Introduction, Goals and Background

A. Introduction

We know each cancer is different, yet we treat them much the same. Many cancer treatments and treatment strategies in routine clinical practice have limited evidence of effectiveness or cost-benefit, especially for those with less common cancer types. A major challenge is that we do not have the information to know ahead of time which treatments will work and which will not. This means that frequently clinicians either overtreat or undertreat cancers, or there is no meaningful treatment at all. This results in significant variation in care across healthcare systems and unsustainable growth in healthcare expenditure as populations age and cancer risk is increased.

This is important as cancer incidence and deaths are rising worldwide as a result of the growth and aging of the human population. There were 17 million new cases of cancer (all cancers combined excluding non-melanoma skin cancer) worldwide in 2018 and it is predicted there will be 27.5 million new cancer cases worldwide each year by 2040; an increase of 61.7% from 2018, if recent trends in incidence of major cancers and population growth continue globally.[1]

The ability to rapidly generate massive ‘omics datasets, at an ever-decreasing cost, has driven a new era in the world of medicine which promises to optimally manage disease, leading to improvements in outcome and efficiency. Whilst efforts over the last decade have mapped the genomic alterations that characterise many cancer types, the time has come to translate this knowledge and approaches to improve outcomes for people affected by cancer. The next phase of the International Cancer Genome Consortium (ICGC); Accelerating Research in Genomic Oncology (ARGO), has been designed with patients at the centre of the mission; aspiring to better address the questions every cancer patient deserves an answer to, such as ‘which treatment may be most effective for me and what might be the likely outcome’?

Numerous platforms for various cancer types have already been established, and more are emerging to address these vital questions in many countries around the world. Whilst these build on our knowledge base, there are currently no mechanisms to standardise the complex analyses that are being used, or the mechanisms for efficient data sharing that will enable composite and pooled analyses of accumulated granular data from around the world. Based on the 10-year ICGC experience and resultant infrastructure, ARGO stands poised to accelerate cancer research for the international community through its established infrastructure, expertise and workflows.

The Era of Precision Medicine

Few scientific fields have witnessed the level of dramatic advancement that has occurred in genomics. The last decade has seen rapid progress from individual gene sequencing to highly parallel whole exome and genome sequencing supported by enhanced computational infrastructure and innovative analytical algorithms. These advances have created unprecedented opportunities to characterise the molecular attributes of disease. Interpreting the accumulating data and generating robust and impactful insights has become the focus of research and investment in many fields. This strategy underpins a transition towards what is variably termed personalised, individualised, stratified or precision medicine. However, rather than this approach being a 'Revolution', it is simply the natural 'Evolution' of healthcare, where an enhanced understanding of the fundamental basis of disease, as it always has, informs the way we research, diagnose and treat. Central is the use of molecular pathology to complement clinical and morphological data that characterise the patient and their disease in greater and greater detail. This, in turn, informs the development and application of selective approaches to prevention, diagnosis and treatment.

In oncology, genome sequencing has revealed a subset of cancer-associated aberrations called 'driver' mutations. Accumulating experimental data demonstrates that these are responsible for many of the properties that transform normal cells to cancer. The 'Hallmarks of Cancer' include uncontrolled growth, metastasis, evasion of apoptosis, angiogenesis, and the ability to escape immune surveillance; many mutations result in the acquisition of these attributes. The identification of these aberrations has already defined cancer vulnerabilities and new drugs and diagnostic tests that guide treatment, based on an individual patients' inherent characteristics and their cancer's molecular attributes, has shown great promise in many cancer types.

Although the rate of scientific discovery in the 'omics era has opened the door to exciting new possibilities, much work is needed before these can be implemented in existing healthcare delivery systems. Healthcare systems need to develop the processes, policies and computational capacity to handle the generation and interpretation of 'omics data. More importantly, most current clinical approaches are limited to detect discrete genomic aberrations in a small number of genes (which is usually less than 0.01% of the genome), rather than providing a broad view of the oncogenic events in the context of the clinical attributes of an individual patient. We need to move beyond these narrow approaches to generate clinically meaningful insights into cancer, and to pioneer the application of these more advanced methodologies into the clinic.

B. ARGO Goals

ICGC-ARGO will analyse specimens from cancer patients with high quality clinical data to address outstanding questions that are vital to our quest to defeat cancer. ICGC-ARGO will use key clinical questions and patient clinical data to drive the interrogation of cancer genomes and bring experts together to translate this knowledge in a way that beneficially impacts patients.

Over the next ten years ICGC-ARGO aims to deliver a million patient-years of precision oncology knowledge to the world.

