



International
Cancer Genome
Consortium
for Medicine

The Case for the International Cancer Genome Consortium for Medicine



Goals of ICGCmed

THE GENOMICS REVOLUTION

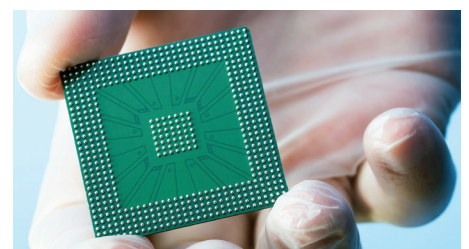
Few research fields have witnessed the dramatic advances experienced in genomics during the last 20 years. In the last decade alone, there has been a rapid progression from targeted gene sequencing using PCR and Sanger methods to highly parallel targeted, whole transcriptome, or whole genome sequencing platforms, supported by innovative bioinformatics algorithms for data analysis. In addition to DNA sequencing, new technologies have produced data characterizing gene expression, genome methylation, histone packaging, regulation of transcription, and other regulatory protein binding positions, enabling the construction of data sets of unprecedented size and complexity. The ability to rapidly generate massive 'omics datasets, at an ever decreasing cost, has driven the development of sophisticated data storage and analysis systems and ushered in a new era in the world of medicine.

THE ERA OF PRECISION MEDICINE

Making sense of the accumulating data has become the focus of research and investment in many fields and underpins the growing trend towards precision medicine. Precision medicine uses molecular profiling, and other patient specific data, to inform the development of targeted approaches to the prevention, diagnosis and treatment of disease, based on the specific profiles of both the individual and their disease. In oncology, genome sequencing has revealed a subset of cancer-associated mutations called "driver" mutations that are responsible for many of the properties that transform normal cells into malignant ones, such as uncontrolled growth, metastasis, evasion of apoptosis, and angiogenesis, and also contribute to the ability of tumours to escape immune surveillance. The identification of these driver mutations has already shown great promise in the development of new drug targets and diagnostic tests for the delivery of tailored treatments for individual patients.

Although the rate of scientific discovery in the 'omics era has opened the door to exciting new possibilities in the prevention and treatment of cancer, much work is needed before these possibilities can be implemented in existing infrastructures and healthcare systems. Healthcare systems need to develop the pipelines, policies and computational capacity to handle the generation and interpretation of 'omics data. More importantly, the current approaches taken are limited to sequencing gene panels to identify mutations, rather than providing a broad view of the oncogenic events in the context of the clinical setting and non-genomic characteristics of the individual patient.

The Human Genome Project, completed in 2003, required hundreds of sequencing machines, took over a decade, and cost about \$3.5 billion. Today, it is possible to fit the genome of one person onto a computer chip the size of the palm of a hand, and to complete the sequencing in 2-3 days for just a few thousand dollars.



The success of a precision medicine approach depends not only on the availability of high quality genetic and other molecular data, combined with effective therapies, but also on the availability of data on large, well-annotated population cohorts that include biological samples and clinical information linked to accessible administrative databases.

Improved knowledge in this area will benefit patients as well as healthcare providers and payers. This high quality data will address the currently insufficient information linking tumour genome, transcriptome and methylome profiles with clinical outcomes, such as response or resistance to new but expensive targeted therapies.

Many countries are preparing for the implementation of precision medicine across their healthcare systems and a number of national initiatives have recently been launched, including:

- France's National Cancer Plan, which includes a goal of sequencing 50,000 exomes a year for clinical medicine;
- Genomics England, which aims to sequence 100,000 whole genomes by 2017; and
- the U.S.' Precision Medicine Initiative, which includes plans to assemble a cohort of one million Americans to study the genetic and environmental causes of many diseases, including cancer, as well as plans to expand the National Cancer Institute's work on precision medicine in oncology.

The goal of this White Paper is to explain how the research achievements of the ICGC can be linked to clinical data to accelerate the development and implementation of effective cancer control measures and treatments.

THE INTERNATIONAL CANCER GENOME CONSORTIUM FOR MEDICINE (ICGCmed)

Our growing understanding of the biology of cancer combined with revolutionary new treatment approaches has brought us to an 'inflection point' where years of data, expertise, and technology can now come together to transform cancer prevention and treatment. Cancer genomics – the analysis of the genetic makeup of tumours – has emerged as a powerful tool for understanding the molecular basis of the disease and informing the discovery of innovative cancer therapies that specifically target tumour vulnerabilities, predict toxicities and more recently, predict response to immunotherapies that harness the patient's natural defense system to fight off cancer. By combining the data and ingenuity of clinicians and scientists from around the world, and the selfless contribution of patients worldwide to allow access to their disease history and biology, there is a genuine opportunity to accelerate the pace of progress towards effective cancer control.

Within the context of powerful genome sequencing technologies, and in anticipation of the new era of precision medicine, ICGCmed will link the wealth of genomic data already amassed, as well as new genomic data being generated, to clinical and health information. This will include linkages to lifestyle, patient history, cancer diagnostic data, and response to and survival following therapies, across the cancer continuum from pre-neoplastic lesions to metastases. Using this large-scale integrated data, researchers, scientists, policymakers and clinicians will be able to work with patients, health care providers and others to develop preventative strategies, markers for early detection of disease, more specific criteria and methods for diagnoses and prognoses, and interventions based on matching the patient's disease molecular subtype with the most effective combinations of therapies.

