# RESEARCH PROTOCOL

**Pre-treatment dihydropyrimidine dehydrogenase (DPYD) genotyping to individualise fluoropyrimidine-based chemotherapy: An evaluation of clinical implementation**

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**Statement of Compliance**

This document is a protocol for a research project. This study will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC *National Statement on Ethical Conduct in Human Research (2007) – Updated 2018*, and the NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2018)*. If the project is a clinical trial, it will comply with the *Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95)*.

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# Study Synopsis

*Please provide a brief summary of the information provided in the Protocol.*

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| **Title:** | **Pre-treatment dihydropyrimidine dehydrogenase (DPYD) genotyping to individualise fluoropyrimidine-based chemotherapy: An evaluation of clinical implementation** |
| **Short Title:** | Pre-treatment dihydropyrimidine dehydrogenase (DPYD) genotyping to individualise fluoropyrimidine-based chemotherapy dosing |
| **Study Sites:** | Royal Brisbane and Women's Hospital<br>North Lakes Health Precinct<br>The Prince Charles Hospital |
| **Study Objectives:** | **Objective 1**. Perform pre-treatment DPYD genotyping for all new patients commencing fluoropyrimidine-based chemotherapy between 1 July 2021 and 30 June 2022.<br>**Objective 2.** In those patients with pathogenic DPYD variants, reduce their fluoropyrimidine dose as per recommended international guidelines<br>**Objective 3**. Compare rates of treatment toxicity and hospital admissions related to fluoropyrimidine toxicity to historical controls<br>**Objective 4.** Establish the DPYD genotyping testing process at Pathology Queensland and identify/remedy any implementation issues |
| **Study Design:** | Prospective, multi-centre, non randomised implementation and feasibility study<br>Retrospective cohort of all patients who received fluoropyrimidines at RBWH between 2018 and 2019 |
| **Study Outcome Measures:** | Primary endpoints:<br>Incidence of severe treatment related toxicity (CTC grade 3 or higher) within 60 days of a patient beginning fluoropyrimidine treatment.<br>Secondary endpoints:<br>Unplanned hospital admissions related to treatment within 60 days of a patient beginning fluoropyrimidine treatment |

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| | Prevalence of the four DPYD variant allele carriers in the patient population<br>Rates of fluoropyrimidine dose intensity/delays<br>Documented practical clinical implementation issues including testing timeframes |
| **Study Population:** | Adult cancer patients which treatment with a fluoropyrimidine is deemed clinically appropriate, who have not previously received fluoropyrimidine treatment |
| **Number of participants:** | Up to 300 |
| **Translation to Clinical Practice:** | The primary purposes of the study are to provide pre-treatment DPYD testing for patients for the first time in a Queensland Public Hospital and identify any clinical implementation issues. Whilst data relating to participants will be collected and assessed with the aim of analysis and publication, the evidence supporting pre-treatment DPYD and dose modification is established. |
| **Key Ethical and Safety Considerations:** | Ensuring that results are available in a clinically appropriate timeframe to minimize any potential delays in treatment<br>Ensuring that appropriate dose adjustments occur based on the result of *DPYD* testing<br>Data collection and security<br>Adverse event reporting |

# Glossary of Abbreviations, Terms, and Acronyms

| Abbreviation, Term, Acronym | Definition (using lay language) |
|---|---|
| **DPYD** | Dihydropyrimidine dehydrogenase gene |
| **BSA** | Body surface area |
| **5-FU** | 5-Fluorouracil |
| **SNP** | Single Nucleotide Polymorphism |

## Background

In 2019, approximately 300 patients were commenced on fluoropyrimidine-based chemotherapy at the Royal Brisbane and Women's Hospital. Fluoropyrimidines are a class of anti-cancer drugs known as anti-metabolites. Fluoropyrimidines interfere with the synthesis of pyrimidine containing nucleotides and therefore DNA synthesis and repair.

The fluoropyrimidines, 5-Fluorouracil and the oral pro-drug Capecitabine are used worldwide with a proven benefit in treatment of a wide range of solid organ malignancies (Upper Gastrointestinal, Colorectal, Breast, Head and Neck, Bladder).

