combinations of 5FU with oxaliplatin (58%), capecitabine in monotherapy or radiotherapy in neoadjuvant (33%). Four patients with *DPYD* deficit (1.1%) were found. Two patients with a complete deficit that started capecitabine adjuvant at 50%, increasing to 75% in the 2nd cycle with G1 diarrhea as a relevant toxicity. Another two patients with DPYP heterozygous deficit decided to change treatment scheme to ralitrexed every 3 weeks. Enzymatic deficit in the metabolic pathways related to 5FU are rare, and probably do not influence the initiation of chemotherapy treatment, but it is very important to avoid toxicity to the patient if deficits are present.	https://www.annalsofoncology.org/article/S0923-7534(19)49026-1/fulltext
Prospective case series (Etienne-Grimaldi et al 2017)	New advances in *DPYD* genotype and risk of severe toxicity under capecitabine	243 advanced breast cancer patients receiving capecitabine were analysed (88.5% capecitabine monotherapy). Grade 3 and grade 4 capecitabine-related digestive and/or neurologic and/or haemato-toxicities were observed in 10.3% and 2.1% of patients, respectively. *DPYD* exome, along with flanking intronic regions 3'UTR and 5'UTR, were sequenced on MiSeq Illumina. DPD phenotype was assessed by pre-treatment plasma uracil (U) and dihydrouracil (UH2) measurement. Combined analysis of deleterious variants *2A, I560S (*13) and D949V showed significant association with grade 3-4 toxicity (sensitivity 16.7%, PPV 71.4%, RR 6.7, p<0.001) but not with grade 4 toxicity. Considering additional deleterious coding variants D342G, S492L, R592W and F100L increased the sensitivity to 26.7% for grade 3-4 toxicity (PPV 72.7%, RR 7.6, p<0.001), and was significantly associated with grade 4 toxicity (sensitivity 60%, PPV 27.3%, RR 31.4, p = 0.001), suggesting the clinical relevance of extended targeted *DPYD* genotyping.	https://pubmed.ncbi.nlm.nih.gov/28481884/
Retrospective case series (Jolivet et al 2021)	Implementing *DPYD*2A Genotyping in Clinical Practice: The Quebec, Canada, Experience	Retrospective chart review of 2,617 patients who tested positive for a heterozygous or homozygous *DPYD*2A* (c.1905+1G>A, IVS14+1G>A, rs3918290) variant. 25 patients tested positive, 24 of whom were heterozygous (0.92%), and one was homozygous (0.038%). Data were available for 20 patients: 15 were tested upfront, whereas 5 were identified after severe toxicities. Of the 5 patients confirmed after toxicities, all had grade 4 cytopenias, 80% grade ≥3 mucositis, 20% grade 3 rash, and 20% grade 3 diarrhea. Eight patients identified with *DPYD*2A mutation prior to treatment received 5-FU-based chemotherapy at reduced initial doses. The average fluoropyrimidine dose intensity during chemotherapy was 50%. No grade ≥3 toxicities were observed. *DPYD*2A test results were available in an average of 6 days, causing no significant delays in treatment initiation.	https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13626

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Retrospective case series (Lunenburg et al 2018)	Standard fluoropyrimidine dosages in chemoradiation therapy result in an increased risk of severe toxicity in *DPYD* variant allele carriers	Medical records of 828 patients who received FP-based CRT were reviewed from three centres. *DPYD* variant allele carriers treated with standard dosages (N = 34) showed an increased risk of severe gastrointestinal (adjusted OR = 2.58, p = 0.045) or severe haematological (adjusted OR = 4.19, p = 0.015) toxicity compared with wild-type patients (N = 771). *DPYD* variant allele carriers who received dose reductions (N = 22) showed a comparable frequency of severe gastrointestinal toxicity compared with wild-type patients, but more (NS) severe haematological toxicity. Hospitalisations for all *DPYD* variant allele carriers were comparable, independent of dose adjustments; however, the mean duration of hospitalisation was significantly shorter in the dose reduction group (P = 0.010). Standard FP dosages in CRT resulted in an increased risk of severe toxicity in *DPYD* variant allele carriers.	https://pubmed.ncbi.nlm.nih.gov/30361102/
Retrospective case series and cost analysis (Toffoli et al 2019)	The genotype for *DPYD* risk variants in patients with colorectal cancer and the related toxicity management costs in clinical practice	A cost analysis was conducted on the toxicities experienced by 550 patients with CRC treated with FP-based chemotherapy. Genotyping for *DPYD**2A, *DPYD**13, *DPYD*c. 2846A>T, *DPYD*-HapB3, and UGT1A1*28 was done retrospectively and did not affect patient treatment. Carriers of at least one *DPYD* variant experienced higher toxicity management costs (€2,972) than non-carriers (€825, p< 0.0001) and had a higher risk for toxicity requiring hospitalisation (odds ratio, 4.14). In patients receiving fluoropyrimidine/irinotecan, the incremental cost between *DPYD* variant and UGT1A1*28/*28 carriers and non-carriers was €2,975. Toxicity management costs during FP-based therapy are associated with *DPYD* and UGT1A1*28 variants and supports the utility of genotyping.	https://pubmed.ncbi.nlm.nih.gov/30339275/
Retrospective case series and cost analysis (Fragoulakis et al 2019)	Estimating the Effectiveness of *DPYD* Genotyping in Italian Individuals Suffering from Cancer Based on the Cost of Chemotherapy-Induced Toxicity	571 patients with a histologically confirmed diagnosis of cancer, who received a fluoropyrimidine-based treatment, were retrospectively genotyped in the *DPYD* gene. *DPYD* extensive metabolisers (528 individuals) had greater effectiveness and lesser cost, representing a cost-saving option over *DPYD* intermediate and poor metabolisers (43 individuals) with mean QALYs of 4.18 versus 3.02, respectively. There are some indications for differences in survival between the two groups (p > 0.05), while the cost of *DPYD* extensive metabolisers was significantly lower (p < 0.01) compared with those belonging to the group of intermediate/poor metabolisers.	https://pubmed.ncbi.nlm.nih.gov/31155283/