As a worldwide consortium, ICGCmed has the research and organizational expertise to implement the ambitious project of analyzing the genomes of more than 200,000 patients by the end of 2025 and linking this data to high-quality clinical information including treatment information and outcomes. ICGCmed will investigate all samples by extensive sequencing for mutation detection (by exome and/or whole genome sequencing), and undergo analysis of copy number alterations and rearrangements. Transcriptome and methylation analyses will be conducted when reliable. 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. By pooling large numbers of samples together with clinical information, such as medical history and response to and outcome of therapy, the consortium approach proposed by ICGCmed will provide the statistical power necessary to enable researchers to achieve a number of goals, and subsequent adoption of evidence-informed health care services and policies. ICGCmed will enable us to:

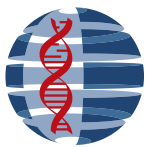
- understand why individual patients respond differently to therapies (chemo-, radiation, targeted and immune therapies) and have different adverse events, as well as enabling us to characterize these differences in various populations around the world;
- understand the link between cancer genomics and tumour microenvironment, including immunological response or tolerance;
- provide relevant information to patients on the best treatments based on their efficiency in the same genomic context;
- understand the relevance and potential clinical impact of tumour genomic heterogeneity before and during treatment in the identification and interpretation of emerging resistance mechanisms to all types of therapies;
- describe and analyze the links between cancer genomes, cancer biology and disease characteristics;
- develop more comprehensive molecular portraits using RNA sequencing;
- develop new technologies and standards to support pan-cancer analyses;
- enable and support new drug discovery programs;
- share technology and international benchmarking exercises to improve analyses and reproducibility of experimental data;
- identify particular mutation signatures linking prior exposures to cancer onset;
- improve algorithms for the prioritization of molecular therapy targets based on genetic findings, available drugs, clinical response; and
- actively contribute to primary and secondary prevention.

ICGCmed's systematic effort to evaluate cancer genomes linked with clinical information will ultimately lead to more effective prevention strategies, better and faster access to therapies that are safer and more effective than current options, and improved outcomes. For patients and their families, this represents hope and a path forward.



As a worldwide consortium, with an ambitious goal of analyzing the genomes of more than 200,000 patients by the end of 2025 and linking this data to high-quality clinical information including treatment information and outcomes.

The International Cancer Genome Consortium (ICGC)



**International
Cancer Genome
Consortium**

ICGC has evolved into an effective and efficient organization, managed by a Secretariat located at the Ontario Institute for Cancer Research (OICR) in Toronto, Canada.

T **O APPRECIATE THE POTENTIAL** of ICGCmed, the foundational contributions of the International Cancer Genome Consortium (ICGC), on which ICGCmed is founded, provide insight and understanding. Launched in 2008, ICGC has been an international global community effort that has provided important insights into the causes and biology of cancer, paving the way for the next international undertaking – applying the information gained in “real time” to reduce the burden of cancer worldwide. ICGCmed aims to deliver on this promise.

The International Cancer Genome Consortium was launched as one of the most ambitious biomedical research endeavours since the Human Genome Project. Designed to coordinate efforts towards elucidating the genomic changes present in cancers of clinical and societal importance across the globe, ICGC rapidly became a collaborative initiative of unprecedented international scope. The initial ICGC objectives were to:

- sequence the tumour genomes of 25,000 patients around the world by 2018;
- help reduce the global burden of cancer by increasing the knowledge of cancer mutations;
- provide standardization across studies to enable data merging and comparison of data sets;
- reduce duplication of effort; and
- accelerate the dissemination and uptake of genomics data by end-user groups to benefit the patients

ICGC ORGANIZATIONAL STRENGTHS

Over the past eight years, ICGC has evolved into an effective and efficient organization, managed by a Secretariat located at the Ontario Institute for Cancer Research (OICR) in Toronto, Canada. The Secretariat provides essential support for a number of core infrastructures, committees and working groups, including: the ICGC Executive Committee; the International Scientific Steering Committee and its International Committees/Working Groups/Subgroups; the Pan-Cancer Analysis of Whole Genomes Steering Committee and its Scientific/Technical Working Groups; and ICGCmed Scientific Planning Committee and its Working Groups/Subgroups. Under the guidance of the ICGC Executive Committee and International Steering Committee, these Working Groups have evolved to address emerging issues arising in ethics, policy, data access, privacy, technology, analysis, and data coordination and management. During the transition from ICGC to ICGCmed, the core ICGC infrastructure and the existing committees, working groups and sub-groups will further adapt to meet the changing needs of the consortium in its new role.

ICGC member countries are committed to making the data they collect broadly available to researchers around the world as quickly as possible, with minimal restrictions, in order to accelerate research on the causes and control of cancer. Data from participating ICGC projects are submitted to the ICGC Data Coordination Centre (DCC) at OICR and accessed through the ICGC Data Portal. The ICGC Data Portal contains annotated data that displays mutations belonging to a certain gene and their location within that gene, as well as linking to known functional information about the gene, and clinical and pathology information specific to cancer patients with such mutations.

Patient/individual data protection is an ICGC priority to minimize the risk of identification, the ICGC has established the policy that datasets be organized into two categories, Open and Controlled-Access. The first category, Open Access Datasets, is available without restrictions. Controlled Access Datasets that contain more sensitive data types and are only available to scientists and institutions with formal authorization by the Data Access Compliance Office (DACO).

To facilitate data access around the globe, ICGC has adopted cloud-based solutions to enable users to perform compute-intensive analyses. Initiatives such as ICGC in the cloud involve non-commercial (the Cancer Genome Collaboratory managed by OICR and the University of Chicago) as well as commercial solutions.

ICGC PROJECTS TO DATE

As of April 2016, the ICGC had received commitments from funding agencies in Asia, Australia, Europe, North America and South America, supporting 88 projects in 17 jurisdictions (16 countries and the European Union), to study over 25,000 tumour genomes in 26 different tumour types (See Table 1). The genomic analyses of these tumours are now available through the DCC via the ICGC website: www.icgc.org.

