FULL PROTOCOL TITLE

GENESCREEN Program: *DPYD* and *UGT1A1* Genotyping for Fluoropyrimidine and Irinotecan dose personalisation to reduce severe toxicity

STUDY CHAIRS

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Please contact research@gicancer.org.au for information on this trial.

LINK TO STUDY

https://gicancer.org.au/clinical-trial/genescreen-5-fu/

TRIAL IDENTIFIER

ACTRN12622000963729

COORDINATING CENTRE

Hunter Medical Research Institute

FUNDING SOURCES

University of Newcastle School of Medicine Public Health 2021 Pilot Grant

PRESENTER

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FINANCIAL DISCLOSURE

None to disclose.

AIM/S

1. Determine the frequency of *DPYD* and *UGT1A1* genotypes in an Australian population;
2. Determine the feasibility, clinical efficacy and cost-effectiveness of *DPYD/UGT1A1* guided dosing to prevent fluoropyrimidine (FP)/irinotecan (IRI) toxicity;
3. Identify new variants in *DPYD/UGT1A1* in people with severe toxicity.

BACKGROUND

At least 4 *DPYD* and 3 *UGT1A1* variants are associated with severe, potentially fatal, toxicity in patients treated with standard doses of FP/IRI requiring hospitalisation and costly resource utilisation. Identification of these variants is now standard practice in Europe leading to adjusted chemotherapy dosing to avoid severe toxicity and its economic burden, without compromising anti-tumour effects. Australia has not yet implemented pharmacogenomics (PGx) guided dosing due to a lack of evidence on feasibility, clinical efficacy in an Australian context, and cost-effectiveness.

GENESCREEN aims to address these gaps, providing prospective clinical evidence on feasibility of implementing *DPYD/UGT1A1* testing routinely, its clinical efficacy/impact and cost-effectiveness. In addition to providing the evidence to support a Medical Services Advisory Committee (MSAC) submission for Medicare rebates for this testing, this program will facilitate updated clinical practice guidelines, and identify other variants in *DPYD/UGT1A1* to implement in a comprehensive program to increase sensitivity of PGx guided dosing.

STUDY DESIGN

Single arm, non-randomised prospective trial. Patients heterozygous for any of 4 *DPYD* variants will be advised to start with a FP dose of 50% of standard dose IRI; patients with specific *UGT1A1* genotypes will start with 70% of standard dose IRI. Subsequent dose adjustments will be up or down according to toxicity experienced in previous cycles, to achieve a tolerable G1 or 2 toxicity.

ELIGIBILITY CRITERIA

Any patient >18 years intended for treatment with FP and/or Irinotecan (single agent or combination) according to EviQ guidelines, and willing to provide a single pre-treatment blood sample, informed consent and comply with dosing strategy.

