Australian Government

Department of Health

Consultation Survey on MSAC Application 1760

DPYD genotyping to predict fluoropyrimidine-induced toxicity

MSAC welcomes input on MSAC applications for public funding from individuals, organisations representing health professionals or consumers and/or carers, and from other stakeholders. Please use this template to prepare your input. You may also attach additional information if you consider it may be useful in informing MSAC and its sub-committees.

Sharing consultation input

Submitted consultation input will be routinely shared with the applicant and with MSAC and its sub-committees.

- The applicant will receive a summary of comments from individuals, with the individual's name and other identifying information removed.
- MSAC and its sub-committees will receive both the summary and copies of the comments, with the name of the individual and other identifying information removed.
- Consultation input from groups or organisations will be provided in a complete form to both the applicant and to MSAC and its sub-committees.

Consultation input may also be shared with HTA Assessment Groups from time to time to inform their reports to MSAC or with state and territory health representatives where the application is for a service to be delivered through public hospitals. Please do not include information in your input that you do not want shared as outlined above. In addition, to protect privacy, do not include identifying personal (e.g., name) or sensitive (e.g., medical history) information about third parties, such as medical professionals or friends/relatives.

How consultation input is used

MSAC and its sub-committees consider consultation input when appraising an application, including to better understand the potential impact of the proposed medical technology/service on consumers, carers, and health professionals. A summary of consultation input will be included in the Public Summary Document (PSD) published on the MSAC website once MSAC has completed its appraisal. The PSD may also cite input from groups/organisations, including the name of the organisation. As such, organisations should not include information or opinions in their consultation input that they would not wish to see in the public domain.

Consultation deadlines. Please ensure that your consultation input is submitted by the pre-PASC or pre-MSAC consultation deadline for this application. Consultation deadlines for each PASC and MSAC meeting are listed in the PASC, ESC, MSAC key dates available on the MSAC website. They are also published in the MSAC Bulletin. Consultation input received after the respective deadlines may not be considered.

For further information on the MSAC consultation process please refer to the MSAC Website or contact the Consumer Evidence and Engagement Unit on email: commentsMSAC@health.gov.au.
Thank you for taking the time to provide consultation input. Please return your completed survey to:

Email: commentsMSAC@health.gov.au

Mail: MSAC Secretariat,
MDP 960, GPO Box 9848,
ACT 2601.

PART 1 – PERSONAL AND ORGANISATIONAL INFORMATION

1. Respondent details

Name: Michael Quinn

Email:michael.quinn3@health.qld.gov.au

Phone No:0736460185

2. Is the feedback being provided on an individual basis or by a collective group?

☐ Individual
☒ Collective Group

If an individual, specify the name of the organisation you work for

If a collective group, specify the name of the group

Australian Genomics

3. How would you best identify yourself?

☐ General Practitioner
☐ Specialist
☒ Researcher
☐ Consumer
☐ Care giver
☐ Other

If other, please specify

PART 2 – CLINICAL NEED AND PUBLIC HEALTH SIGNIFICANCE

4. Describe your experience with the medical condition (disease) and/or proposed intervention and/or service relating to the application summary

Australian Genomics is an Australian Government initiative supporting genomic research and its translation into clinical practice. Through broad engagement and a national collaborative approach, it achieves two key objectives: to improve efficiency, reach and timeliness of genomic research projects, and to support Commonwealth, State and Territory health departments in the implementation of genomics research outcomes by refining and communicating evidence to inform policy development.

Australian Genomics engages with current and emerging government policy and priorities to identify gaps and opportunities, to support policy and action for integrating genomic technologies into the health system. By interfacing with consumers, government, industry and global genomics initiatives, Australian Genomics drives change and growth in the sector.

Australian Genomics has investigated clinical implementation of genomic testing into a range of rare diseases and cancer diseases. This has included a somatic project that investigated clinically actionable variants in a range of cancer types. Another project (ICCon) investigated the genetic causes of rare hereditary cancers.

5. What do you see as the benefit(s) of the proposed medical service, in particular for the person involved and/or their family and carers?