Most cytotoxic medications such as fluoropyrimidines are dosed according to Body Surface Area (BSA). BSA is estimated based on a simple formula calculated on a patient's height and weight. The recommended BSA based dose for a cytotoxic regimen is usually the highest effective dose with acceptable levels of toxicity. In general, patients are commenced on a dose based on their calculated BSA and then adjustments to this dose are usually made due to treatment toxicity.

Unfortunately, fluoropyrimidines have significant inter-individual variability in drug clearance and a relatively narrow therapeutic window (Longley, Harkin, & Johnston, 2003). Consequently, side effects from treatment are common but the severity of toxicity is usually unpredictable when treatment is based on BSA alone. Gastrointestinal and haematological toxicity including diarrhoea, hand-foot syndrome, nausea/vomiting, mucositis and myelosuppression is reported in up to 40% of patients (Chen, Wang, & Xu, 2019; Mikhail, Sun, & Marshall, 2010). Severe fluoropyrimidine-related toxicity can lead to treatment-related death in up to 1% of patients (Feng et al., 2020; Hoff et al., 2001)

Over the past decade, increasing research has focused on pharmacogenomics - the impact of individual genetic differences on how drugs interact with a patient's body. Genetic variations can result in increased susceptibility to severe adverse reactions when given a certain drug. In relation to fluoropyrimidines, arounds 80% of the administered dose is metabolised by a rate-limiting enzyme dihydropyrimidine dehydrogenase (DPD) (Longley et al., 2003). If DPD activity is reduced, excess 5-FU accumulates resulting in increased toxicity.

A major cause of DPD deficiency is the presence of certain variants of the encoding gene *DPYD*.

The encoding gene *DPYD* is located on chromosome 1p22 with 4,399 nucleotides in 23 coding exons (Wei et al., 1998). Whilst many *DPYD* single nucleotide polymorphisms (SNPs) variants have been reported, only four SNPs (listed in table 1 below) have been identified to date as clinically relevant due to their population frequency and statistically significant association with decreased DPD enzyme function and increased risk of toxicity (Henricks et al., 2015). Heterozygous SNP carriers in these four variants have been reported in up to 8% of the population (Henricks et al., 2018). Functional SNPs in these alleles can lead to reduced DPD activity in heterozygous individuals, or complete loss of DPD activity in some homozygous genotypes.

*Table 1. Most clinically relevant DPYD single nucleotide polymorphisms*

| ***DPYD* single nucleotide polymorphism** | **Reduced DPD enzyme activity (heterozygotes)** |
|---|---|
| **c.1905+1G>A** (rs3918290 -also known as IVS14+1G>A or *DPYD**2A) | 50% |
| **c.1679T>G** (rs55886062, *DPYD**13, I560S), | 50% |
| **c.2846A>T** (rs67376798, D949V) | 35% |
| **c.1236G>A** (rs56038477, E412E, in haplotype B3). | 25% |

Recent published international studies have demonstrated that up-front genotype directed dosing of fluoropyrimidine dose, based on prospective testing for the above *DPYD* SNPs resulted in significant reduction of severe treatment related toxicity (Deenen et al., 2016; Henricks et al., 2018). In one study, researchers prospectively tested 2,038 patients for the *DPYD**2A variant. Those patients found to have the variant received a 50% dose reduction of their fluoropyrimidine based on known toxicity data. The risk of grade >3 toxicity for patients with the variant was reduced from 73% in historical controls to 28% (Deenen et al., 2016) .

Pharmacokinetic serum testing revealed that those patients with the *DPYD**2A variant who received a 50% dose reduction had comparable drug plasma exposure to the wild-type population who received 100% recommended dose. This study also found that testing was feasible and cost effective when compared to reductions in costs related to toxicity and hospital admissions.

A subsequent study, expanded testing to the four *DYPD* variants listed above and prospectively tested 1103 patients receiving fluoropyrimidines (Henricks et al., 2018). Based on known toxicity data, any patient identified with any of the four genotypes would receive an upfront specified fluoropyrimidine dose reduction as per the international pharmacogenetic guidelines at the time of the study which are listed in table 2 below.

