Genomic Cancer
Clinical Trials Initiative

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FEBRUARY 2021 WORKSHOP REPORT

This report was finalised on 27 April 2021

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Introduction

The Genomic Cancer Clinical Trials Initiative (GCCTI) was established and funded by Cancer Australia in 2013. The GCCTI is a technical service that supports the national cancer cooperative trials groups (CTGs) funded under Cancer Australia's *Support for Cancer Clinical Trials* program to develop **mutation-specific clinical trials concepts** and **grant applications involving cancers from more than one primary site and more than one CTG**.

The GCCTI is led by the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC) in partnership with Zest. Scientific and technical input is provided by the NHMRC CTC, with project management, stakeholder engagement and communications undertaken by Zest. The GCCTI project team, in collaboration with GCCTI's Scientific Steering Group (SSG), held a one-day virtual **grant development workshop** on **Friday 26 February 2021.**

Purpose of the workshop

The GCCTI annual workshops aim to provide a forum for Australia's leading cancer researchers, CTGs, and the GCCTI SSG to discuss ideas and opportunities for studies and grants involving cancers from multiple primary sites and multiple CTGs. This grant development workshop focused on strengthening grant submissions for the upcoming 2021 rounds, and generating ideas for grants to submit beyond 2021.

The February 2021 workshop focused on:

- Grant opportunities, guidelines, assessment criteria, recent changes and other news
- Mock grant review and peer input into planned grant submissions
- Updates on current and imminent studies of genomic profiling to guide cancer treatment
- Discussion of ideas for grants to submit beyond 2021, especially those including multiple cancer types and multiple CTGs

The workshop program is included in the Appendix

Genomic Cancer
Clinical Trials Initiative

Overview of the GCCTI

The scope and key deliverables of the GCCTI are to:

- Host an annual workshop with all CTGs and key stakeholders to identify potential targets for developing mutation-specific cancer clinical trial protocols.
- Develop clinical trial concepts and protocols that involve collaboration with more than one CTG and that include more than one cancer type
- Submit grant applications for funding of these trials, including preparation of budgets
- Include quality of life and pharmaco-economic measures, where applicable (to be developed collaboratively with the Cancer Australia Chair in Quality of Life and Cancer Research Economic Support Team [CREST])

The intended outcomes and benefits include:

- Increased capacity for the conduct of genomic cancer clinical research
- Molecularly-focused networks of researchers, clinicians and scientists
- Structures to support the conduct of trials that include multiple primary sites and multiple CTGs
- Strategies for managing challenges associated with trials of targeted treatments

There are several ways that individuals can engage with the GCCTI:

- Contribute to idea generation and prioritisation by attending GCCTI workshops and communicating with other CTGs, researchers and the GCCTI project team
- Developing and submitting concepts/ideas to GCCTI, further information here.
- Working with GCCTI and other CTGs to design trials based on identified concepts.
- Input into grant applications by joining GCCTI supported grant development teams.

1.0 2021 Grants and Other News

1.1 Update on NHMRC Grants Programs

Julie Glover (Executive Director, Research Foundations) provided an update on NHMRC grants programs, applicable to both new and experienced applicants. Regarding the suite of grants available, points to note include:

- There is intersecting eligibility criteria across the grant schemes; there is a tool on the website to support applicants in understanding their eligibility
- Ideas grants are not intended for research where a clinical trial or cohort study is the primary objective
- Recent changes to grant programs are outlined at the start of grant guidelines

Changes to the NHMRC grant programs for 2021 are as follows. For investigator grants:

- Revised time period for applications
- The Category and Level Justification element of the application is more nuanced to recognise the complexity of career pathways, with additional communications to help applicants apply at the appropriate level, and introducing the opportunity for applicants to justify their level
- Revised Relative to Opportunity policy; introduction of career context aspect (pilot) of the application to help applicants articulate their career path and to help reviewers asses Relative to Opportunity
- Shift to application centric peer review with panels assembled around applications

For Clinical Trials and Cohort Studies, there have been changes to the time period for applications. Outcomes for 2020 applications are expected to be notified in June 2021, with the 2021 round expected to open in late June 2021 and grants to commence in mid-2022. Synergy grants have additional funding as a result of the round cancelled in 2020.

For Ideas grants, the peer review process will aim to include five rather than four reviewers per application. The format will move away from grant review panels; this will allow a broader group of reviewers to participate leading to more optimal matching of reviewers to applications, and will reduce the workload for reviewers.