Fluoropyrimidines (FP) are a standard chemotherapy medication used to treat patients with a variety of solid tumours including breast, colorectal, head and neck, and gastric cancer. The most common treatment is called Fluorouracil (5-FU). A high proportion of 5-FU is metabolised by the liver, into inactive metabolites by the dihydropyrimidine dehydrogenase (DPD) enzyme, encoded by the *DPYD* gene. Variants of this gene (up to 30 are reported) can affect enzyme function. Four variants have been well characterized in Caucasian populations (rs3918290, rs55886062, rs67376798 and rs75017182) and result in impaired enzyme function, with individuals who carry that variant being at risk of FP toxicity. Genotyping provides the overarching benefit of allowing the right treatment dose or alternative treatment (removing the risk of treatment side effects), at the right time to the patient without delaying treatment options.

The proposed medical service is concerned with the genotyping (via PCR on DNA extracted from peripheral blood cells) of at least these four *DPYD* variants that result in decreased function of DPD enzyme activity. Genotyping would identify patients who are 'intermediate' (partial DPD deficiency) and 'poor' (complete DPD deficiency) metabolisers, with their chemotherapy treatment for fluoropyrimidine (FP) being adjusted accordingly as described below. In Caucasians, 5-7% of the population will have partial DPD deficiency, and between 0.01 and 0.2% will have complete DPD deficiency.

Without the proposed medical service, a subset of patients would not be identified as being at risk of toxic events after FP treatment. Symptoms of a toxic event can include nausea, stomatitis, mucositis and neutropenia. For the 'intermediate' metabolisers a reduced dose of FP treatment will reduce the risk of adverse effects and keep the plasma levels of 5-FU and its metabolites at a therapeutic dose (see also dose recommendation for specific DPYD variants outlined by Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (Amstutz *et al.*, 2018)). In the 'poor responder' subset of patients, alternative treatment options can be considered, such as uridine triacetate. Due to the expected short turnaround time of the genotyping (estimated at 5-6 days in a NATA accredited diagnostic laboratory), there should be a timely change in clinical management if needed. We note this turnaround time is likely to be long in regional, remote and very remote parts of Australia as diagnostic laboratories are centre in metro areas.

The proposed medical service will greatly contribute to patient comfort levels and wellbeing in this subset of patients. It has been noted in the application and associated literature that genotyping of individuals is a more standardised approach compared to technicalities involved with phenotypic testing. As outlined in Henricks *et al*. (2015), the highest standard of phenotyping would be DPD enzyme activity measurement in extracted peripheral blood cells. However, this is very technical and not easily implemented as a routine test.

Although further study would be required, the successful implementation of the proposed medical service to optimise FP dosage in patients with impaired tolerance of FP regimens would have follow-on implications for improved cancer-related outcomes including disease-free survival, progression-free survival and overall survival of cancer patients. This would also positively impact quality of life and mental health measures for these patients and their families and carers by removing uncertainty about adverse effects of chemotherapy treatment at an already challenging time.

Approval of this medical service would be consistent with England and other countries (including Italy (Bignucolo *et al*., 2023) and Greece (Ragia *et al*., 2023)) which have adopted the 2020 European Medicines Agency recommendations of *DPYD* genotype testing. NHS England has testing available through their seven national NHS genomic laboratory hubs, funded by government. Canadian provinces including Ontario (Ontario, 2021) and British Columbia (Wu *et al*., 2023) have also adopted genotyping as standard of care for pre-chemotherapy evaluation of DPD enzyme activity. In the United States, as of June 2023, the FDA does not have any statements recommending pre-screening of DPYD genotyping prior to treatment, despite a 2020 Citizens petition by a patient advocate (Hertz *et al*., 2023). The petition asked for updated FP drug labels to recommend *DPYD* testing.

As stated in the application, it is estimated that 10,000 Australians receive FP treatment each year. Overall, we believe implementation of this test will improve treatment safety and outcomes for this patient group.

6. What do you see as the disadvantage(s) of the proposed medical service, in particular for the person involved and/or their family and carers?