STUDY UPDATE

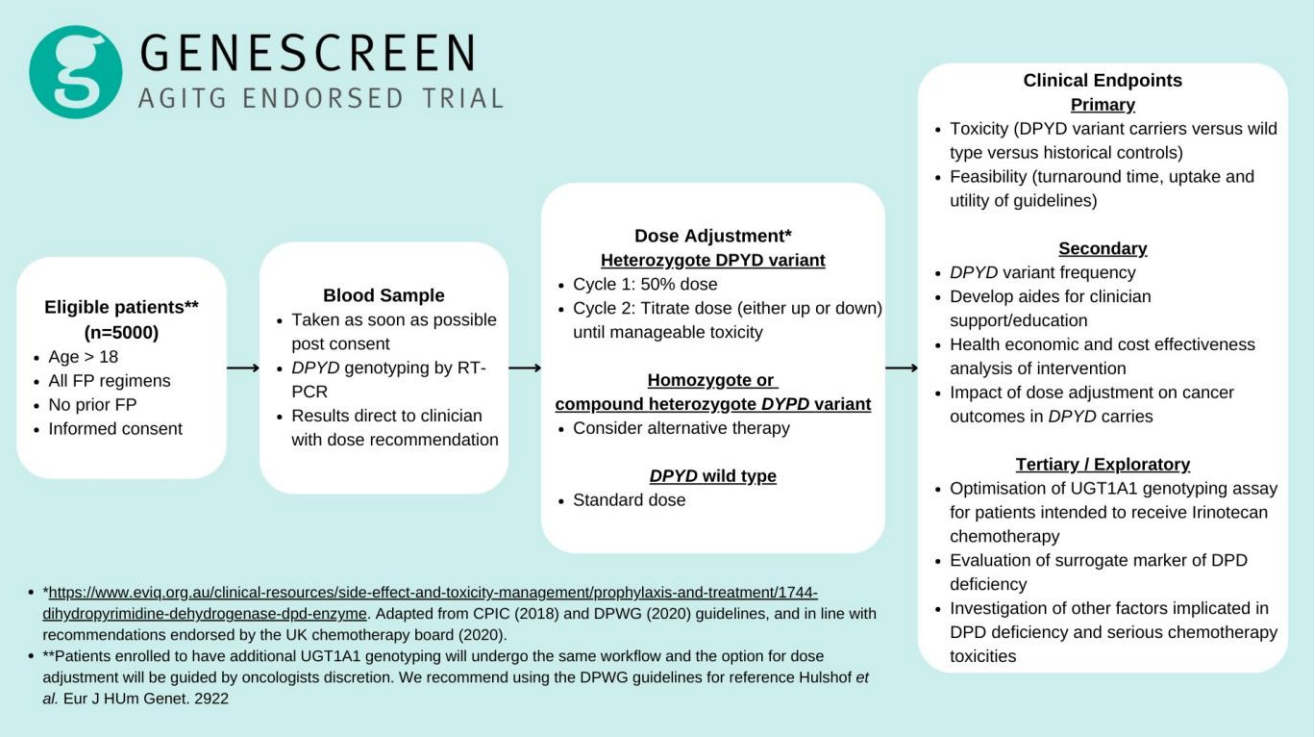
- A preliminary feasibility study based in 4 Newcastle hospitals (104 pts, no FP dose modification) has demonstrated a turn-around time (TAT) for *DPYD* genotyping of 7 days, 16 cases with variants (15 heterozygotes and one homozygote, 10 of whom required hospitalisation for toxicity management, including 2 ICU admissions and one death.
- Implementation data collected from 30 stakeholder questionnaires identified common barriers and enablers, including resources, education, trial experience, and beliefs.
- We are now in a funding position to begin a large study in at least 7 major metropolitan and regional health districts in 3 states, under the guidance of 14 chief investigators (disciplines: medical oncology, genomics, pharmacology, biomedical science, health economics,

supportive care, discovery science, predictive modelling, pharmaco- and immune-genetics – including 8 AGITG members) and supported by 4 consumer advocates/community representatives, and a comprehensive statistical service. We aim to recruit 5000 patients in 2 years (end 2025), including all ethnic groups, and specifically target all eligible cases with indigenous heritage by engaging closely with indigenous leadership groups. Clinical follow up for toxicity will be limited to 60 days, and long-term cancer outcomes will be evaluated.

TRANSLATIONAL RESEARCH

- Patients with a *DPYD* variant will be invited to contribute to genotype-phenotype correlation by assessment of plasma UH2/U concentration ratio on the pre-treatment blood sample. In patients without one of the 4 known *DPYD* variants who develop severe toxicity we will sequence *DPYD* and associated genes for other potentially causative variants. We aim to develop the evidence to support routine *UGT1A1* genotyping in the Australian health system.
- Residual Samples and data from each consenting patient will be retained for future cancer PGx research.

STUDY SCHEMA



- *https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-treatment/1744-dihydropyrimidine-dehydrogenase-dpd-enzyme. Adapted from CPIC (2018) and DPWG (2020) guidelines, and in line with recommendations endorsed by the UK chemotherapy board (2020).
- **Patients enrolled to have additional UGT1A1 genotyping will undergo the same workflow and the option for dose adjustment will be guided by oncologists discretion. We recommend using the DPWG guidelines for reference Hulshof *et al.* Eur J HUm Genet. 2922