Tips for preparing a grant application include:

- Set up a GrantConnect user account to be notified of newly released guidelines and common FAQs
- Set up a Sapphire account early to become familiar with the system and to be ready for grant teams to add you to a grant
- Seek any necessary review and eligibility advice from your Research Administration Officer (RAO) early

1.2 Update on MRFF Grants Programs

Stephanie Lehoczky (A/g Director, Patients and Infrastructure, Department of Health) provided an update on MRFF grants programs.

MRFF funding for clinical trials includes $614.2 million over 10 years, and includes two key initiatives: Rare Cancers, Rare Diseases and Unmet Need (RCRDUN) and International Clinical Trials Collaborations (ICTC). Grant opportunities are grouped under the four themes of Patients, Researchers, Research missions, and Research translation.

Points to note in applying for MRFF funding include:

- Applications remain through NHMRC or the Business Grants Hub (BGH), but all opportunities are on GrantConnect, which MRFF use to flag new grant opportunities
- Assessment panels have national and international representation, health service delivery and implementation expertise, and also consumer input

Tips for preparing a grant application include:

- Set up a GrantConnect user account to be notified of grant opportunities
- Read the Grant Opportunity Guidelines carefully as these include past and upcoming changes
- Pay careful attention to the objectives and selection criteria/scoring matrix
- Visit the MRFF website for the latest information and upcoming activities
- Maximum of one application per grant opportunity

Recent news and activities to look out for:

- MRFF's medical research and innovation strategy will be updated, with upcoming consultations and information on the website about how to get involved.
- Mission consultation – a way to input in to the future of Missions
- Summaries of MRFF Initiative evaluations

1.3 Update on Cancer Australia Grants

Dr Paul Jackson (Head of National Research & Data, Cancer Australia) provided an update on the status of Cancer Australia's annual research grants program.

Priority-driven Collaborative Cancer Research Scheme (PdCCRS)

The PdCCRS is Cancer Australia's annual national research grants funding scheme, in which the agency joins with other government and non-government organisations to collaboratively fund national cancer research projects in areas of identified priority.

Applications to the Standard Project grant category (A) of the PdCCRS can be submitted via the NHRMC Ideas Grant or the NHMRC Clinical Trials and Cohort Studies (CTCS) Grant schemes; applications to Early Career Researcher Grant categories (B, C, D) in the PdCCRS can be submitted via the NHMRC Ideas Grants scheme only.

Key points to note in relation to the 2020 round:

- Due to the impact of COVID-19, timelines for the assessment of applications to the PdCCRS round have been amended.
- Assessment of applications received through the Ideas Grant scheme has been completed, and well underway for applications received through the CTCS Grants scheme.
- There will be two announcements of successful applications to the 2020 PdCCRS round: the first announcement in April 2021 will focus on applications received via the NHMRC Ideas Grant scheme only; a second announcement in May 2021, is likely to include applications received to both the Ideas Grant and CTCS Grants schemes.

Key points to note in relation to the 2021 round:

- Early career researchers applying to both NHMRC and PdCCRS must be the sole CI on the PdCCRS application, the CIA on the NHMRC submission, and the project must be a maximum of 3 years in length.
- Completed PdCCRS Questions forms must be submitted by the RAO directly to Cancer Australia no later than one week after closing of the corresponding NHMRC Grant scheme.
- It is expected that successful PdCCRS applicants will be notified after 1 February 2022.
- In terms of assessment criteria used for applications to both the Ideas Grant scheme and the CTCS Grant scheme, answers to PdCCRS questions comprise half (Early Career Researcher categories) or more than half (Standard Project Grants) of the overall score, so it is important that answers are comprehensive and convincing.

Cancer Australia has secured 8 Funding Partners with separate research priorities for the 2021 PdCCRS Funding Round. These research priorities build on Cancer Australia's 2021 Research Priorities, which remain unchanged from the 2020 round, and include priorities in prevention, cancer health service delivery, and some general priorities.

As in previous years PdCCRS Standard Project Grants (Category A) are capped at a maximum of 3 years and funding of $200/000 *per annum* (maximum $200,000). Early Career Researcher categories are capped at one year and $100,000 (Category B), up to two years and $200,000 (Category C) and up to $100,000 for one year (Category D), and focused towards researchers with up to three years post qualification (Category B) or from four to seven years (Category C) or up to seven years post qualification (Category D).

1.4 PoCoG's perspective on psycho-social questions in genomic studies

A/Prof Haryana Dhillon (SAC Chair, PoCoG) presented PoCoG's perspectives on psycho-social questions in genomic studies.