We note that the proposed medical service is for four genotypes to be assessed, which are best characterised in Caucasian populations. There have been over 30 genetic polymorphisms described for *DPYD* (Henricks et al., 2015). Additionally, the absence of the four *DPYD* variants characterized in the proposed service does not eliminate the risk of toxicity (NHS England). It has been reported that a combined test for the four variants predicts 20-30% of early-onset life threatening 5-FU toxicities (Amstutz *et al*., 2018). Other genetic, physiological and environmental factors play a role in patient response.

As reported in the application there is no data on *DPYD* genotype frequency in Aboriginal and Torres Strait Islander Peoples, nor any direct genotype-phenotype correlations or investigation into effects on toxicity. Summary genotype data for *DPYD* variants is similarly not available for other Australian populations from different backgrounds. For example, not all of the four variants tested here are present in non-Caucasian populations, indicating a role for other genotypes in FP-induced toxicity for these groups. We investigate this issue in greater details in Q15. We see the proposed medical service as an important step in mitigating FP-induced toxicity but encourage further research to allow equitable and best practice treatment delivery for all Australians.

One further risk to the proposed medical service is a lack of uptake due to lack of awareness or suitable education programs. We also address this issue in Q15.

7. What other benefits can you see from having this intervention publically funded?

Reimbursement may act as a catalyst for adoption of *DPYD* testing as best practice. A study in Italy identified that reimbursement of the test helped changed the practice for FP prescription (Bignucolo *et al*., 2023). A dramatic increase in pre-treatment *DPYD* genotyping was noted after nationwide test reimbursement in Italy. In Australia, eviQ recommends that clinicians discuss DPYD gene testing for patients planning to start FP treatment, encouraging decision-making to occur between clinician and patient. Several barriers to routine FP testing listed by eviQ would be alleviated by the proposed medical intervention. These include the lack of available testing and current lack of reimbursement for genotype testing (thus reducing patient payment)

There is also evidence of a reduced financial cost to the healthcare system. Those of an intermediate phenotype for *DPYD* will benefit from a reduced dose, resulting in a less likely chance of adverse effects and possible hospital admission. The testing will also make the likelihood of extreme adverse toxic events in poor responders. A study by Brooks *et al.,* (2022) found *DPYD* to be a cost-effective strategy in colon cancer, to prevent the infrequent but severe and possibly fatal toxicities of FP chemotherapy. Although the study found a small incremental survival benefit for *DPYD* testing of 0.0038 QALY, this masks the considerable benefit for individuals with detectable pathogenic variants in *DPYD*, with 1 in 764 patients avoiding death, and 1 in 48 avoiding grade 3 or grade 4 toxicities (Brooks *et al*., 2022). Ontario Health also conducted literature reviews of health economic studies, finding two studies from the Netherlands which indicated the intervention of genotype testing to be slightly less costly compared to no testing, largely attributed to an avoidance of severe FP-related toxicities (Ontario Health, 2021). Ontario Health estimated in their health technology assessment that *DPYD* treatment in Ontario Canada (population 15 million) would save $714,963 over the next 5 years assuming a slow uptake and accurate estimates of service delivery and implementation costs.

8. What other services do you believe need to be delivered before or after this intervention, e.g. Dietician, Pathology etc?

This service will mainly be delivered by medical oncologists and oncology pharmacists.

As the testing and treatment will be predominantly coordinate by medical oncology services, our understanding is that there will be limited direct involvement of genetic services. As noted in the application there is no benefit to cascade testing of family members.

In relation to the use of other healthcare resources in conjunction with proposed health technology delivery, there may be some additional healthcare professional resources needed around test result interpretation, delivery, and report storage. However, these resources would be a minor cost compared to the health sector cost at risk if there is no intervention and/or an at-risk patient was treated with FP.

PART 3 – INDICATION(S) FOR THE PROPOSED MEDICAL SERVICE AND CLINICAL CLAIM

9. Do you agree or disagree with the proposed population(s) for the proposed medical service?

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

Given the estimated population of 10 000 Australians annually that would receive this treatment and estimate of 5-8% for prevalence of *DPYD* gene variant related DPD enzyme-deficiency in Caucasian populations, the proposed medical service would affect a significant number of patients.

