ORAL ABSTRACTS

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ProNGF AS A NEW BIOMARKER IN THYROID CANCER

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Background: Nerve growth factor (NGF) and its precursor proNGF are increasingly described for their role in cancer progression. Although NGF has been reported in thyroid cancer, the expression of proNGF is unknown and their clinicopathological significance is unclear.

Aims: Define the expression and clinicopathological significance of proNGF in thyroid cancer and determine its potential clinical value as a diagnostic or prognostic biomarker.

Methods: ProNGF protein expression was analysed by immunohistochemistry in two cohorts of thyroid tumours versus adenomas versus normal thyroid tissues.

Results: ProNGF expression was detected specifically in thyroid epithelial cells but not in other stromal cell types. In the two cohorts, there was a marked overexpression of proNGF in cancers as compared to adenomas and normal thyroid tissues (p < 0.0001). High levels of proNGF were found in about 74% of cancers, particularly in the papillary and follicular forms, as compared to only 5% of normal tissue samples (p < 0.0001). The area under the ROC curve was 0.90 (p < 0.0001). There was no significant association with age, gender, tumour size, stage, lymph node invasion or nerve infiltration.

Conclusions: These data reveal that proNGF is increased in thyroid cancer and suggests its potential value as a diagnostic biomarker. Further studies are warranted to determine the mechanisms leading to this proNGF increase in thyroid cancer and its impact on tumour progression.

Translational Research Aspect: This research is applicable to the T1 translational pipeline.

IDENTIFICATION AND SYNERGISTIC TARGETING OF FLT3-ACTIVATED PATHWAYS IN ACUTE MYELOID LEUKAEMIA

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Background: Acute Myeloid Leukaemia (AML) is the most lethal form of leukaemia, carrying a 5-year survival rate of 21%. Current treatments include high dose chemotherapy and bone marrow transplantation; however development of chemotherapy resistance and relapse is common. Internal Tandem Duplication (ITD) mutation of the receptor tyrosine kinase FLT3 is the most frequent driver mutation in AML (~35%), and is associated with poor prognosis. Due to development of resistance mechanisms, targeted FLT3 inhibitors have displayed limited therapeutic success in AML. Characterisation of the oncogenic signalling pathways activated in FLT3-mutant AML patients is required to develop improved therapeutic strategies.

Aims: 1. Identify differentially expressed phosphoproteins in FLT3-ITD+ and FLT3-wildtype AML patients
2. Investigate the utility of the identified proteins as novel biomarkers and drug targets

Methods: AML blasts were isolated from 7 patients (3 x FLT3-wildtype, 4 x FLT3-mutant). Protein was extracted and labelled with iTRAQ8plex, and the phosphoproteome subsequently quantified by LC-MS/MS. AML cell lines MV4/11 (FLT3-ITD+) and HL-60, Kasumi-1, and THP-1 (FLT3-wildtype) were utilised to assess drug toxicity through resazurin assay. Drug synergy was evaluated using the method of Chou-Talalay.

Results: Phosphoproteomic analysis in AML patients identified significant overrepresentation of oncogenic pathways including PI3K, MAPK, mTOR, PKC, and STAT. Comparison of FLT3-ITD+ versus FLT3-wildtype patients revealed differential activation of c-myc, and ribosome biogenesis pathways; along with novel AML-associated proteins including DNA-PK. Targeting of DNA-PK with specific inhibitor NU7441 displays synergistic lethality with low doses of AML chemotherapy agents cytarabine and daunorubicin in FLT3-ITD+, but not FLT3-wildtype AML cell lines.

Conclusions: Combined targeting inhibition of FLT3 signalling pathways with standard chemotherapy agents in FLT3-ITD+ AML has the potential to improve response to therapy in this poor responding AML subtype.