Distress is a normal reaction to a traumatic life event and is prevalent in cancer patients. For many, distress settles over time, and this can happen more effectively if people receive psychosocial education. Psychosocial morbidity is also high; meta-analyses shows that

around a third of patients in Acute Cancer Clinics suffer from a psychiatric comorbidity. Not addressing psychological morbidity has substantial costs including poor adherence to anti-cancer treatment, increased cancer treatment side-effects, higher use of health care resources, severe depression and suicidal ideation.

Synthesis of data across 40 years of screening shows that screening in a primary care setting alone does not improve patient outcomes and we need clear clinical pathways with institutional commitment. PoCoG is currently implementing a distress screening process and a clinical pathway for anxiety and depression management in 12 NSW hospitals, demonstrating this is possible in clinical practice.

Current questions that PoCoG have proposed within MOST:

- Survivorship experience of exceptional responders
- Communication of genomic results and a dynamic consent platform (underway)
- Development and pilot of information, consent materials and platform

Other questions/ideas that PoCoG are looking to focus/expand on:

- Should we be screening for distress at the time of tumour profiling (and how)?
- What are the psychosocial impacts of results and what interventions will support psychosocial adjustment?
- What is the level of fear of progression/recurrence in these patients?
- Do current FCR/FOP interventions work?
- Do self-management interventions work to reduce FCR/FOP/anxiety to follow-up?
- What is the best way to present results and treatment options?

PoCoG's key activities include:

- Advice and input into concepts/protocols/grants
- Recommending measures for inclusion in genomic studies
- Contribute to and guide qualitative data collection
- Piloting and trialing interventions

A video of this presentation, and slides, can be found here.

2.0 Mock grant review and peer input for upcoming submissions

2.1 Rank-ligand blockade and immune checkpoint inhibition

Angelina Tjokrowidjaja (Medical Oncologist and GCCTI Research Fellow) presented an open-label, randomised phase 2 basket trial to evaluate the activity of denosumab and immunotherapy in advanced cancers.

Immune checkpoint inhibition (ICI) has improved survival outcomes in a range of advanced solid malignancies compared with other treatments such as chemotherapy, however there is still a range in the response rate to immunotherapy monotherapy from 13-40%. Doubling ICI is associated with increased response and benefit, but is costly and is associated with significant toxicity, therefore there is still an unmet need to improve the benefit of ICI without increasing financial cost or toxicity.

Combination ICI and RANKL blockade is proposed as a synergistic and immuno-modulatory strategy in advanced solid malignancy without additional toxicity expected:

1. Tumour cells express RANK and RANKL
2. RANK/RANKL have been associated with worse prognosis
3. High RANK/RANKL expression are associated with tumour growth and proliferation
4. RANK/RANKL signaling has central and peripheral immuno-modulatory effects
5. Clinical reports and case series suggest synergism of RANKL blockade and ICI

We propose a randomised basket trial of combining denosumab with a PBS-subsidised ICI in advanced cancers including non-small cell lung cancer, urothelial cancer, clear-cell renal cell cancer, melanoma, and head and neck cancers. Patients will be randomised 2:1, stratified by tumour stream, to either PBS-subsidised immunotherapy plus denosumab versus PBS-subsidised immunotherapy alone. The primary end point is investigator-assessed PFS. The target sample size is 300 recruited over 2-years.

The concept-development team includes Angelina Tjokrowidjaja, Martin Stockler, Chee Lee, Craig Gedye, and Chris Brown. The aim is to submit a grant application to NHMRC Clinical Trials and Cohort Studies in August 2021.

2.2 Stereotactic radiation as consolidation following immunotherapy

Eric Hau presented a prospective Phase II Randomised Non-Comparative Study of Consolidation Radiation for Induced/Repeat Oligo-Persistent Disease Following Initial Immunotherapy; an early proposal in development with Chee Lee and Mark Pinkham.

Checkpoint inhibitors are used successfully in many locally advanced/metastatic cancers, however a complete response is rarely achieved. Persistent cancer cells are a major reason for treatment failure, often occurring in sites of previous known disease. Oligometastatic disease, an evolving concept, is where cancers have spread but have not developed the full capabilities of widespread dissemination.

In metastatic/ stage 4 disease, radiation has traditionally been given with palliative care intent, and not known to improve survival. Recently there has been a significant increase in stereotactic radiation, which differs from conventional radiation as it has more precise delivery. Total dose is also higher, as is dose per fraction, which leads to shorter treatment time, increasing convenience for the patient.