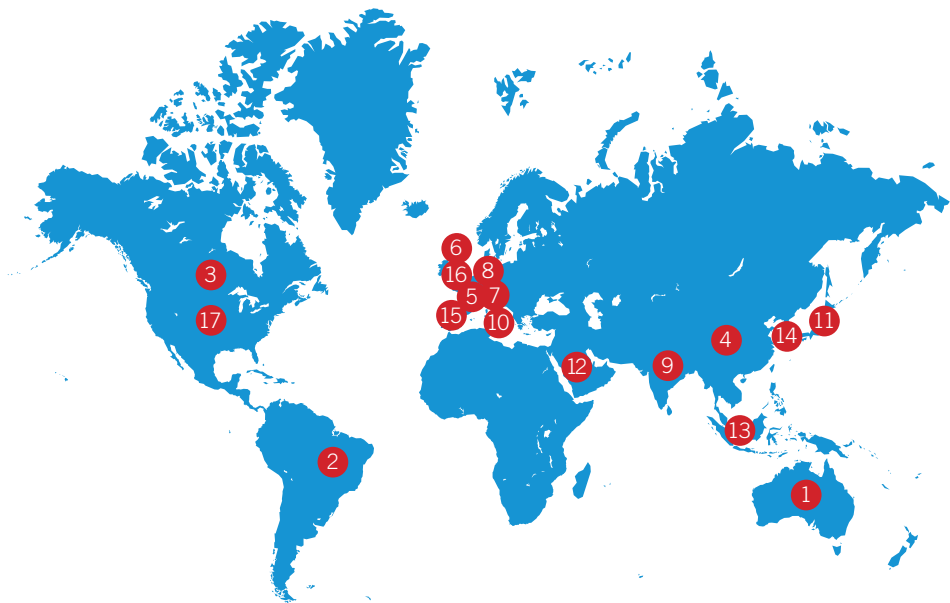


TABLE 1 CANCERS UNDER STUDY BY ICGC MEMBERS	
1.	Australia – ovary, pancreas
2.	Brazil – skin
3.	Canada – pancreas, pediatric brain, prostate
4.	China – brain, esophagus, kidney, lung, stomach, urinary bladder
5.	EU/France – kidney
6.	EU/UK – breast
7.	France – bone/soft tissue, breast, eye, liver
8.	Germany – blood, brain, prostate
9.	India – mouth
10.	Italy – pancreas (neuro endocrine)
11.	Japan – biliary tract, liver, stomach
12.	Saudi Arabia – thyroid
13.	Singapore – biliary tract, blood
14.	South Korea – blood, lung
15.	Spain – blood
16.	UK – blood, bone, breast, esophagus, lung, prostate, skin
17.	USA – adrenal gland, blood, brain, breast, cervix, colon, connective tissues, esophagus, eye, head and neck, kidney, liver, lung, ovary, pancreas, prostate, rectum, stomach, skin, testicle, thyroid, urinary bladder, uterus

ICGC projects cover all major adult tumour types, as well as 18 pediatric tumours. The 2015 Data Release 20 included molecular data for 14,767 tumours generated by 66 ICGC cancer project teams. ICGC is well on its way towards meeting its primary objective of sequencing the tumour genomes of 25,000 patients around the world by 2018, and identifying the major genomic abnormalities including somatic mutations, abnormal expression of genes, and epigenetic modifications in at least 500 tumours and matched normal tissue for each of 50 different tumour types and/or subtypes. ICGC studies to date have made a number of important scientific discoveries, including: uncovering novel tumour signatures; revealing oncogenic processes; identifying driver mutations and their pathways; supporting the analysis of the integration of epigenomes and genomes; and determining the impact of germline alterations, cancer-causing pathogens, and mutations in regulatory regions.

ICGC ACHIEVEMENTS AND OUTCOMES



ICGC owes its success to an unprecedented degree of international collaboration among dozens of teams.

ICGC owes its success to an unprecedented degree of international collaboration among dozens of teams comprising outstanding oncologists, pathologists, geneticists, biologists, bioinformaticians, mathematicians and others. The ICGC has provided a forum for communication, collaboration and coordination, maximizing efficiency among scientists and health practitioners working to understand, prevent and treat cancers. ICGC projects have guided the development of improved strategies for early detection and precision diagnostics for improved clinical interventions.

Over the last eight years, ICGC has worked to bring national and cross-jurisdictional member projects together under a common set of policy frameworks, while allowing for national differences and health priorities. Acknowledging these differences and determining where collaborative work is possible has allowed ICGC to provide guidance and agree on procedures to advance its aims, as opposed to making mandatory rulings that might have conflicted with national regulations. Importantly, such an approach ensures that the cultural norms of ICGC member countries are respected. Examples of some of the many ICGC clinical findings are described in Table 2.