*Table 2: Dose reductions in Henricks et al. (2018) study based on DPYD SNP.*

| **DPYD Variant** | **Heterozygote** | **Homozygote** |
|---|---|---|
| c.1905+1G>A (*2A) | 50% dose reduction | Give alternative treatment |
| c.1679T>G (*13) | 50% dose reduction | Give alternative treatment |
| c.1236G>A | 25% dose reduction | Give alternative treatment |
| c.2846A>T | 25% dose reduction | Give alternative treatment |

Given that some patients carrying decreased or no function variants can tolerate normal doses of 5-fluorouracil (Amstutz et al., 2018), to maintain effectiveness, doses could be increased after 2 cycles in patients experiencing no or clinically tolerable toxicity in the first two chemotherapy cycles or with subtherapeutic plasma concentrations. Similarly, doses were decreased in patients who do not tolerate the starting dose.

The primary endpoint of the study was the frequency of severe fluoropyrimidine-related toxicity. Secondary endpoints included a comparison of the pharmacokinetics of capecitabine and fluorouracil in *DPYD* variant allele carriers and measurement of DPD enzyme activity.(Amstutz et al., 2018)

In this study, 8% (n=85) of the study population were identified as heterozygous SNP carriers in these four *DPYD* variants. Clinical implementation of the study protocol was successful with dosing adjustment recommendations followed by treating clinicians in all but four patients. Unfortunately, one patient (c.2846A>t carrier) was given full dose by mistake, resulting in fatal fluoropyrimidine-related toxicity.

At a median follow up of 71 days, 33 (39%) of the *DPYD* variant allele carriers had severe (grade >3) fluoropyrimidine-related toxicity compared to 231 (23%) of wild-type patients. Hospital admissions related to fluoropyrimidine-related toxicity occurred in 16 (19%) of the *DPYD* variant allele carriers and 140 (14%) of wild-type patients.

The authors calculated the relative risk (RR) of severe toxicity for each of *DPYD* variant alleles. The RR of severe toxicity from historical controls was provided by a previous meta-analysis, where carriers were not identified before starting treatment and were treated with full dose fluoropyrimidine (Meulendijks et al., 2015).

For those patients with a c.1905+1G>A (**2A*) variant, a 50% dose reduction significantly reduced the RR of severe toxicity from 2.87 in historical controls (95% CI 2.14-3.86) to 1.31 (0.63-2.73). For the c.2846A>T variant, a 25% dose reduction significantly reduced the RR of severe toxicity from 3.11 (2.25-4.28) to 2.00 (1.19 -3.34). For the 1236G>A variant, a 25% dose reduction did not reduce the risk of severe toxicity (RR 1.72 v 1.69). The RR of the c.1679T>G (*13) could not be calculated as only one patient with this variant was identified in this study. In the historical cohort the RR was 4.30 (2.10-8.80).

Pharmacokinetic analysis of those with *DPYD* variant alleles treated with a reduced dose was compared to historical controls. Mean exposure to fluoropyrimidines in the *DPYD* variant group treated with a reduced dose was similar to historical controls treated with full dose, suggesting that mean drug exposure was adequate with the dose reduction. Mean DPD enzyme activity was significantly lower in the *DPYD* variants then in the wild-type group consistent with prior research.

Due to the ongoing RR of severe toxicity in patients with c.1236G>A, and c2846A>T variants in this study despite a 25% dose reduction, the International Clinical Pharmacogenetics Implementation Consortium (Amstutz et al., 2018) has recommended that patients with these SNPs receive an increased dose reduction of 50%. In April 2020 based on these studies, the European Medicines Agency has recommended routine pre-treatment *DPYD* genotyping prior to the initiation of fluoropyrimidine treatment (EuropeanMedicinesAgency, 2020).