In terms of the evidence for using stereotactic radiation in oligometastatic disease, the conclusions are that it is generally safe, convenient for patients, and is associated with a high local control rate. We are moving timelines earlier to treat patients with stereotactic radiation whilst tumours are still small, with the rationale being that once cancer has progressed, the tumour becomes bigger and of a higher grade, increasing toxicity and the risk of spreading.

Pre-clinical and some clinical studies have also shown that radiation has an immune-modulatory effect on tumours, and some potential immune effects as well. In clinical trial settings there is some success of combining immunotherapy and radiation. The incidence of abscopal effect is very low.

The hypothesis is that in locally advanced or metastatic cancer settings, where patients are treated with initial checkpoint inhibition, the introduction of stereotactic radiation may improve outcomes. From a biological point of view, the aim is to remove or reduce resistant clones which remain after initial immunotherapy.

The study proposed is a prospective phase II randomised non-comparative trial, randomised 2:1 treatment vs control for patients with locally advanced or metastatic non-small cell lung cancer, melanoma, renal cell cancers and potentially other cancers where initial treatment is either single agent or combination checkpoint inhibitors.

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3.0 Current and imminent studies of genomic profiling to guide cancer treatment / trials

3.1 LUMOS

Hui Gan presented an update on the LUMOS pilot study: Low and Intermediate Grade Glioma Umbrella Study of Molecular Guided Therapies.

In terms of background, Grade 2 and 3 gliomas (G2/3 gliomas) are the second largest group of malignant brain tumours in adults. Although the outcomes for G2/3 gliomas at progression/recurrence closely approach the poor outcomes for glioblastoma, there are virtually no trials for patients with relapsed G2/3 gliomas. These tumours often affect younger people, with recurrence often leading to poor prognosis.

LUMOS is an umbrella study specifically for patients with G2/3 gliomas to match patients with targeted therapies based on molecular testing using contemporaneous tumour tissue. It is a multi-centre, pilot study enrolling a cohort of patients with contemporaneous tissue at the time of progression after prior radiotherapy and chemotherapy, to determine the feasibility of undertaking molecular phenotyping with a molecular panel to aid subsequent treatment selection. The pilot study is led by COGNO and has a target to recruit 10 patients across 5 sites.

Group discussion points:

- Suggestion to unpick some of the acceptability and level of prescription/detail that would be optimal if clinicians are receiving the results reports
- Consider building in a study element of consulting with patients to understand their perspectives on the study and their participation
- Suggestion to consider how the study will be published, in light of small patient numbers and the qualitative mature of the research – study may sit in field of implementation science
- Delivery and interpretation of molecular data is a challenge shared across tumour groups, particularly for clinicians in supporting patients to receive and understand results

- An important question is the level and technicality of information required for clinicians to feel confident in discussing the results and recommendations with patients

3.2 TOPOGRAPH

Frank Lin presented an update on TOPOGRAPH: Therapy-Orientated Precision Oncology Guidelines for Recommending Anti-cancer Pharmaceuticals (an Australian knowledge base for precision oncology).

As background:

- molecular profiling of cancer is becoming more and more common, revolutionized by sequencing technology, and using larger panels yielding more targets than traditional targeted panels
- an information challenge exists when decision-making based on novel biomarkers due to large amounts of knowledge that is frequently “evidence-poor”, issues with drug access, and varied clinical recommendations among expert groups
- the consensus of best practice is rapidly evolving

A number of knowledge bases (KB) exist; structured databases which aim to link biomarkers to a potential therapy by clinical/pre-clinical and to simplify evidence synthesis during the reporting/clinical-decision making; the most well-known KB is OncoKB. Current problems include: most databases focus on the interpretation of variant or biomarker only, patchy and outdated curation of therapy data, therapies not accessible in Australia, and inaccurate recommendations.

There is also a “misnomer of actionability”; current molecular pathology / NGS reports do not consider context about drugs and clinical scenarios, and there is a focus on “treating the mutations” rather than the patient.

TOPOGRAPH aims to brings information together to link the relationship between cancer type, biomarker and therapy and reflects the steps of the drug development process; it is a knowledgebase curated by oncologists for guiding biomarker-driven therapies selection for patients with advanced or metastatic cancers in solid (and hematologic) malignancies.

Therapy selection is based on presence/absence of biomarker (or a biomarker invariably present in disease/cancer type).

Strengths include: it is “therapy-focused” (rather than “mutations”), explicit literature criteria is used for creation, transparency, and it provides a way to structure how clinical decision can be made in “guideline-free” scenarios. In terms of limitations, TOPOGRAPH cannot be used alone for decision-making, and challenges include database maintenance, refining of the tiers for T4 and R2, and limited hematology contents at present.