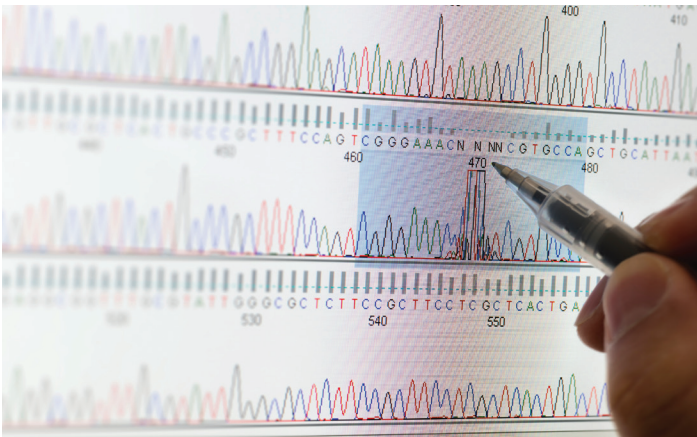
TABLE 2
EXAMPLES OF CLINICAL AND RESEARCH FINDINGS ENABLED BY ICGC

- | |
|---|
| 1. ICGC projects have uncovered driver mutations for many forms of pediatric and adult cancer, paving the way for the development of targeted therapies. |
| 2. Mutation profiles and other genomic signatures have been used to define specific molecular subtypes of tumours that correlate with prognosis and response (or resistance) to therapies, providing clearer information to guide treatment decisions. |
| 3. Using whole genomic sequencing, scientists demonstrated the profound effect that chronic viral infections and inflammation can have on the genetic mutations found in tumours, paving the way to a better understanding of the mechanisms through which chronic infections can lead to cancer. |
| 4. ICGC researchers developed genetic tests to identify more indolent forms of cancers that may only require local surgery from more aggressive tumours that need additional treatment (chemotherapy, radiation and hormone therapy). |

TABLE 2
EXAMPLES OF CLINICAL AND RESEARCH FINDINGS ENABLED BY ICGC (CONTINUED)

- 5. The frequency of mutations has been shown to vary across cancer types. High mutation rates are often related to carcinogens such as ultraviolet radiation for melanoma and tobacco smoke for lung cancers.
- 6. Mutational signatures of specific risk factors such as tobacco, alcohol, aging, exposure to viruses and chemicals have been identified using gene sequencing. For example, associations were found between renal cancer incidence and exposure to aristolochic acid – an ingredient in some herbal remedies. This information is being used by public health organizations to improve prevention strategies.
- 7. A benchmarking study revealed a high degree of heterogeneity in how cancer genome sequencing is done at different institutions across the globe. This lays the foundation for creating guidelines and providing new tools for achieving higher quality data and better diagnosis as cancer genomic technologies move into clinical laboratories worldwide.
- 8. ICGC has coordinated joint analyses by large groups of researchers in initiatives such as the Pan Cancer Analysis of Whole Genomes (PCAWG). PCAWG is studying non-coding regions of cancer genomes, using an impressive collection of 2,800 with whole genome sequencing, supplemented by transcriptome and methylome datasets. This project is expected to identify new cancer mechanisms that may be the basis for alternate ways to block the growth and spread of cancer.

ICGC has produced insights into the biology of cancer, as well as many examples of correlates of clinical importance. However, most ICGC projects were built on biobanked historical cancer specimens rather than linked to prospective clinical trials of patient responses to therapies. In general, the ICGC projects were not structured to provide the information needed to guide clinical decision making. ICGCmed will build on the foundations of ICGC and will take ICGC to the next step by linking patients’ genomic data with carefully-gathered environmental, therapeutic response, and other clinical data.



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ICGCmed

ICGCmed GOALS

The purpose of ICGCmed is to ultimately help people diagnosed with cancer. It is important for patients and patient advocates to have a voice in the research. With their participation, we have to develop a means to share specific data (genomic, clinical, therapeutic outcomes) generated by ICGCmed that will return benefits directly to patients.

ICGCmed will build on achievements of the ICGC by linking genomes, transcriptomes and methylomes with clinical and epidemiological data for patient benefit with a more complete understanding of the causes of cancer. As with ICGC, a worldwide consortium for ICGCmed will enable research advances that would be impossible on a local scale. While some cancers are more prevalent in some regions and will be the focus of study in particular countries, all cancers occur in all countries, and an international consortium will help distribute useful knowledge worldwide. ICGCmed will be globally inclusive, with knowledge being generated from cancer patients in Africa, Asia, Europe, South America and North America. International comparisons will highlight important differences between populations, and inform prevention and treatment strategies that will be based on disease characteristics specific to these different populations and environments.



The major goal of ICGCmed is to sequence samples from at least 200,000 cancer patients over the next decade.

The long-term outcomes of ICGCmed will enrich the patient and cancer community's knowledge of how mutations are linked with the environment, disease types and therapeutic outcomes. These insights are key to informing future clinical interpretation and management, identifying novel causes of cancer and helping to develop prevention strategies. As a corollary to this endeavor, the large number of ICGCmed samples will address an important area of need, the study of rarer mutations and the patterns of mutation co-occurrence and mutual exclusivity that shed light on underlying cancer pathways.

The major goal of ICGCmed is to sequence samples from at least 200,000 cancer patients over the next decade. To achieve this goal, the collection of adequate clinical information will be of utmost importance. The following scenarios are envisioned:

- analyses of prospectively collected samples from patients enrolled in new and ongoing clinical trials (Phases I-III) that are investigator-initiated or industry-sponsored;
- analyses of banked samples from existing clinical trials;
- analyses of samples from research participants enrolled in population-based cohorts and other epidemiological studies;
- analyses of samples from donors recruited at clinical research centers for investigations of unusual clinical response; and
- analyses of samples from specific cohorts collected to study the clinical impact of topographic, subclonal heterogeneity and other characteristics of neoplasms.

ICGCmed IMPLEMENTATION

In moving from cancer mutation catalogues to clinical application, ICGCmed will benefit from the contribution and cooperation of patient advocates, health care providers, clinical trial networks, pathology laboratories, population and disease cohorts, as well as the pharmaceutical and information technology industries. ICGCmed will benefit from working with initiatives such as the Global Alliance for Genomics and Health (GA4GH). As with the ICGC, clinicians and researchers involved in ICGCmed must agree to share data internationally, according to international standards, local regulations and cultural norms.