## Study Aim

In Queensland, *DPYD* testing is available, but not currently funded through Pathology Queensland or the Medicare Benefits Schedule. This study aims to introduce regular *DPYD* genotype testing for the first time in a Queensland Public Hospital and establish the utility of this testing.

## Study Objectives

1. Perform pre-treatment *DPYD* genotyping for all new patients commencing fluoropyrimidine-based chemotherapy between 1 July 2021 and 30 June 2022.
2. In those patients identified with pathogenic *DPYD* variants, reduce fluoropyrimidine dose as per recommended international guidelines
3. Compare rates of treatment toxicity and unplanned hospital admissions related to fluoropyrimidine toxicity between the *DPYD* variant carriers and wild types and to a retrospective historical control group.
4. Establish the DPYD genotyping testing process at Pathology Queensland and identify/remedy any implementation issues
5. Estimate the cost savings from any reductions in treatment toxicity and hospital admissions identified.

## Study design

- This is a prospective, multi-centre, non randomised study investigating the clinical implementation of *DPYD* genotyping in multiple sites across Metro North Health District.
- Up to 300 patients will be recruited between July 1, 2021 and June 30, 2022 (funding for up to 300 patients through SEED grant)

- For comparison, a retrospective review will also be undertaken for all patients who received fluoropyrimidines at RBWH for the first time between 1 January 2018 and 31 December 2019.

## Study Population

1. **Inclusion criteria**
    a. Pathologically confirmed malignancy for which treatment with a fluoropyrimidine at full dose (with or without other chemotherapy agents or radiation) is deemed clinically appropriate
    b. Adult patient (> 18 years)
    c. Receiving their first dose of fluoropyrimidine (either as a single agent or in combination) between 1 July, 2021 and 30 June, 2022.
    d. Willing to provide blood sample for pharmacogenetic testing
2. **Exclusion criteria**
    **a.** Inability to provide informed consent
    **b.** Prior use of fluoropyrimidines
    **c.** Women who are pregnant or breast-feeding
    **d.** Patients with a previously known homozygous polymorphic genotype or compound heterozygous genotype for *DPYD*.

## Recruitment/ Selection

- Eligible patients will be identified prior to receiving fluoropyrimidine chemotherapy from outpatient clinics at the Royal Brisbane and Women's Hospital, North Lakes Health Precinct and The Prince Charles Hospital
- Treating physicians will approach the patient for enrolment in person with the nature and purpose of the study explained to each potential patient. Patients will be given a copy of the informed consent form (PICF) and given opportunity to ask questions.
- Involvement will be voluntary, without coercion and patients who decline will receive standard of care.

## Consent

- Individual informed consent will be obtained for all participants.
- Consent will be documented by the patient's dated signature on the patient information and informed consent form (appendix 1). Consent will be obtained prior to blood collection.
- A qualified interpreter will be used for any patient whose primary language is not English.

## Risk Mitigation and safety issues

1. **Ensuring that results are available in a clinically appropriate timeframe to minimize any potential delays in treatment**
    a. Standardised pathology reports will be available to clinicians through AUSLAB/AUSCARE with information regarding the interpretation of the *DPYD* genotype and recommended action
    b. A weekly report will be created and sent to the study investigators and pharmacy with a list of patients tested during the prior 7 days to identify any patients requiring dose adjustments as soon as possible.
2. **Ensuring that appropriate dose adjustments occur based on the result of *DPYD* testing**
    a. Clinician education regarding the background for testing, interpretation of results and appropriate dose modification will occur prior to commencement of testing on 1 July 2021
    b. As a further safety measure, pharmacy will incorporate a check of the *DPYD* genotyping results prior to release of fluoropyrimidine treatment
3. **Adverse events and withdrawal from study**
    a. All adverse events related to the testing itself, will be recorded, and Serious Adverse Events will be reported to HREC.
    b. Adverse events related to the fluoropyrimidine treatment itself will not be reported to HREC as this is standard of care.
    c. The principles of The NHMRC's National Statement on Ethical Conduct for Human Research will be adhered to throughout the conduct of the study.
    d. A patient may withdraw from the study by choice at any time.