Applications include: a clinical reference and patient communication tool, standardized reporting and collaborative decision-making, electronic/digital tools, and drug development/trial design. Future work underway to improve coverage includes a focus on curation methodology, application in precision oncology, localization, harmonization with existing scales (e.g. ESCAT), and evaluation.

TOPOGRAPH is available online here.

4.0 Ideas for grants to submit beyond 2021

4.1 REZOLV3R

Katrin Sjoquist (Clinical Lead/Senior Research Fellow, NHMRC CTC) presented an update on the REZOLV3R concept, which has developed subsequent to the REZOLVE study.

REZOLVE developed in the context of the following problems:

- malignant ascites is a common and important cause of morbidity in patients with a variety of cancer types including ovarian cancers
- there is no treatment approved in Australia for malignant ascites
- VEGF plays a pivotal role in malignant ascites but Bevacizumab recognises and binds to all major isoforms of human VEGF-A and prevents VEGF from interacting with its receptors and inhibits activation of downstream signaling pathways.

On that basis, a phase 2 trial (REZOLVE) was conducted, led by ANZGOG, of intraperitoneal bevacizumab for symptomatic ascites in patients with chemotherapy-resistant, epithelial ovarian cancer; the results were published online on 23 February 2021.

The conclusion was that IP-bev was safe, active, and warrants further study as a palliative intervention for recurrent ascites in CR-EOC patients receiving best supportive care.

REZOLV3R is proposed as randomised controlled phase III study of (intermittent) IP bevacizumab following therapeutic ascitic drainage of recurrent malignant ascites from refractory (intrabdominal) solid tumours of the Gastrointestinal and gynaecological tracts, compared to placebo. The target population is those with recurrent, cytologically confirmed malignant ascites from primary gynaecological or gastrointestinal tract cancers suitable for paracentesis (ECOG 0-3) and a paracentesis free interval (PFI) of less than 28 days.

Proposed design of REZOLV3R is a randomised multicenter (inter)national phase III placebo controlled trial with stratification by primary tumour site, performance status, median time since prior paracentesis, and perhaps country. Current thinking on the primary objective is to compare paracentesis free survival between arms (or paracentesis free interval). Aspects

currently for discussion include the control arm, crossover, patient population, clinical inclusion criteria, coverage of other primary sites, and pleural effusions.

4.2 BCL-XL in mesothelioma

Tom John (Medical Oncologist, PMCC) presented an update on a Phase 1b trial of AZD0466+cisplatin in platinum sensitive solid organ tumours. This was followed by an update from Cristina Mapagu (Medical Oncologist) on a project looking at anti-apoptotic gene expression and sensitivity to BH3-mimetics in chemo-resistant, high-grade serious ovarian cancer cell lines. These presentations were provided together to generate some insightful discussion for the Phase 1b trial of AZD0466+cisplatin in platinum sensitive solid organ tumours, specifically around possibilities of extending the study to other cancer types.

Phase 1b trial AZD0466+cisplatin in platinum sensitive solid organ tumours

The BCL-2 family of proteins are used as another means of treating cancers. These drugs have entered clinical practice for CLL and have been trialed recently in breast cancer with some interesting preliminary data. This trial looks at a compound called AZD0466 which targets both BCL-2 and BCL-XL.

The study previously looked at protein expression in mesothelioma, finding it to be strongly expressed. It was also found that high expression of these apoptotic proteins was associated with poor survival. *In vivo* and *in vitro* work also shows promising results in terms of this combination leading to tumour reduction and suppression; the results have been published in Cell Death Discovery.

AZD4320 is now also a BCL-XL inhibitor; with one problem being that they cause myelosupression. Novel compound AZD0466 (BCL-XL/BCL-2I) is incorporated into a dendrimer; this agent results in significantly less hematological toxicity in animals (FIH study is ongoing).

The primary aim of the trial is to determine the maximum tolerated dose and recommended phase II dose of combination platinum + AZD0466, and it is hypothesised that the combination will be safe and tolerable. The population are those that have previously had

platinum sensitive tumours; data is largely mesothelioma, but also includes lung and perhaps ovarian cancer. The study design is phase 1, 3+3 dose escalation.