Translational research aspect: T1-2: Quantitative phosphoproteomic analysis has provided phenotypic information about FLT3-ITD+ AML; identifying potential targets for novel treatment strategies.
We intend to expand upon this data and investigate the role of this tyrosine body leads to a markedly decreased colony forming ability in glioma cells. We have shown that pre-radiation treatment with EphA2 anti-

**Conclusions:**

Minimal effect on the growth of cells, however, when used in combination within 16h. Treatment of glioma cells with EphA2 antibody alone had reduced the content of EphA2 and phosphorylated EphA2 in glioma cells, treatment of glioma cells with EphA2 antibody significantly.

**Results:**

U87 glioma cells were chosen for study as they are known to express EphA2 and grow readily in cell culture. U87 glioma cells were used to express EphA2 and phosphorylated EphA2 in glioma cells, within 16h. Treatment of glioma cells with EphA2 antibody alone had minimal effect on the growth of cells, however, when used in combination with radiotherapy the ability of glioma cells to form colonies decreased by 80% (radiation plus EphA2), this effect was significantly greater than the effect of radiotherapy alone (50% reduction), indicative of a synergistic interaction.

**Conclusions:** We have shown that pre-radiation treatment with EphA2 antibody leads to a markedly decreased colony forming ability in glioma cells. We intend to expand upon this data and investigate the role of this tyrosine kinase in radiation sensitivity with the purpose of exploring this therapy in the clinical arena.

**Translational research aspect:** This is a T1/T2 translational project.

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**AIMING FOR THE RIGHT QUALITY IMPROVEMENT TARGET: CROSS-SECTIONAL DATA EXPLORING OUTPATIENTS’ PRIORITIES AND PREFERENCES FOR QUALITY IMPROVEMENT IN TERTIARY CLINICS**

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**Background:** Patient-experience tools have not been designed specifically to inform health service change. Use of this data as a quality improvement mechanism has proven difficult with limited effects. To provide clear and actionable improvement messages, detailed evidence on patients’ preferences and priorities for service change is needed.

**Aims:** To report the: proportion of outpatients selecting each general quality improvement initiative; detailed initiatives corresponding to commonly-selected (>10%) general initiatives; and, commonly-selected initiatives in order of relative priority.

**Methods:** Outpatients completed a touch-screen survey in three tertiary clinics, including two medical oncology clinics. Participants selected up to 23 general initiatives that would improve in-clinic experiences. Using novel survey software, participants could select an additional 110 detailed initiatives and complete relative prioritization exercises.

**Results:** A total of 341 outpatients participated (71.1% consent, 73.1% completion), including 336 (62.0%) oncology outpatients. In order of relative priority, examples of commonly-selected general initiatives included: up-to-date information provision (15.0%); access to information at home (12.8%); reduced wait-times (19.8%); and information on medical emergencies (11.1%). To address general initiatives, 40 detailed initiatives were selected. For example, to improve up-to-date information provision, participants selected: providing information on treatment steps (72.8%) and condition progress when possible (67.9%); and, to receive test results quickly (58.0%). Participants selected access to a list of trust-worthy sources (45.1%) to improve information provision at home. To manage medical emergencies, participants selected information on emergency symptoms (71.7%) and information for family (61.7%) as specific initiatives.

**Conclusions:** Information-based initiatives were commonly-selected and are of relatively greater perceived priority. Improved wait-times was commonly selected but was a relatively lower priority.

**Translational research aspect (T3):** Using this survey approach, patients are able to specify and prioritise strong quality improvement preferences. This data provides clear improvement messages and assists health services to strategically allocate resources to changes of greatest value to patients.

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**THE TOBACCO SMOKING PROFILE OF CLIENTS ATTENDING A MEDICALLY SUPERVISED INJECTING CENTRE**

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**Background:** Medically supervised injecting centres offer a professionally supervised environment that is legally sanctioned for clients to inject pre-obtained illicit drugs. Among people who inject drugs (PWIDs), the rate of smoking exceeds 80% making this population particularly susceptible to tobacco-related illnesses and in need of intervention. The Medically Supervised Injecting Centre (MSC) may be a potential setting to address tobacco smoking among PWIDs.