ICGCmed will prioritize patients' data and will engage in ongoing critical discussions exploring how patient-specific genomic data can be used effectively to inform prevention, diagnosis and therapeutics, while protecting the directions and expectations of patients about their data and their use. Clinical studies show that individual genomic data can be used effectively both in the research and treatment settings. The Ethics and Governance Committee of ICGCmed will examine how the traditional doctor-patient relationship can be transferred into the setting of a multi-national research consortium. The ICGCmed Communications Committee will involve participants and practitioners, creating opportunities for input in evolving topics such as the return of patient-specific data, and will ensure that public communication regarding ICGCmed is suitably disseminated.

Access to comprehensive clinical, environmental and genomics datasets will allow researchers, scientists and clinicians to work with patients, caregivers and others to investigate and develop preventative measures, markers for early detection of disease, and markers for more specific diagnoses and prognoses.

Scientific activity in ICGCmed will initially be organized into four subgroups (see Appendix): Clinical trials methodology subgroup; Molecular pharmacology subgroup; Germline and pharmacogenomics subgroup; Epidemiology and signatures subgroup. Additional subgroups will be formed, as needed.



ICGCmed will address the challenges of optimizing tissue sample quality for 'omics studies, standardization of genomic and analytical methodologies, standardization and quality control of clinical annotations, data management related to the large-scale nature of the genomic data with clinical datasets, functional and clinical interpretation of the findings and overcoming barriers to making genomic, baseline and partial outcome data from clinical trials publically available before the official end of a study.

GA4GH brings together over 400 leading institutions working in healthcare, research, disease advocacy, life science, and information technology. GA4GH partners have created a common framework of harmonized approaches to enable the responsible, voluntary, and secure sharing of genomic and clinical data.

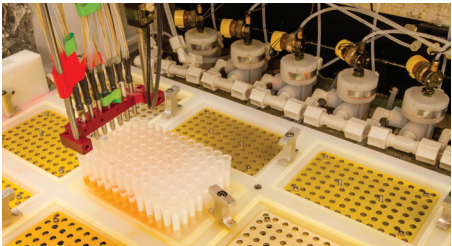
Samples will be drawn from cohorts and clinical trials (see Table 3). Existing and newly-generated genetic information will be linked to personal information, including the patient’s lifestyle, clinical history, and response to treatment. ICGC focused on developing extensive catalogues of molecular information primarily from advanced primary cancers. Building on this work ICGCmed will tackle a range of cancers, including pre-neoplastic lesions, early cancers and metastases, and accelerate the translation of this information into clinical outcomes by guiding prevention, early detection, diagnosis and prognosis, matching each patient’s disease with the most effective therapy.

TABLE 3
POTENTIAL DONOR SOURCES FOR ICGCmed PROJECTS

Patients with exceptional responses, or unexpected resistance to treatments.
Basket clinical trials that match mutation profiles in cancer patients to one or more targeted agents.
Large randomized clinical trials of chemotherapy or other or experimental therapies, including targeted and immune therapies.
Umbrella trials linked to a series of “subsequent” adaptive trials/treatment arms.
Cancer patients selected from epidemiological studies who have distinct underlying risk factors.
Retrospective genomic analysis of patient cohorts with extensive clinical follow up data.

International research consortia, informed patients’ contribution, and open access data sharing are reshaping how we approach genomic research in cancer and how it is governed. ICGCmed will provide guidance to projects that involve sharing of genomic data across international borders. There are tensions between the need for coherence at the international level and the differences in laws, ethical norms, and regulations at the national level.

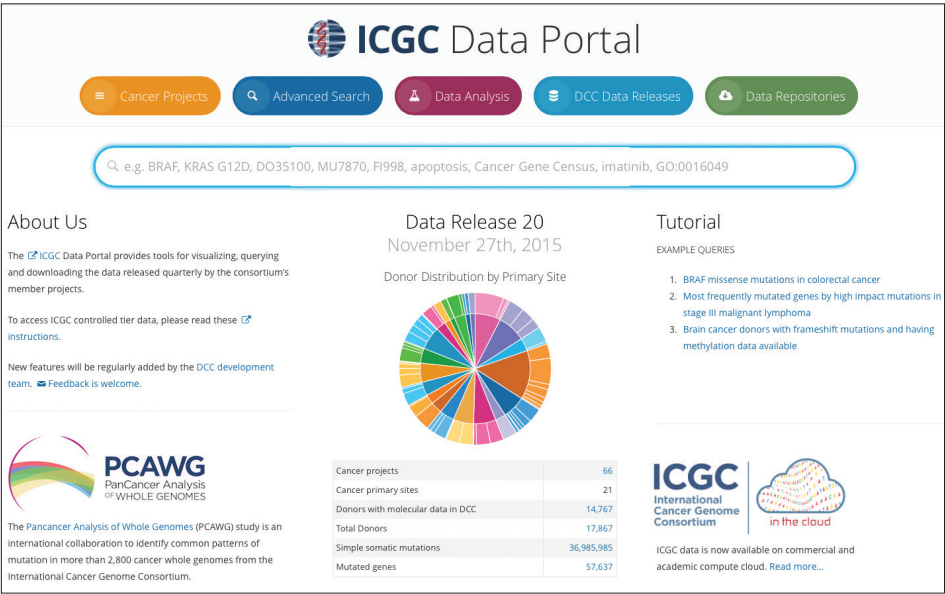
ICGCmed will tackle a broad range of cancers, including pre-neoplastic lesions, early cancers and metastases, and accelerate the translation of this information into clinical outcomes by guiding prevention, early detection, diagnosis and prognosis, matching each patient’s disease with the most effective therapy.