**e.** Any patients who withdraw from the study after enrolment will be included in the cumulative final data analysis unless specifically requested

4. **Data collection/security**
    a. Anonymity and confidentiality of all information collected during the study will be protected.
    b. Data collection and storage procedures are listed in the relevant section below
5. **Retrospective audit**
    a. For comparison purposes, a retrospective audit will also be completed reviewing the rates of severe fluoropyrimidine toxicity and hospital admissions between 2018-2019.
    b. All data from this project will also be inputted into the REDCap system.

## Outcome Measures

1. **Primary data endpoint**
    a. The primary data endpoint is the incidence of severe treatment related toxicity (CTC grade 3 or higher) within 60 days of a patient beginning fluoropyrimidine treatment.
2. **Secondary data endpoints**
    a. Unplanned hospital admissions related to treatment within 60 days of a patient beginning fluoropyrimidine treatment
    b. Prevalence of the four *DPYD* variant allele carriers in the patient population
    c. Rates of fluoropyrimidine dose intensity/delays
    d. Documented practical clinical implementation issues including testing timeframes

## Study procedure

1. **Screening process/baseline assessments**
    a. Signed, written informed consent
    b. Inclusion and exclusion criteria
    c. Baseline demographics and malignancy history (see attached appendix 2)
    d. Enrolled patients will be required to provide a 4ml sample of blood in an EDTA-tube for *DPYD* variant testing (in addition to standard pre-chemotherapy bloods such as full blood count and clinical chemistry)
    e. They may have blood collected at RBWH, TPCH, Redcliffe or Caboolture Hospital Pathology Collection Centres.
    f. The sample will be sent to the Pathology Queensland at Royal Brisbane and Women's Hospital

2. **DPYD testing process**
    a. Pathology Queensland will perform Sanger DNA sequencing on the blood sample provided to identify the four *DPYD* variant genotypes most associated with increased toxicity - single nucleotide polymorphisms c.1905+1G>A (*2A, rs3918290), c.1679T>G (*13, rs55886062), c.2846A>T (rs67376798), and c.1236G>A (rs56038477, E412E, in haplotype B3).
    b. Pathology Queensland will upload the results of testing to the relevant patients URN on AUSLAB/AUSCARE for viewing by the treating physician.
    c. Results should be available ideally with 7 calendar days and no later than 14 calendar days from specimen collection, to minimise delays of starting treatment and to allow dose modifications if necessary.
    d. *DPYD* testing will be performed once only

3. **Results of DPYD**
    **a.** Those patients identified with a *DPYD* variant will receive a 50% dose reduction as specified below based on the current Clinical Pharmacogenetics Implementation Consortium Guidelines mentioned in the background section.

