GeneScreen 5-FU: *DPYD* Genotype-guided Personalised Fluoropyrimidine Dosing: Feasibility and Implementation

Cassandra White[1], Andrew Ziolkowski[2], David Mossman[2], Christine Paul[1], Rodney J Scott[1,2,3] and Stephen Ackland[1,4]

[1] University of Newcastle, College of Health, Medicine and Wellbeing, School of Medicine and Public Health, Callaghan NSW 2308; [2] Department of Molecular Genetics, Pathology North John Hunter Hospital, New Lambton Heights NSW 2305; [3]University of Newcastle, College of Health, Medicine and Wellbeing, School of Biomedical Science and Pharmacy, Callaghan NSW 2308; [4] Hunter Cancer Centre, Lake Macquarie Specialist Medical Centre, Gateshead NSW 2290

Background

~ 10,000 Australians are prescribed fluoropyrimidine (FP) chemotherapies per annum for colorectal, upper GI, breast and head & neck cancers.

~30% patients develop ≥ grade 3 toxicity potentially resulting in hospitalization, ICU admission and death.

~10% of the population are deficient in **Dihydropyrimidine Dehydrogenase** (DPD), the critical enzyme for FP metabolism.

Four *DPYD* gene variants (encoding DPD) are implicated in DPD deficiency: **c.1905+1G>A (*DPYD**2A), c.1679T>G (*DPYD**13), c.2846A>T and c.1236G>A/ Haplotype B3.**

Several countries within Europe and the UK recommend **upfront *DPYD* genotyping**, and genotype-guided dose adjustment in accordance with international guidelines, as **standard of care** for patients commencing FP chemotherapy. This follows data illustrating **improved patient safety and cost effectiveness**. Australia is yet to adopt upfront genotyping.

Objectives

To determine the **turn-around time** for *DPYD* genotyping in a public hospital service laboratory

Determine the stakeholder and patient enablers and barriers effecting implementation (results not presented)

Methods and Results

- 77 patients were recruited from four sites across Hunter New England and Central Coast health districts, including Hunter Cancer Centre, Gateshead.
- *DPYD* genotyping was conducted using PCR amplification using allele specific primers and a universal probe-based reporter system to detect target variants.
- 12/77 (15.6%) patients were identified to carry a *DPYD* variant, all heterozygote carriers (Table 1).

Mean turn around time for testing was 6.5 days

Table 1: DPYD variant frequency

DPYD Variant	No. Patients (%)
c.1236G>A/ Haplotype B3	7 (9%)
c.1905+1G>A	3 (3.8%)
c.1679T>G	1 (1.3%)
c.2846A>T	1 (1.3%)
No variant detected	65 (84%)
	Total: 77

Discussion

The turn-around time exhibited is sufficient to allow clinicians to pursue prospective FP dose adjustment, based upon international consortia guidelines, in order to improve patient safety.

Turn around time could be further significantly reduced with bi-weekly genotyping.

Implementation data collected will help to inform strategies for larger scale development

Future Direction

We are utilizing this feasibility data to develop a **larger scale prospective *DPYD* genotyping program,** encompassing sites within regional and metropolitan NSW.

Program endpoints will incorporate:

- Clinical safety and efficacy
- Implementation research outcomes
- Cost effectiveness / other health economic analyses

Our goal is to develop a reliable and equitable *DPYD* genotyping service for all Australian cancer patients requiring treatment with FP chemotherapies.

For more information contact Cassandra White: cassandra.white10@uon.edu.au; Steve Ackland: stephen.ackland@newcastle.edu.au