Anti-apoptotic gene expression and sensitivity to BH3-mimetics in chemo-resistant, high-grade serious ovarian cancer cell lines

In terms of background, primary treatment of epithelial ovarian cancer is well-established with debulking surgery and primary platinum-based chemotherapy. Despite high response rates to first line chemotherapy in high-grade serous ovarian cancer (HGSOC), recurrence and development of chemotherapy resistance is common. There are multiple options for systemic therapy at disease relapse, however there is no reliable predictive test to determine which treatment is best for which patients. Better understanding of the mechanisms underlying resistance in HGSOC is important in developing new treatment strategies and improving outcomes.

The project looked at cell line models of resistant HGSOC. In newly established AOCS cell lines, lines of treatment for each patient from which the cell lines are derived and subsequent responses were evaluable.

Conclusions from the project include:

- Cell lines derived from ascites of women with relapsed HGSOC are useful models of drug resistance. Since resistance of these cell lines developed *in vivo,* it makes them ideal models for studying potential resistant mechanisms and testing new treatment combinations.
- Inhibition of apoptosis was identified as a potential mechanism of paclitaxel resistance in high-grade serous ovarian cancer cell lines.
- Over-expression of anti-apoptotic genes: BCL2L1 (BCL-XL), BCL2 and BCL2L2 (BCL-W) increases sensitivity to BH3-mimetics (ABT-737 and Navitoclax) and may be used as a potential biomarker of sensitivity to these drugs.

Presentation slides can be found here.

4.3 DPYD Genotype-guided Personalised Fluoropyrimidine Dosing

Cassandra White (Medical Oncologist) provided an update on the GENESCREEN 5-FU study.

Fluoropyrimidine chemotherapy is commonly prescribed across a range of tumour streams and can produce severe toxicities, placing a burden on patients and hospital resources. Up to 70% of severe toxicity can be explained by DPD (dihydropyrimidine dehydrogenase) deficiency, the critical enzyme for metabolism. DPYD, of which there are many variants, is the underlying gene responsible for DPD expression. Patients who carry a DPYD variant that causes a functional effect can be prescribed a reduced fluoropyrimidine dose that allows them to safely have chemotherapy with less toxicity.

Currently we predict clinical toxicity through a combination of DPD phenotyping and DYPD genotyping; the correlation of tests is quite variable and requires ongoing improvement. Barriers at the moment to upfront testing are limited facilities, poor turnaround time, and out of pocket expense to patients. France, the UK and the Netherlands have commenced routine upfront pre-treatment screening which has shown improvement in patient safety and likely cost effectiveness, and several working groups recommend upfront screening.

Recruitment started in in February 2021 for the GENESCREEN 5-FU feasibility study, with an aim to recruit 50 patients. The primary aim of the study is to establish the feasibility of genotype testing within the Hunter New England LHD, with the aim of a turnaround test of 7 days. Any patient receiving fluoropyrimidine chemotherapy is eligible, and their blood samples are taken at the same time as pre-treatment blood collection. Results are processed locally, and decisions regarding chemotherapy dosing are made at clinician discretion.

The study also incorporates implementation science endpoints to be analysed from stakeholder and patient questionnaires, to understand the barriers and enablers to the implementation and utilisation of a genotype testing service, the results of which will be incorporated into the development of a larger scale interstate program.

The longer-term plan is a larger scale inter-state program, which will be the first oncology-based pharmacogenomics study in Australia. The primary goal is to offer a pre-treatment screening service to any patient in Australia who will have fluoropyrimidines chemotherapy,

with the view to improve patient experience by improving safety, and improve, cost effectiveness within the health care system. Whilst the primary partnership is with PMCC the study is looking to identify additional sites for collaboration. The plan is to recruit 1000 patients using testing facilities across at least two states.

4.4 Molecular colonoscopy

Alex Dobrovic (Head, Translational Genomics and Epigenomics Lab, University of Melbourne) presented an update on a molecular colonoscopy proposal, which is being worked on by a team at the Austin Hospital, including gastroenterologists, hepatobiliary surgeons, and scientists.

As background, there are commonly long waitlists for colonoscopy at most Australian public health services, which, particularly if you have a later stage disease with a delayed diagnosis, can have severe consequences. Although there is a triage system already in place to identify the more urgent cases, molecular testing can make this triage more accurate based on screening plasma using a panel of DNA methylation markers, to reduce the harm from the burgeoning colonoscopy waitlists.

There has been a reluctance in the willingness of patients to participate in both Australia and Europe, with patients more likely to participate with a blood withdrawal rather than submit a faecal sample. This process leverages circulating tumour DNA, used to detect occult disease. Another way to identify markers is to use a toolbox of DNA methylation markers; they are more frequent in colorectal cancer than individual mutations.