**Aims:** The aim of this study is to examine MSC clients’ tobacco smoking-related behaviours.

**Methods:** An online cross-sectional survey was conducted in November 2015 to January 2016. Eligible individuals were current MSC clients aged ≥18years, self-reported tobacco smokers, who had satisfactory English comprehension and were able to provide informed consent.

**Results:** Of the 214 eligible individuals, 202 consented to participate (94%); 200 (99%) were daily smokers who were moderately to heavily nicotine dependent (n = 156, 77%). Most (n = 186, 83%) had made at least one quit attempt in their lifetime. Previous quit attempts were largely unaided relying mostly on will power (n = 52, 70%). The majority (n = 138, 68%) indicated that they would like to quit smoking and would like to receive access to smoking cessation strategies while at a MSC.
Conclusions: MSIC clients are highly nicotine dependent, interested in quitting smoking and would like their smoking to be addressed.

Translational research aspect: This research will provide novel information to shape program development for smoking cessation care in MSICs. This is T1 research.

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DEVELOPMENT OF ACTION LIMITS FOR PATIENT ERROR DETECTION FOR AN EPID-BASED REAL-TIME DELIVERY VERIFICATION SYSTEM

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Background: The application of in vivo dosimetry using electronic portal imaging device (EPID) has been clinically implemented to improve the quality of treatment in external beam radiotherapy (EBRT). EBRT is a complex radiation treatment technique, which uses non-intuitive fluences, and a large dose can be delivered to the patient. The traditional and routine quality assurance (QA) programs are used to prevent treatment errors. However, the main drawback of most of the QA programs used in the clinic is that they are unable to detect some serious errors during treatment, such as patient anatomy changes, data transfer issues, accidental plan modification, wrong patient position setup, failed dose delivery, and immobilization issues. We developed and clinically implemented an EPID-based real-time patient treatment verification, comparing predicted EPID image to measured EPID image in real-time. Our proposed system can ensure the quality of radiation treatments.

Aims: The aims of this study are to develop statistically based evaluation tools for error detection during real-time EPID-based patient treatment verification for IMRT and VMAT based on verification results.

Methods: The real-time verification system (Watchdog) utilises a comprehensive physics-based model to generate a series of predicted transit cine EPID image as a reference data set, and compares these to measured cine-EPID images acquired during treatment. The agreement between the predicted and measured transit images is quantified using chi-comparison (currently 4%, 4 mm) on a cumulative frame basis.

Cine-EPID images were acquired from the first two fractions of 137 IMRT patients to generate the lower control limit using Statistical Process Control (SPC) technique; 82 Prostate treatments, 37 head and neck treatments, and 18 Rectum treatments. An action limit was determined based on an integration of real-time verification result and the calculation of process capability index. The action limit sensitivity were tested to ensure the system is able to detect patient position misalignment, dose delivery errors, wrong patient treatment, and wrong plan. For clinical study, 15 IMRT Patients were treated and operated with Watchdog used to evaluate the treatment outcome as well as to determine the source of error.

Results: The derived lower control limits (4%, 4 mm) after 2 seconds of image acquisition for prostate, head and neck, and rectum IMRT were 75.62%, 71.29%, and 71.11% respectively. For a clinical study of 15 patients, on average 7% of the entire treatment failed under the action limit and were identified for further investigation regarding the source of error (see figure a). A case study of a head and neck patient (see figure b), showed an error detected toward the end of the treatment course that was correlated with weight loss shown on CBCT scans.

Conclusions: We have developed an evaluation method for a real-time EPID based treatment verification system (Watchdog). These action limits are designed to be applied to real-time verification during treatment with immediate intervention during SBRT treatments and post-delivery investigation during standard fractionation. Initial results found that the system detected significant changes in patient contour due to weight loss for a head and neck treatment.