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).

Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC

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Single arm trial	GeneScreen 5-FU Genotype-guided Personalised Fluoropyrimidine Dosing: Feasibility and Implementation Pilot Study	Adult patients with solid organ tumours intended to or already undertaking Fluoropyrimidine chemotherapies are eligible for inclusion. Patients submit a blood sample to be collected either by phlebotomy trained nurse or usual blood collection facility) for DPYD genotyping to identify DPYD variants that carry important clinical significant for fluoropyrimidine related toxicity. Samples are genotyped and results provided back to oncologist. This is a feasibility study measuring turnaround time of testing. Any decisions regarding DPYD variant results are at clinician discretion.	ACTRN12622000963729	Date of last data collection February 2023
Single arm trial Historical controls	Pre-treatment dihydropyrimidine dehydrogenase (DPYD) genotyping to individualise fluoropyrimidine-based chemotherapy: An evaluation of clinical implementation and treatment-related toxicity.	Pre-treatment dihydropyrimidine dehydrogenase (DPYD) genotyping in patients receiving fluoropyrimidine (5-Fluorouracil or Capecitabine) chemotherapy: A clinical implementation study of the effect of individualised dosing on treatment related toxicity. Treatment toxicity compared between those who have a variant and those who don't. For further comparison, a retrospective review will also be undertaken of toxicity rates for all patients who received fluoropyrimidine treatment at the Royal Brisbane and Women's Hospital in 2019.	ACTRN12621001117808	Date of last data collection Sept 2022
Single arm trial Historical controls	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.	The intervention comprises of single time-point pharmacogenetics screening for: 1. DPYD gene test for patients newly commencing on 5-fluorouracil and capecitabine chemotherapy 2. UGT1A1*28 gene test for patients newly commencing on irinotecan chemotherapy	ACTRN12621000251820	Date of last data collection Aug 2024

Comparative, non-randomised	Evaluating a Pharmacogenetic Testing Panel in Patients Suspected to be at Increased Risk for Pharmacogenetics-related AEs While Receiving Fluoropyrimidine or Irinotecan Therapy	Comparison of outcomes in patients with either *DPYD* or *UGT1A1* variants to patients where genetic information was not known prior to receiving treatment with fluoropyrimidine or irinotecan.	NCT05583422	Estimated Study Completion Date: February 2025
Single arm trial	Implementing Pharmacogenetic Testing in Gastrointestinal Cancers (IMPACT-GI)	All patients will be screened for twelve single nucleotide polymorphisms (SNPs) in *DPYD*: *DPYD**2A, *5, *6, *8, *9A, *10, *12, *13, rs2297595, rs115232898, rs67376798, HapB3, with the results used to guide treatment.	NCT04736472	Estimated Study Completion Date: June 2023
Randomised controlled trial	The PhOCus Trial: Implementation of Pharmacogenomic Testing in Oncology Care	860 gastrointestinal or head and neck cancer patients to be enrolled into either the control group – who will receive standard chemotherapy without guidance from genetic information – or the pharmacogenomics group, where treatment will be guided by the results of genetic testing (*DPYD* or UGT1A1 variants).	NCT04541381	Estimated Study Completion Date: March 2028
Prospective observational cohort	Identifying Novel Variants in the DPYD Gene in Patients of Non-Western Descent (DPYD-NOW)	600 patients of non-Western descent with an indication for treatment with fluoropyrimidine-based chemotherapy will undergo sequencing to identify *DPYD* variants associated with an increased risk of developing severe fluoropyrimidine-related toxicity.	NCT04300361	Estimated Study Completion Date: August 2022
Patient Registry	Implementation and Quality Assurance of DPYD-genotyping in Patients Treated With Fluoropyrimidines.	722 patients with an indication for treatment with fluoropyrimidine-based chemotherapy will undergo sequencing to identify *DPYD* variants to guide treatment.	NCT05266300	Estimated Study Completion Date: Oct 2022

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