ICGCmed ORGANIZATIONAL STRUCTURE

One huge advantage for ICGCmed is that the core infrastructure has already been developed for ICGC. After eight years, the ICGC Secretariat is well equipped to manage the evolution of ICGC to ICGCmed and has the necessary resources in place to achieve a seamless transition. As was the case for ICGC, the primary coordination groups within ICGCmed will be an Executive Committee (EXEC) comprised of representatives of each of the participating funding agencies and/or organizations, and an International Scientific Steering Committee (ISSC) comprised of the principal investigators leading programs in the ICGC and members of the EXEC. The EXEC and ISSC will be supported by a number of established ICGC committees, which will be adapted to provide ICGCmed guidance on scientific planning and oversight; data management and coordination, including clinical data coordination; ethics and governance; and communications and outreach. Further, the ICGC Data Portal, DCC and DACO, will serve as essential core support structures for ICGCmed.

A detailed description of the context, roles, responsibilities, and activities of the many components of the proposed ICGCmed organizational structure can be found in the Appendix.



The ICGC Data Portal, Data Coordination Centre and Data Access Compliance Office, will serve as essential core support structures for ICGCmed.

ICGCmed LOGISTICS

Funding Requirements

With the anticipated goal of analyzing tumour genomes, clinical history and outcomes from more 200,000 cancer patients over the next decade, ICGCmed’s success will require significant commitments from the international community. ICGCmed will partner with funding agencies (or equivalent organizations) and their designated teams that will support a range of projects of varying sizes that in aggregate will commit to comprehensively analyzing over 4,000 genomes and that agree to carry out their efforts according to a set of commonly agreed-upon policies. Full membership in ICGCmed will require investment of at least USD\$10 million per 5 years, depending on the size and complexity of the studies. Organizations willing to support projects that will study a minimum of 1,000 tumours but less than 4,000 will be considered for Affiliate Status. In addition to the project-specific costs required for patient recruitment, sample collection, clinical and pathological annotation, long-term follow-up of clinical outcomes, genome sequencing and data submission, ICGCmed will require contributions to fund core consortium-wide service centres such as the ICGCmed Secretariat, the DCC and the DACO.

Proposed Timeline

The anticipated timelines in Table 4 have been determined by the ICGC Executive Committee and the International Scientific Steering Committee in consultation with Consortium members, guided by past experience during ICGC. The ultimate goal is to have completed the linkage of at least 200,000 genomes with clinical information by 2025, opening the door to more effective treatment options and/or improved diagnosis.

TABLE 4
ICGCmed TIMELINE

April 2016	ICGCmed White Paper and RFA template to be sent to potential funding agencies.
September 2016	Launch of ICGCmed: RFAs posted and initial funding commitments confirmed.
2016-2020	Open period for RFAs: applications received and reviewed and ICGCmed projects launched.
2018-2025	Data deposition in ICGCmed.
2022	50,000 cancer genomes linked with clinical information on the Data Coordination Centre website.
2025	200,000 cancer genomes linked with clinical information on the Data Coordination Centre website.

With the anticipated goal of analyzing tumour genomes, clinical history and outcomes from more 200,000 cancer patients over the next decade, ICGCmed’s success will require significant commitments from the international community.



CONCLUSION

The launch of ICGCmed presents an opportunity for countries around the world to combine their efforts to reduce the global burden of cancer. Preceded by the eight highly successful years of ICGC, ICGCmed will “hit the ground running”, immediately positioned to build on the existing core infrastructures, policies and guidelines of ICGC. The support structures for ICGC are both extensive and amenable to adaptation to suit the specific needs of ICGCmed, and are underpinned by an unprecedented level of commitment from the clinical and basic research communities, as well as an impressive cadre of international funders.

ICGC has laid the foundations and framework to enable the translation of a wide range of ‘omics data into tangible clinical benefits for cancer patients. In this new era of precision medicine, it is only through initiatives such as ICGCmed that the mountains of genomic data being collected by international projects, such as ICGC, can be applied to generate new paradigms in prevention, diagnosis and treatment. ICGCmed is the next logical step in the progression of international large-scale sequencing efforts and with appropriate governance, will link the wealth of genomic data already amassed to clinical and health information, including lifestyle, patient history, response to therapies and cancer diagnostic data.

ICGCmed provides a unique opportunity for members of the global cancer control community to be part of a coordinated effort to advance their strategies for the implementation of precision medicine in cancer control. Current funders in ICGC are already seeing returns on their investments, and ICGCmed will take these returns to the next level. Both existing and new funders are needed to support this truly transformative initiative to accelerate the translation of cancer genomics into precision oncology for the benefit of cancer patients and health systems worldwide.

ICGCmed will accelerate discovery, improve our understanding of the causes of cancer, inform on better ways to manage cancer patients, improve the cost-effectiveness of cancer control interventions and will foster the development of innovative therapies.