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ASSESSMENT OF BLOOD TRANSFUSION PRACTICES IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES IN THE ERA OF HYPMETHYLATING AGENTS.

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Background: Myelodysplastic syndromes (MDS) are heterogeneous groups of primary bone marrow disorders characterized by ineffective or reduced blood cell production. Supportive management comprising of blood transfusion is still the corner stone of the management of MDS. Around 80% of patients with myelodysplasia develop anaemia at diagnosis or during the course of the disease and will need a transfusion. Hypomethylating agents like azacitidine has been developed with the aim of reducing the transfusion burden and hence the risk of transfusion associated complications. Clinical
trials have shown efficacy of azacitidine in reducing the frequency of blood transfusions but the benefit has not been established outside clinical trials.

**Aims:** Evaluation of usage and change in frequency of blood products in Hunter area since the availability of azacitidine for treatment in MDS.

**Methods:** A cross sectional study of 256 transfusion dependent MDS patients from 1st January 2008 to 31st May 2015 has been undertaken at the haematology department Mater hospital. Patients have been divided into groups as per treatment with or without azacitidine. Blood transfusion data has been collected from the blood bank at Pathology north for assessment.

**Results:** The analysis has shown reduction in the blood transfusion frequency in transfusion dependent MDS patients. However, it has been demonstrated that reduction in blood transfusion is not a sustained response and after six to eight months of azacitidine, the requirement for blood product increases again.

**Conclusions:** Azacitidine reduces the blood transfusion burden after commencement secondary to improvement of bone marrow function. However this response is not sustained and with continuation of treatment this response is lost. This phenomenon has not been demonstrated in the clinical trials.

**Translational research aspect:** This project is T2 research as it will help to further structure the blood bank according to the requirements of the patients to reduce the wastage of blood products. Our study results need confirmation from larger prospective studies in the future.

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**PREDICTORS OF MDT REVIEW AND THE IMPACT ON LUNG CANCER SURVIVAL FOR HNELHD RESIDENTS TREATED IN THE PUBLIC SECTOR**

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**Background:** Review by an MDT has been shown to lead to increased rates of surgical resection, radiotherapy, chemotherapy and timeliness of care. Most recently, the Victorian lung cancer patterns of care study have found that MDT review is an independent predictor of lung cancer survival.

**Aims:**
1. To examine predictors of lung cancer MDT review. If MDT review is an independent predictor of survival then this variable should be collected from each patient.
2. To determine if MDT review is an independent predictor of survival.

**Methods:** Hunter New England residents diagnosed with lung cancer between January 1st 2009 and June 30th 2013 obtained from the Clinical Cancer Registry linked to MDT surveys obtained from ARIA. Logistic regression was used to estimate predictors of MDT review and proportional hazards regression modelling was used to analyse survival.

**Results:** Of the 2,167 individuals with lung cancer 411 or 20% were reviewed at the MDT. The odds of MDT review were higher for stage II patients; if cytological or histologically verified; four times more likely if treated at Calvary Mater or John Hunter; if undergoing radiotherapy and if seen by a specialist nurse. Lower odds of MDT review occurred for patients with stages III and IV, or unstaged; those referred to Palliative Care and those who died within a month of diagnosis. MDT review was found to be an independent predictor of survival with a 21% lower hazard of death (HR 0.79 95% CI 0.62-0.99) after adjustment for covariates. Further stratification by stage showed that stage III patients had the most marked survival advantage HR (0.59 95%CI 0.45-0.77) followed by stage IV with a 20% reduction in the hazard of death HR (0.80 95%CI 0.66-0.97).

**Conclusions:** Current guidelines recommend that all lung cancer patients be reviewed at an MDT given that this is not feasible.

**Translational research aspect (T3)** targeting stage III patients would appear to confer the greatest survival advantage.