The team have embarked on a current proof of principle study, having received a grant from the University of Melbourne. Blood is taken at the time the patient presents for colonoscopy; cell-free plasma is immediately prepared and the DNA isolated and tested for the presence of colorectal cancer-specific DNA markers. Sensitivity and specificity is then compared with cancer-specific DNA methylation marker-based digital PCR assays, and the study is also adding the BRAF V6000E molecular marker.

Point of discussion include:

- Strategy to move in to an interventional study, once sufficient specificity and sensitives have been established (it will be a minor intervention of fast-tacking some patients for a colonoscopy)
- Statistical design
- Appropriate funding mechanism
- Appropriate collaborators

Technique would likely be of interest to multiple CTGs (a detection study that is most appropriate for high risk populations).

Workshop evaluation

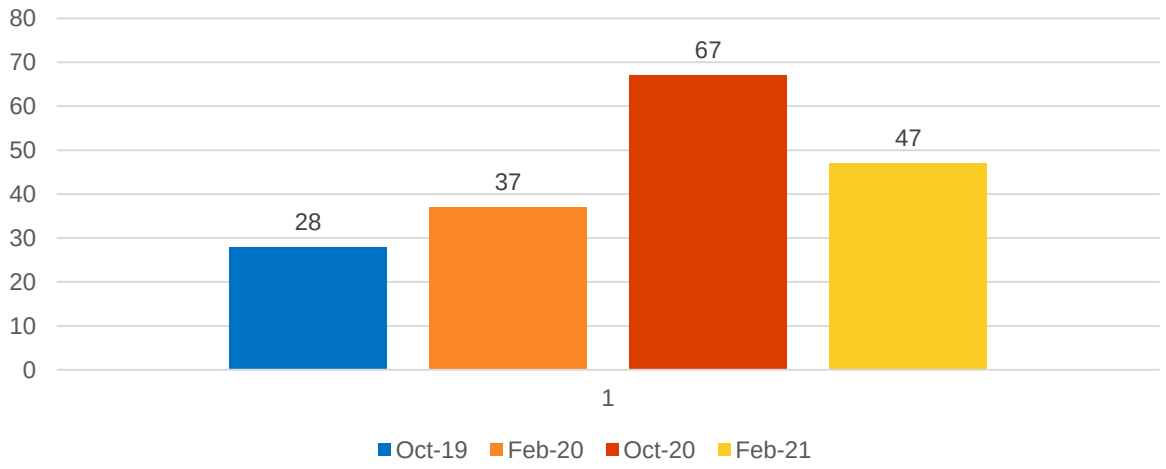
Introduction

The GCCTI is committed to continuous quality improvement and values workshop participants' feedback to help identify opportunities to improve future workshops. Workshop participants completed an online survey to provide feedback.

Participation and survey response rate

47 participants attended the GCCTI February 2021 workshop.

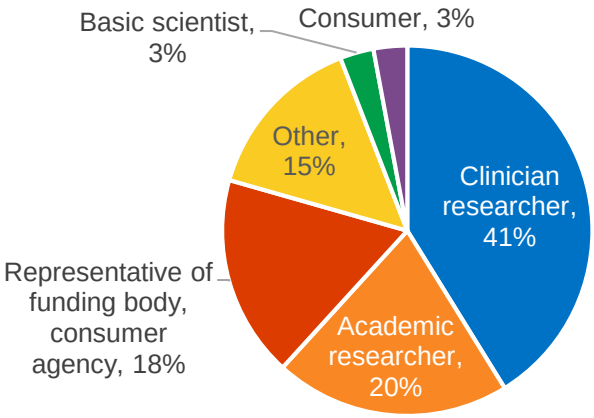
Figure 1: Number of participants at GCCTI workshops (frequency)



25 of the 47 participants who attended the workshop completed the survey (a 53% response rate), a decrease in the response rate from the previous workshop, which was 66%.

The majority of survey respondents identified as clinicians (41%), followed by academic researchers (20%).

Figure 2: Participant roles (frequency and proportion)



Organisations/groups in attendance

Participants from organisations/groups across Australia attended, including one international participant.