As outlined previously and in Q15, we encourage further work on the genotype frequencies, genotype-phenotype correlations and the possibility of novel *DPYD* variants associated with FP toxicity in non-Caucasian populations, to allow the best standard of care regarding FP chemotherapy for all Australians.

10. Have all the associated interventions been adequately captured in the application summary?

☒ Yes
☐ No

Please explain:

The technology used for this test of PCR on DNA extracted from peripheral blood cells has been described. Turnaround time is estimated at 5-6 days in a NATA accredited diagnostic laboratory in line with NPAAC guidelines.

11. Do you agree or disagree that the comparator(s) to the proposed medical service?

☒ Strongly Agree
☐ Agree
☐ Disagree
☐ Strongly Disagree

Please explain:

We agree with the comparator of no *DPYD* genotyping.

12. Do you agree or disagree with the clinical claim made for the proposed medical service?

☐ Strongly Agree
☒ Agree
☐ Disagree
☐ Strongly Disagree

Specify why or why not:

The proposed medical service will provide funding for a diagnostic test that will improve the standard of care for patients with a range of solid tumours, undergoing chemotherapy in both curative and palliative situations. There is a strong evidence base in the literature for the *DPYD* genotype – phenotype association in Caucasian populations and the clinical impact on management of FP related toxicities using dose reduction (Henricks *et al.*, 2018, see also clinical trials section of NHS England policy statement on *DPYD* pharmacogenomic testing). We encourage further work on assessing associations in other unrepresented populations.

PART 4 – COST INFORMATION FOR THE PROPOSED MEDICAL SERVICE

13. **Do you agree with the proposed service descriptor?**

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

It is also noted that the item descriptor refers to 'at least four *DPYD* variants'. This will allow for testing of additional *DPYD* variants if further work identifies other variants as being significant to FP-toxicity in Caucasian and other populations.

14. **Do you agree with the proposed service fee?**

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

It is noted that no out of pocket expenses are expected. The price point is consistent with a targeted PCR and similar to the $95-160 range described by eviQ for current testing in Australia through commercial providers.

PART 5 – ADDITIONAL COMMENTS

15. Do you have any additional comments on the proposed intervention and/or medical condition (disease) relating to the proposed medical service?

We believe there is a clear and substantial evidence base for the proposed intervention to be adopted. As mentioned in previous parts of this document, this evidence includes clinical validity, clinical utility, strong evidence for treatment effectiveness of a reduced fluoropyrimidine dose and reductions in cost to the health service. The intervention will limit the likelihood of exposure to FP related toxicities, have a positive effect on wellbeing of those of intermediate phenotypes and bring Australia in line with standards of care in similar health systems globally. Taken together, Australian Genomics supports the proposed medical service.

We do note a few points for consideration:

Expanding data on *DPYD* variants and genotype – phenotype associations for *DPYD* including in Aboriginal and Torres Strait Islander Peoples and other non-Caucasian Populations:

There is a lack of genome-wide variant level data for several non-Caucasian populations generally, which has implications for variant calling of pathogenic variants from sequence data in a range of rare diseases. This greatly limits access to personalized medicine. Specific to the current application, there is no data describing *DPYD* frequency or variants in Aboriginal and Torres Strait Islander Australians (White *et al*., 2020).

DPYD genotype frequencies vary in different populations – for example from *1000 Genome project* data the expected frequency of carrying at least one *DPYD* variant (of the four outlined in the application) is 4.8% in Caucasians; 0.16% in African origin patients and <0.001% in South Asian Peoples (Innocenti *et al*., 2020). 23andMe data on two *DPYD* variants estimates that 2% of the USA population may have impaired DPD activity (Innocenti *et al*., 2020). Studies have found an absence of certain *DPYD* variants in non-Caucasian population samples – for example as summarised in White *et al*., (2020), the poor metaboliser associated variant rs3918290 was absent in studies of patients from East Africa, China, and Japan.