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**MONTE-CARLO SIMULATIONS OF THE CLINICAL BENEFITS FROM THERAPEUTIC DRUG MONITORING OF SUNITINIB IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMOURS**

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**Background:** Therapeutic drug monitoring (TDM) is being considered to individualize cancer treatment with tyrosine kinase inhibitors like sunitinib. However, TDM’s potential benefit for eligible patients in terms of clinical outcomes, such as time to tumor progression (TTP), remains unclear.

**Aims:** To estimate the expected improvement of TTP from a TDM program in patients with gastrointestinal stromal tumors (GIST) treated with sunitinib at a starting dose of 37.5 mg/day.

**Methods:** A Monte-Carlo simulation of 10,000 patients was performed, using published models of the pharmacokinetics and pharmacodynamics of sunitinib. The simulation included two TDM-guided dose increases of 12.5 mg/day on day 21 and 42, for patients with total (sunitinib + metabolite SU12662) trough levels (TTL) below the pharmacokinetic target of 50 ng/ml.

**Results:** Without TDM, only 45.3% of patients had a TTL of at least 50 ng/ml, but two rounds of TDM increased this proportion to 76.2%. The TDM program increased median time to tumour progression in initially underdosed patients from 214 to 285 days.

**Conclusions:** This simulation study does not take dose-limiting toxicity into account; in a clinical setting, not all patients will tolerate a TDM-guided dose increase. However, this Monte-Carlo simulation study suggests that an improvement in time to tumor progression might be achieved with TDM in underdosed patients that tolerate dose increases.

**Translational research aspect:** This work suggests clinical outcome in eligible patients with GIST can be improved by implementing a TDM program. Evaluating the clinical benefit of a TDM intervention *in silico* is consistent with T2 in the translational pipeline.

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**OR15**

**PANEL TESTING FOR BREAST CANCER RISK ASSESSMENT: IS IT JUST BECAUSE WE CAN RATHER THAN SHOULD?**

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Since the identification of BRCA1 and BRCA2, a number of other genes have been reported to be associated with an increased risk of breast cancer. Many of these genes have now appeared on commercial massively parallel sequencing (MPS) panels and are increasingly used for assessing breast cancer risk in women who developed disease at unusually young ages. Apart from BRCA1 and BRCA2 where there is considerable evidence associated with disease risk as well as strategies to mitigate the effects of mutation carriage there is little if any information about the consequence of mutations in the more recently identified breast cancer susceptibility genes. This includes knowledge about the histopathology conferred by the loss of expression of a particular gene, the influence of environmental factors on disease risk as well as the most effective treatment strategies for disease prevention or disease treatment. For
many of the genes listed on commercial panels knowledge about disease frequency in affected populations compared to control populations is lacking thereby undermining the veracity of breast cancer susceptibility claims.

To help address the shortfall in information about some of the more recently identified genetic risk factors to breast cancer we undertook a study of 2000 cases and 2000 controls to estimate the prevalence of mutations in a panel of genes that are commonly included in commercial testing. The results reveal that MPS panel testing must continue under a research setting so that more information can be gathered to understand what is meant by the term “genetic predisposition” to breast cancer for a large proportion of genes that are currently under scrutiny. At present only four genes can be used unequivocally in a diagnostic setting for the assessment of genetic risk of disease in most countries.

PATIENT PERSPECTIVES ON ISSUES OF ACCESS TO CANCER CARE ACROSS THE CARE CONTINUUM

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Background: Differences in cancer incidence and mortality are associated with inequalities at each step in the process of preventing or developing cancer, diagnosis and care provision. Patient perspectives are an important part of gaining a full understanding of how the care continuum operates. These data can assist us in identifying priority opportunities for change.

This presentation will explore Australian data regarding patient perspectives on their access to care from the prevention of cancer, to obtaining a diagnosis and treatment. Data regarding perceptions on the quality of care received, preferences for change, affordability and financial impacts of cancer will be described.

An understanding of these issues allows us to consider where our research efforts might focus in order to translate evidence into practice in an equitable way and deliver a more equitable and patient-centred care.