GENESCREEN 5-FU

GENOTYPE-GUIDED PERSONALISED FLUOROPYRIMIDINE DOSING: FEASIBILITY AND IMPLEMENTATION PILOT STUDY

PROF STEPHEN ACKLAND,
PROF RODNEY SCOTT,
PROF CHRISTINE PAUL,
DR CASSANDRA WHITE

HUNTER CANCER RESEARCH ALLIANCE
AND UNIVERSITY OF NEWCASTLE

BACKGROUND AND RATIONALE

- Fluoropyrimidine (FP) chemotherapy (5FU, capecitabine, Lonsurf)
  - Colon, Upper GI, Breast and Head and Neck cancers (>10,000 Australians/ year) (30% toxicity)
  - DPD enzyme critical for metabolism and excretion
    - DPD deficiency → excess FP → toxicity (hospitalization, ICU, death) (Up to 60% of toxicity)
  - DPYD gene responsible for DPD production (8% Caucasian population have functional variant)
    - Up to 50% of DPD deficient toxicity due to 1 of 4 DPYD gene variants

- Netherlands, UK, France
  - DPD enzyme and DPYD genotype screening PRIOR to delivery of FP chemotherapy
  - Safer prescribing, less toxicity, cost effectiveness

- **Can this be offered in Australia?**
- **What are the barriers and enablers to delivering this service in Australia?**

Henricks et al 2015, Pharmacogenomics
Henricks et al 2018, Lancet Oncology
Muelendijks et al 2015, Lancet Oncology
Deenen et al 2016, Journal Clinical Oncology

METHODS, AIMS AND OBJECTIVES

PART ONE: GeneScreen 5-FU Feasibility Study

- HNELHD and CCLHD (six sites)

Eligible patient recruitment
Aim 100 pts

→ Pre treatment blood sample
RT-PCR and biobanking

→ Genotype result to Oncologist
Prior to chemotherapy

Initial Questionnaire
Health Care Providers
Prior to recruitment

→ Follow up Questionnaire
Health Care Providers
Patient
After recruitment commenced

Clinical Intervention Objectives

Primary endpoint:

- feasibility of testing turnaround

Secondary endpoints:

- determine the effectiveness of genotype screening
  - toxicities, hospital/ ICU admission, death
  - outcomes of dose individ'n with cape/ Lonsurf

Tertiary endpoints:

- Cancer outcomes (DFS, PFS, OS), phenotypic correlations, future genomic DPD correlations (biobank)

Implementation Objectives

- Identify stakeholders and predict behaviours toward testing
- Identify barriers and enablers to implementation of pre-treatment genotype screening
- Apply the lessons from the pilot to larger scale collaboration for interstate programme. Implement strategies to overcome barriers identified and enhance enablers and evaluate effectiveness

IMPLEMENTATION METHODS

- Rationale: Pre-screening adopted in UK and Europe
- Martens *et al,* 2020 conducted analysis following introduction of testing in Netherlands
  - Enablers: Clear protocols and instructions for ordering/ reporting
  - Barriers: lack of consensus on test approach, long turn around time
- **Theoretical Domains Framework**

HCP Questionnaires:
Domains: skills, knowledge, beliefs (actions/ consequences), intent (actions/ consequences)

Patient Questionnaire:
Domains: knowledge, memory/ attention, beliefs

- Adjustments to approach (HCP, patients, laboratory) based upon outcomes (clinical and implementation)
- Implementation Evaluation in Larger Scale Program
  - Incorporation of Discrete Choice Experiment and Health Economics Analysis

Martens et al 2020, Frontiers in Pharmacology

FUTURE PROJECTIONS AND QUESTIONS

PART TWO: Larger Scale GeneScreen 5-FU Programme

NSW, Vic, Others. Aim 1000+ patients

Clinical Objectives

- Chemo safety data
- Dose reduction data (capecitabine and Lonsurf)
- Cancer outcomes

Implementation Objectives

- Inclusion of hosp executives and health system managers
- Discrete Choice Experiments
- Implementation analysis

Health Economics Objectives

- Cost effectiveness analysis compared to historical cohorts
- DCEs

Future Research Objectives

- Genomic research (related DPD genes/ DPD activity markers)
- Genetic variants related to specific ethnic groups