In the context of *DPYD* genotyping there are issues around 1) lack of accurate genotype frequency data from individuals of different backgrounds, 2) lack of detailed evidence base for non-Caucasian populations regarding the genotype/phenotype correlation between the four genotypes outlined here and DPD metabolism, 3) different clinical impacts of variants and measured DPD activity in non-Caucasian populations. For example, the poor DPD metaboliser SNP rs3918290 has a 5.42 increased toxicity in Caucasian carriers, but no increase in toxicity compared to wildtype in Iranian carriers (White *et al*., 2021). Similarly, there are novel variants outside of the four SNPs outlined in the present intervention, which have clinical impact in non-Caucasian populations. For example, the rs115232898 variant (not in the group of four variants outlined in the current submission) in African-American patients causes toxicity after FP chemotherapy (Saif *et al*., 2013).

Projects such as *ourDNA (https://populationgenomics.org.au/projects-ourdna/)* should contribute to a more complete genetic variant database for Aboriginal and Torres Strait Islander Peoples. This MRFF funded program aims to increase genomic representation of Australian communities from a variety of backgrounds including African, Asian, Middle Eastern, Oceanic and Aboriginal and Torres Strait Islander communities. Australian Genomics encourages further work in this area to achieve equitable and best practice standard of care access for *DPYD* genotyping related to FP-induced toxicity.

Potential barriers to successful implementation:

Morris *et al*., (2023) indicates that although evidence-based guidelines through a pharmacogenetic lens have been detailed such as by the Dutch Pharmacogenetics Working Group (DPWG) (Lunenburg *et al*., 2020), there is a lack of testing recommendations by oncology professional organizations. In Australia, eviQ has existing guidelines for clinicians regarding current dose recommendations for the four genotypes outlined in the current application.

The importance of educational material for both patients and medical oncologists has also been highlighted (Morris *et al*., 2023, Innocenti *et al*., 2020). This would aid in increasing awareness of the availability of the test to oncology services and the standardisation of a national approach. Information should be provided for patients explaining the need to perform the test and possible outcomes, to allow them to make informed decisions in consultation with their healthcare professional.

It is noted that the application outlines that the Database of Adverse Event Notifications (TGA) is voluntary and does not require patient ethnicity of be reported. We encourage further education and advice around reporting such adverse events. We also extend this to the need for better recording of ethnicity in clinical trial databases generally.

16. Do you have any comments on this feedback survey? Please provide comments or suggestions on how this process could be improved.

This application was part of an RCPA project that was supported by Australian Genomics. Australian Genomics had no direct involvement in the development of this application.

We anticipate the role of pharmacogenomics in Australian healthcare to continue to grow. We note the need for future application formats to similarly include sections on clinical validity, health outcomes, change in clinical management, patient risk and international exemplars. It is likely with other proposed interventions in this area that the point of treatment will be the most important clinical involvement, with the need to upskill the workforce at this point of care.

References

Amstutz, U., Henricks, L. M., Offer, S. M., Barbarino, J., Schellens, J. H. M., Swen, J. J., Klein, T. E., McLeod, H. L., Caudle, K. E., Diasio, R. B., & Schwab, M. (2018). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther, 103(2), 210-216. https://doi.org/10.1002/cpt.911

Bignucolo, A., De Mattia, E., Roncato, R., Peruzzi, E., Scarabel, L., D'Andrea, M., Sartor, F., Toffoli, G., & Cecchin, E. (2023). Ten-year experience with pharmacogenetic testing for DPYD in a national cancer center in Italy: Lessons learned on the path to implementation. Front Pharmacol, 14, 1199462. https://doi.org/10.3389/fphar.2023.1199462

Brooks, G. A., Tapp, S., Daly, A. T., Busam, J. A., & Tosteson, A. N. A. (2022). Cost-effectiveness of DPYD Genotyping Prior to Fluoropyrimidine-based Adjuvant Chemotherapy for Colon Cancer. Clin Colorectal Cancer, 21(3), e189-e195. https://doi.org/10.1016/j.clcc.2022.05.001

EviQ DPD clinical implications. https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-treatment/1744-dihydropyrimidine-dehydrogenase-dpd-enzyme#clinical-implications