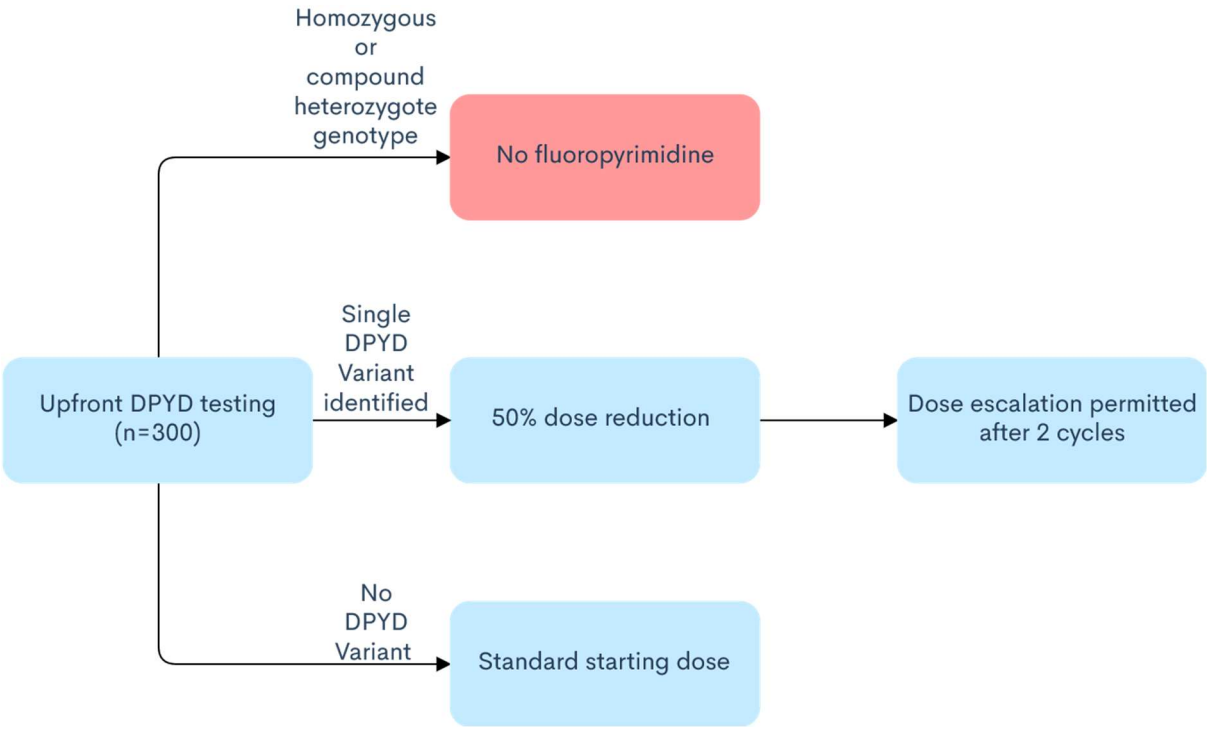
**b.** For safety reasons, any patients identified as a homozygous genotype or compound heterozygote should not receive fluoropyrimidines and alternative treatment should be sought.

**c.** Dose escalation is permitted after the first two cycles to achieve maximal safe exposure, provided the treatment was well tolerated, and at the discretion of the treating physician.

**d.** Patients with no identified *DPYD* variant will receive standard care as per the treating physician.

e. In the event that the *DPYD* genotyping result is delayed greater than 14 calendar days due to technical reasons, clinicians may at their discretion proceed with treatment without the result of testing, if it is considered in the best interests of the patient.

| **DPYD Variant** | **Heterozygote** | **Homozygote** |
|---|---|---|
| c.1905+1G>A (*2A) | 50% dose reduction | Give alternative treatment |
| c.1679T>G (*13) | 50% dose reduction | Give alternative treatment |
| c.1236G>A | 50% dose reduction | Give alternative treatment |
| c.2846A>T | 50% dose reduction | Give alternative treatment |




## Data Collection and storage

1. **Storage of hard copies**
    a. The patient information and consent form (PICF) will be distributed to the patients in paper copy. The questionnaires and consent form will be collected and then manually entered into the Research Electronic Data Capture (REDCap) database.
    b. Once uploaded, all hard copies will be stored in a locked cabinet in a locked room.
    c. This data will only be able to be accessed by the Principal researcher or nominated proxy
    d. The data will be stored to meet NHMRC guidelines and thus will be stored for a minimum of 15 years post study closure
2. **Electronic data system**
    a. REDCap is a secure web-based software platform specifically design for the collection and management of research data.

b. REDCap is installed under a not-for-profit end-user license agreement between Vanderbilt University and Metro North Hospital and Health Service (Metro North).
    i. This may change during the course of the program from MNHHS to Queensland Health, however, will remain under the same data governance rules and requirements.
c. Currently the MNHHS instance is housed on a MNHHS server behind a Queensland Health firewall, but a project is underway to create a Queensland Health-wide instance housed in the demilitarised zone (DMZ), allowing access outside of MNHHS servers. The electronic data will only be able to be accessed by the Principal researcher or nominated proxy.