To achieve this ICGC ARGO will:

1. Coordinate the integration of genomic and phenotypic data on 200,000 cancer patients enrolled in clinical trials or from well annotated cohorts within research programs around the world
2. Use this detailed clinical and genomic data to address key clinical and biological questions of relevance to specific cancer types
3. Make the data available to the entire research community in a rapid and responsible way, to accelerate research into the causes and control of cancer

ICGC ARGO Data Sets will have the following features:

- **Robustness**, whole genome sequences, or an equivalent assay when WGS is not feasible, and parallel whole transcriptomic sequencing
- **Comprehensive annotation**, with clinical data describing lifestyle, co-morbidity, diagnostics, toxicity and response to therapy and survival
- **High quality**, using common quality standards for pathology and technology
- **Harmonisation**, using central analysis and pipelines through regional data processing centres
- **Based on control data**, generated from matched non-tumor tissue, to distinguish somatic aberrations from inherited sequence variants where practical
- **Longitudinal**, including longitudinal data along each patient journey

The ARGO project will aim to address the following specific questions:

1. How do we use current treatments better?

a. Refine current treatment selection for standard of care therapies; identifying which treatment will work and which will not for an individual ahead of time

2. How does a cancer change with time and treatment?
    a. Understand treatment induced tumour evolution, how treatments affect cancer and their genetic makeup after treatment
    b. Define early the prognosis of an individual cancer to minimise over and undertreatment
3. How do we practically implement these approaches in healthcare and drug development?
    a. Accelerate the creation of a global learning healthcare system; the continuous generation and implementation of knowledge from molecular oncology 'embedded' within healthcare delivery through electronic medical records
4. How do we advance early detection and ultimately prevent cancer?
    a. Improve determinants of a person's individual risk for developing cancer based on their genetic predisposition and their environmental and lifestyle exposure
    b. Develop metrics that distinguish and better characterize germline therapeutically actionable variants in the context of the tumour

The project size and scope will enable an understanding of the regional differences in disease around the world, the heterogeneity of cancer, the diversity of environmental risk factors, as well as describing new cancers with a common genomic background, and common outcomes; and the many different combinations of therapeutic interventions.

C. Background to ARGO

The International Cancer Genome Consortium (ICGC)
The ICGC has evolved significantly since its inception in 2007.[2] Over the past decade, ICGC has established itself as an effective and efficient organization, managed by a Secretariat previously located at the Ontario Institute for Cancer Research (OICR) in Toronto, Canada. Under the guidance of the ICGC Executive Committee, the International Steering Committee, and the various ICGC Working Groups, ICGC has addressed emerging issues in ethics, policy, data access, privacy, technology, analysis, data coordination and data management.

At its heart, ICGC is a consortium of experts in genomics and informatics. Its initial project was to define the genomes of 25,000 primary untreated cancers (the 25K initiative) which to date has produced >20,000 tumour genomes for 26 cancer types. The results of the analyses of these data are available through the ICGC data portal (DCC). The ICGC was the first step to broadly and comprehensively map the structural aberrations of genomes and begin to understand the molecular basis of cancer. It was appropriately focused on cancer that had not yet been treated, and on the tumour at its origin (primary cancer). It achieved these goals with over 20,000 primary cancers of many organs already available, and the remainder sequenced and in process for upload and sharing. The ICGC also extended beyond its initial mandate from genomes to also include the transcriptome and epigenome for many cases. Data generated through the ICGC has transformed research strategies in academia and industry alike, with hundreds of seminal works published directly using ICGC data, with landmark articles in the world's elite scientific journals. No therapeutic is developed today without, in some way, applying the knowledge that ICGC has provided the world.

The second ICGC project, the Pan Cancer Analysis of Whole Genomes (PCAWG), began in 2013 and continues to analyse ~3,000 of the highest quality whole cancer genomes of multiple cancer types.[3] In 2015, the ICGC, in response to the realization of the potential of genomics in healthcare, released a position "white paper" on the evolution of ICGC move directly to impacting on human health.[4] Emanating from this ICGC for Medicine (ICGCmed) white paper is ICGC's next project, which aims to Accelerate Research in Genomic Oncology (ARGO). Although the ICGC has achieved much, there is a long way to go. Pivotal outstanding challenges remain to be addressed; unanswered questions remain that are vital in our quest to defeat cancer.

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[1] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018), Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68: 394-424. doi:10.3322/caac.21492.
[2] Hudson TJ, Anderson W, Aretz A, Barker AD, Bell C, Bernabe RR, et al. International network of cancer genome projects. Nature. 2010;464(7291):993-8.
[3] See https://docs.icgc.org/pcawg.
[4] The Case for the International Cancer Genome Consortium for Medicine. 2016. Available at: https://icgcmed.org/files/ICGCmed_White_Paper_April_2016.pdf.