- Austin Health
- Binzhou Medical University, Shandong, China
- Cancer Australia
- Commonwealth Department of Health
- Garvan Institute of Medical Research
- Hunter Cancer Research Alliance (HCRA)
- ISLHD Cancer Care Services
- Kinghorn Cancer Centre
- Luminesce Alliance
- Monash University
- NHMRC Clinical Trials Centre
- Peter MacCallum Cancer Centre
- St Vincent's Hospital
- The University of Sydney
- Walter and Eliza Hall Institute of Medical Research (WEHI)
- Western Sydney Area Health Service
- Westmead Institute for Medical Research (WIMR)
- Cooperative Clinical Trials Groups (CTGs)
    1. AGITG
    2. ALLG
    3. ANZGOG
    4. ANZSA
    5. ANZUP
    6. COGNO
    7. MASC
    8. PaCCSC & CST
    9. PoCoG
    10. TOGA
    11. TROG
    12. ANZCHOG
    13. BCT

Understanding the workshop's aim and purpose

91% of respondents indicated that they had a clear understanding of the aims and purpose of the workshop

58% of respondents ‘agreed’, and 33% of respondents ‘strongly agreed’. 9% of respondents were ‘undecided’. One respondent noted:

"Both preliminary information and reminder during the introduction of the workshop made purpose and goals of the workshop very clear"

"I am happy I spent a wonderful half-day on this workshop, and I believe more and more young researchers like me will be attracted when they get to be involved"

Usefulness and relevance of the presentations

84% of respondents indicated that they found the content of the workshop presentations useful and relevant.

64% of respondents ‘agreed’, and 20% of respondents ‘strongly agreed’. One respondent noted:

"This workshop not only covered the consideration of grant application and changes or rules of this year, but also brought a new concept for the clinical research"

Organisation of workshop

All respondents (100%) indicated that the workshop was well organised

48% of respondents ‘agreed’, and 52% of respondents ‘strongly agreed’. One respondent noted:

“A well planned and executed zoom meeting”

"Some of speakers' slides or plan were supplied beforehand which is easier for me to understand and think about the questions before the workshop starts"

Topics/aspects most interesting/useful

Participants were asked to comment on which workshop topics and aspects they found most interesting. Participants found all elements of the workshop interesting and useful, including:

- Updates on current grant opportunities and recent changes
- Mock grant review and peer feedback
- Current and imminent genomic studies
- Discussion of research proposals, new trial ideas and concepts in development
- Opportunities to interact across disciplines

On respondent noted:

"A fabulous collection of great thinkers who have ideas that will change cancer practice"

Additional comments/suggestions to enhance future workshops

Participants were asked for suggestions to further improve workshops; the following suggestions were provided:

- A mix of face-to-face and virtual workshops
- Additional time allocated for discussion after each presentation
- Increase the number of stories of successful grants and how funding was achieved
- Increased emphasis on clinical and scientific topics

Genomic Cancer Clinical Trials Initiative

Appendix – Workshop agenda

Location Virtual Workshop via Zoom

Date/Time Friday 26 February 2021, 9.00am – 3.15pm

Purpose The February workshop will focus on strengthening grant submissions for the upcoming 2021 rounds, as well as generating ideas for grants to submit beyond 2021.

Time	Session:	Presenter
9:15–9:30am	**Welcome and introductions**	*Martin Stockler*
	Overview of GCCTI and achievements to date	*Martin Stockler*
9:30–10.15am	**2021 Grants and Other News**	
	Update on NHMRC Grants Programs	*Julie Glover*
	Update on MRFF Grants Programs	*Stephanie Lehoczky*
	Update on Cancer Australia Grants	*Paul Jackson*
	POCOG's perspective on psycho-social questions in genomic studies	*Haryana Dhillon*
10:15am–10:30am	*Morning Tea*	
10:30am–12:30pm	**Mock grant review and peer input for 2021 submissions**	*Group Discussion*
	Attendees present 2021 grants proposals to receive feedback from expert peers, according to the standard NHMRC processes. *proposed grants should be those for submission in 2021, but need not be eligible for GCCTI support.*	
	Rank-ligand blockade and immune checkpoint inhibition	*Angelina Tjokrowidjaja*
	Stereotactic radiation as consolidation following immunotherapy	*Eric Hau*
12:30–1:15pm	*Lunch*	
1:15–2:00pm	**Update on current and imminent studies of genomic profiling to guide cancer treatment and trials**	
	LUMOS	*Hui Gan*
	TOPOGRAPH	*Frank Lin*
2:00–3:00pm	**Ideas for grants to submit beyond 2021**	*Group Discussion*
	Especially those including multiple tumour types and multiple CTGs	
	REZOLVE3R	*Katrin Sjoquist*
	BCL-XL in mesothelioma	*Tom John/ Cristina Mapagu*
	DPYD Genotype-guided Personalised Fluoropyrimidine Dosing	*Cass White*
	Molecular Colonoscopy	*Alex Dobrovic*
3:00–3:15pm	**Wrap-up and close**	*Martin Stockler*