**3. Toxicity data**

a. The formal completion of comprehensive toxicity data (case report forms) related to treatment prior to each treatment cycle is not required as the toxicity from fluoropyrimidine treatment is well established.
b. Grade 3 – 5 toxicity data will be captured by identifying patients from CHARM (electronic prescribing system), patient admissions records and subsequent manual chart reviews
c. This data will be retrospectively entered into the REDCap database from 60 days after the patient first commences fluoropyrimidine treatment
d. Once toxicity data is entered, the patients record will be considered completed and will be de-identified for the purposes of data analysis
e. Toxicity data will be compared between those with the DYPD variant, those without and a retrospective audit.

## Data Analysis and Statistical Considerations

- Prevalence rates of DYPD variants will be summarized as frequency (percent)
- Fluoropyrimidine dose/intensity will be summarized as a mean (percentage) for each different population group.
- Patient and treatment characteristics will be compared between pre and post DYPD testing implementation groups, as well as between those with and without a variant in the post DYPD testing implementation group, using chi-square or Fisher's exact tests

for categorical characteristics and t-tests or Mann-Whitney U tests for continuous characteristics as appropriate.

- For the primary outcome of toxicity experienced within 60 days of beginning fluoropyrimidine and the secondary outcome of having a readmission within 60 days of beginning fluoropyrimidine, univariable binary logistic regression analyses will be performed to observe the effect on these outcomes of pre and post DYPD testing implementation, and potential covariates.
- Covariates with a p-value < 0.2 will be considered further in multivariable logistic regression analyses alongside pre and post DYPD testing implementation groups.
- Covariates will be removed via a variable selection process to obtain a final adjusted model. Cohort will be forced to remain in the model.
- Statistical significance will be indicated at $p < 0.05$. A similar process will be performed for the comparison between having a variant and no variant in the post DYPD testing implementation group.

## Translation to Changes in Clinical Practice

- The primary purposes of this study are to provide pre-treatment *DPYD* testing for patients for the first time in a Queensland Public Hospital and identify/remedy any clinical implementation issues.
- Whilst data relating to participants will be collected and assessed with the aim of analysis and publication, the evidence supporting pre-treatment *DPYD* and dose modification is established as per the background mentioned.
- The investigators of this study are working closely with Pathology Queensland to establish efficient workflows and testing processes to ensure sustainability and scalability of the clinical implementation of pre-treatment DPYD testing across Queensland.
- Education and engagement with key pharmacy, pathology and oncology representatives will be undertaken throughout the duration of the study to raise awareness and identify and mitigate implementation risks.

## Evaluation

- Evaluation of the effectiveness of the clinical implementation of this study will be facilitated by the Genomic Institute, Metro North Hospital and Health Service. This evaluation will focus on outcomes of the implementation itself rather than the outcomes of treatment, which has already been established in the trials noted in the "Background" section of this protocol.
- It is anticipated that the evaluation findings will be used to develop a business case for ongoing funding (including expansion funding), which will be presented to the Statewide Cancer Clinical Network for consideration.
- There is already well documented evidence that screening for DPD deficiency with DPYD genotyping is a cost-effective strategy for preventing infrequent but severe, sometimes fatal toxicities of fluoropyrimidine chemotherapy. Therefore, the scope of the evaluation of this study will include assessment of:
    - factors (and resourcing implications) to be considered if this testing is to be continued and expanded to other tertiary facilities, including aspects of the processes that could, potentially, be made more efficient (implementation evaluation). As part of this analysis, we will collect and a number of datapoints as discussed in the statistical section above. For ease of reference, each datapoint collected is included in the data dictionary in Appendix C. The primary outcomes from an implementation perspective will be testing turnaround time and total amount of patients tested during the financial year.
    - the extent to which the study has achieved the intended outcomes (outcome evaluation)
    - budget impact (cost of labour and non-labour resources to undertake testing versus cost of adverse events as a result of fluoropyrimidine toxicity) and long-term return on investment of pre-treatment DPYD genotyping (economic evaluation).

## Funding and Resources

- Funding of $88,488 has been provided through the Metro North SEED/LINK innovation project for testing of up to 300 patients between 1 July 2021 and 30 June 2022 only.
- The project will be led by the Medical Oncology clinical research fellow whose time spent on the project will be in kind support from the Medical Oncology department.

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