Henricks, L. M., Lunenburg, C. A., Meulendijks, D., Gelderblom, H., Cats, A., Swen, J. J., Schellens, J. H., & Guchelaar, H. J. (2015). Translating DPYD genotype into DPD phenotype: using the DPYD gene activity score. Pharmacogenomics, 16(11), 1277-1286. https://doi.org/10.2217/pgs.15.70

Hertz, D. L., Smith, D. M., Scott, S. A., Patel, J. N., & Hicks, J. K. (2023). Response to the FDA Decision Regarding DPYD Testing Prior to Fluoropyrimidine Chemotherapy. Clin Pharmacol Ther, 114(4), 768-779. https://doi.org/10.1002/cpt.2978

Innocenti, F., Mills, S. C., Sanoff, H., Ciccolini, J., Lenz, H. J., & Milano, G. (2020). All You Need to Know About DPYD Genetic Testing for Patients Treated With Fluorouracil and Capecitabine: A Practitioner-Friendly Guide. JCO Oncol Pract, 16(12), 793-798. https://doi.org/10.1200/OP.20.00553

Lunenburg, C., van der Wouden, C. H., Nijenhuis, M., Crommentuijn-van Rhenen, M. H., de Boer-Veger, N. J., Buunk, A. M., Houwink, E. J. F., Mulder, H., Rongen, G. A., van Schaik, R. H. N., van der Weide, J., Wilffert, B., Deneer, V. H. M., Swen, J. J., & Guchelaar, H. J. (2020). Dutch Pharmacogenetics

Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. Eur J Hum Genet, 28(4), 508-517. https://doi.org/10.1038/s41431-019-0540-0

Morris, S. A., Moore, D. C., Musselwhite, L. W., Lopes, K. E., Hamilton, A., Steuerwald, N., Hanson, S. L., Larck, C., Swift, K., Smith, M., Kadakia, K. C., Chai, S., Hwang, J. J., & Patel, J. N. (2023). Addressing barriers to increased adoption of DPYD genotyping at a large multisite cancer center. Am J Health Syst Pharm, 80(19), 1342-1349. https://doi.org/10.1093/ajhp/zxad117

NHS England DPYD policy statement. https://www.england.nhs.uk/wp-content/uploads/2020/11/1869-dpyd-policy-statement.pdf

Ontario, H. (2021). DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines: A Health Technology Assessment. Ont Health Technol Assess Ser, 21(14), 1-186. https://www.ncbi.nlm.nih.gov/pubmed/34484488

Ragia, G., Maslarinou, A., Atzemian, N., Biziota, E., Koukaki, T., Ioannou, C., Balgkouranidou, I., Kolios, G., Kakolyris, S., Xenidis, N., Amarantidis, K., & Manolopoulos, V. G. (2023). Implementing pharmacogenetic testing in fluoropyrimidine-treated cancer patients: DPYD genotyping to guide chemotherapy dosing in Greece. Front Pharmacol, 14, 1248898. https://doi.org/10.3389/fphar.2023.1248898

Saif, M. W. (2013). Dihydropyrimidine dehydrogenase gene (DPYD) polymorphism among Caucasian and non-Caucasian patients with 5-FU- and capecitabine-related toxicity using full sequencing of DPYD. Cancer Genomics Proteomics, 10(2), 89-92. https://www.ncbi.nlm.nih.gov/pubmed/23603345

White, C., Scott, R. J., Paul, C., Ziolkowski, A., Mossman, D., & Ackland, S. (2021). Ethnic Diversity of DPD Activity and the DPYD Gene: Review of the Literature. Pharmgenomics Pers Med, 14, 1603-1617. https://doi.org/10.2147/PGPM.S337147

Wu, A., Anderson, H., Hughesman, C., Young, S., Lohrisch, C., Ross, C. J. D., & Carleton, B. C. (2023). Implementation of pharmacogenetic testing in oncology: DPYD-guided dosing to prevent fluoropyrimidine toxicity in British Columbia. Front Pharmacol, 14, 1257745. https://doi.org/10.3389/fphar.2023.1257745