WEBSITES

International Cancer Genome Consortium (ICGC)

<https://icgc.org>

ICGC Data Coordination Center (DCC)

<https://dcc.icgc.org>

Data Access Compliance Office (DACO)

<https://icgc.org/daco>

ICGC in the cloud

<https://dcc.icgc.org/icgc-in-the-cloud>

Cancer Genome Collaboratory

<http://www.cancercollaboratory.org>

Global Alliance for Genomics and Health (GA4GH)

<https://genomicsandhealth.org>

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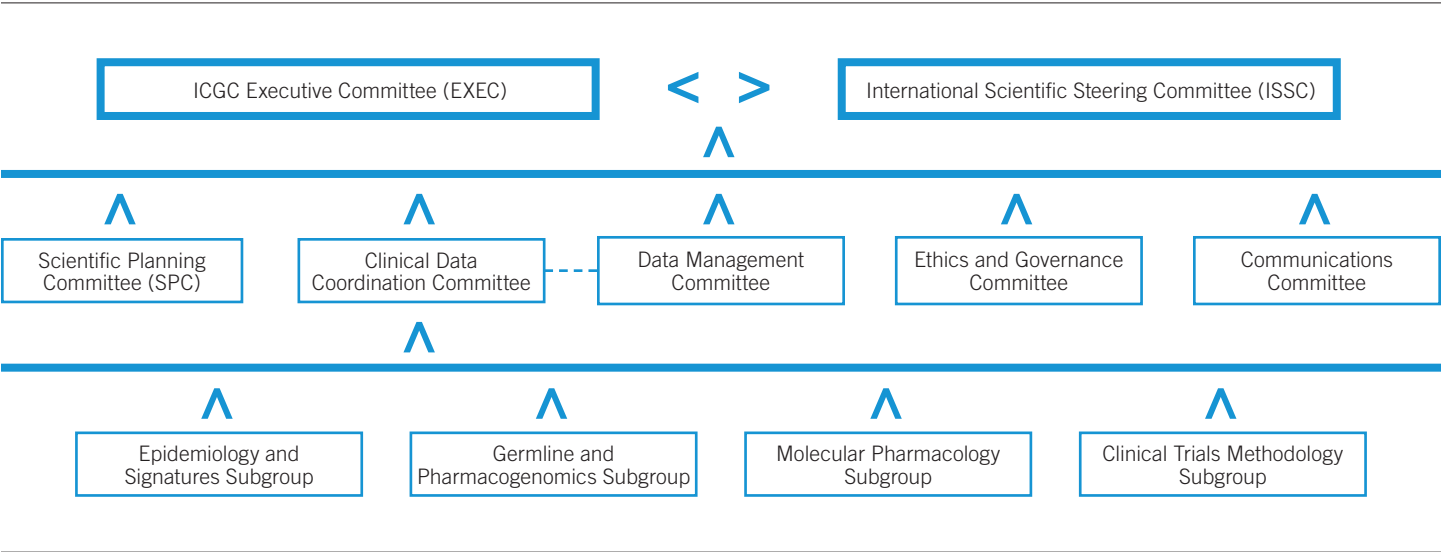
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APPENDIX

ICGCmed ORGANIZATIONAL STRUCTURE AND GUIDELINES

The proposed organizational structure for ICGCmed is based on the successful model developed and modified over the last eight years to support ICGC (Figure 1).

FIGURE 1
PROPOSED ORGANIZATIONAL STRUCTURE FOR ICGCmed



KEY COMMITTEES AND WORKING GROUPS

The committees, working groups and subgroups listed in the organogram above will guide ICGCmed in the following areas:

EXECUTIVE MANAGEMENT

The Executive Committee (EXEC): Initially, the EXEC will be composed of representatives of existing funding agencies participating in the ICGC, which currently include representatives from Australia, Brazil, Canada, China, France, the European Union, Germany, Japan, India, Italy, Saudi Arabia, Singapore, South Korea, Spain, the United Kingdom, and the United States. Other countries with a serious intent to participate are also welcome. Dr. Fabien Calvo (France) was nominated by the ICGC Executive Committee to oversee the set-up of ICGCmed, and is the ICGCmed Scientific Director. As chair of the ICGCmed Scientific Planning Committee (SPC), Fabien Calvo brings recommendations from the SPC to the EXEC to review, amend, and approve policies and guidelines that will enable ICGCmed to both reach its goals and respect local laws and regulations; adopt scientific and operational strategies for the international consortium; and identify new requirements related to ICGCmed coordination structures, including the ICGC Secretariat and the Data Coordination Center currently located at the Ontario Institute for Cancer Research or the Data Access Compliance Office (DACO) at P3G, which is hosted at McGill University.

SCIENTIFIC GUIDANCE AND PLANNING

International Scientific Steering Committee (ISSC): Members of the ISSC are leading scientists in the fields of cancer, genomics, ethics, and bioinformatics research. ISSC includes principal investigators leading programs in ICGCmed and representatives of the EXEC. The ISSC will act as a science coordinating body to evaluate the progress of ICGCmed. It will address issues arising of a scientific nature, including those related to samples, consent, ethics, quality standards, evolving technologies; exchange protocols and standard operating procedures; ISSC will establish temporary or permanent subcommittees that would be assigned focused tasks; and establish quality control (QC) standards.

Scientific Planning Committee (SPC): The SPC is composed of ICGC leaders and others who have been involved in the development of the ICGCmed White Paper. SPC working groups with additional expertise have been established where appropriate as follows:

- **Quality Standards:** The SPC has developed (and will continue to refine) a set of data quality standards for ICGCmed participants. They have developed guidelines for participating investigators for normal and cancer biospecimen quality to ensure sample consistency. Important recommendations include the requirement for pathology confirmation for all specimens with images made available to consortium members and data users. The SPC has defined minimum data quality standards for each technology platform and is recommending regular data comparisons and benchmarking exercises among the multiple ICGCmed research sites;
- **Genome Analysis:** ICGCmed member projects will undertake comprehensive genomic characterization of biospecimens obtained from clinical trials, cohorts and other studies that meet ICGCmed guidelines. The definition of “comprehensive” may change as technologies advance, and may vary with disease. It is expected that, at a minimum, all samples will be investigated by extensive sequencing for mutation detection (by exome and/or whole genome sequencing), and undergo analysis of copy number alterations and rearrangements. The SPC recommends that transcriptome and methylation analyses be conducted when reliable. The SPC will consider the need for a phased approach to generating genomics datasets that takes into account the high likelihood that technologies will evolve significantly during the course of the ICGCmed initiative; and
- **Data Tiers (privacy protection):** Currently, two data categories are used: 1) fully open and 2) controlled access for data types that could potentially be used to identify a subject. Together with GA4GH, ICGC med is building a registered access tier for less sensitive, minimal risk data. This approach is already in place for ICGC, but the Ethics and Governance Committee (EGC) will continue to monitor and adapt policies and practices. Methods to harmonize data access procedures across multiple and potentially disparate databases will be required. The SPC will make recommendations for end-stage management of ICGC data.

DATA MANAGEMENT AND COORDINATION

Data coordination and management have been key strengths of ICGC, and the lessons learned and strategies and policies developed will be invaluable to ICGCmed. ICGCmed is considerably larger in scale than ICGC, and involves a far richer and more complex set of clinical and environmental information. In consideration of this difference in scale and complexity, some structural changes will be necessary to ensure the sound management of ICGCmed data through bodies such as the:

- **Regional Data Processing Centres:** Two or three Regional Data Processing Centres will coordinate the management of ICGCmed data. Each centre will have the responsibility of accepting clinical and genomic data from ICGCmed sequencing centres, validating the submissions of genomics and clinical data, and processing the sequencing data through a standardized series of data analysis pipelines to identify genomic mutations;
- **ICGCmed Data Distribution Centre:** The validated submissions, along with quality control metrics, will be sent to a central site for integration with other ICGCmed data sets and dissemination to the scientific and lay communities. Processed sequencing data will be archived in one or more public sequence archives, and mirrored to several cloud compute providers, where qualified researchers will be granted the right to perform additional analyses on the data in a secure and ethically responsible fashion;
- **ICGCmed Software Engineering Group:** The ICGCmed software engineering group will support the operations of the ICGCmed Regional Data Processing Centres and the ICGCmed Distribution Centre and will be responsible for developing and distributing the software systems and protocols required for the operation of these centres;
- **ICGCmed Quality Assurance Group:** It is envisioned that the ICGCmed Quality Assurance Group will be responsible for testing the software, protocols and the data processing centre output to ensure a consistently high degree of accuracy and completeness in the ICGCmed outputs.

The use of regional data processing centres and cloud compute providers together give ICGCmed considerable flexibility in where the data is physically stored. This will allow the project to successfully navigate the changing landscape of international policies on human genetic data storage and distribution. Carefully written software will allow researchers to compute across data from ICGCmed donors that are stored in multiple localities and to return analytic results that span the entire distributed data set.

Data Management Committee: Many international genome projects have made major contributions to biomedical research by rapidly releasing high quality data to the global research community. ICGCmed will have clear quality requirements for data, sequence, and clinical information. The ICGCmed Data Coordination Centre (DCC) will incorporate new IT solutions to handle data from 200,000 consenting patients over a 10-year period.

Reflecting on DCC experiences in the first phase of ICGC, the following changes are proposed for ICGCmed:

- Since it will be critical to receive complete clinical data, criteria for accepting data sets will be stricter. The DCC will have the right to refuse incomplete or inadequate data. Submitted data and metadata will undergo extensive QC checks;
- Tailored clinical fields will be required for all projects. Because of the range of projects expected, the clinical fields required from each project will be negotiated with members dealing with specific tumour types (such that similar projects will collect the same information). Similarly, QC requirements will be generated for each project. Written agreements will be developed for each project that can be revisited as needed;
- All raw and processed data and metadata will be submitted to the DCC. The DCC will perform core analytical steps across all projects. Additional analyses can be added to the DCC;
- To make the core analyses rigorous, ongoing benchmarking activities will be conducted. The benchmarking activity will be done by the DCC or by an independent body working with the DCC. Responsibilities may include developing gold standard sets for benchmarking, sponsoring competitions, laboratory validation, and recommending best practices for core analyses;
- The DCC needs to be scalable. A series of regional data analysis centers will process information and feed the data back into the central DCC where biocurators, software engineers, and support staff create packages of analytical software. Processing data in a distributed way will be helpful in meeting regional privacy regulations;
- Clouds will be used (pending approval of individual members regarding jurisdictions where cloud infrastructures are located). The EPC will facilitate the process through additional policy research and consultation with individual groups as required; and
- The DCC will develop mechanisms that will enable local centres to point to patient/donor pages in the DCC portal, allowing projects to pilot approaches to for donors to access their own data.

CLINICAL DATA COORDINATION

To facilitate the sharing of sensitive clinical data among different healthcare systems and their practitioners with the ICGCmed Data Control Centre, ICGCmed will follow the lead of ICGC by using a tiered system of approval to safely share data with approved researchers from around the world, using categories such as open access, registered users and controlled access, depending on the sensitivity and identifiability of the data. As with ICGC, applications will be reviewed and access granted through the Data Access Compliance Office (DACO).

Clinical Data Coordination Committee: To address ICGCmed goals and specific needs, the Clinical Data Coordination Committee has formed four subgroups, whose work is summarized below:

- Epidemiology and signatures subgroup
- Germline and pharmacogenomics subgroup
- Molecular pharmacology subgroup
- Clinical trials methodology subgroup

Epidemiology and signatures subgroup: Mutational signatures have long been known to result from specific exposures (e.g., tobacco smoking and specific P53 mutations). Recent results reveal that high-throughput sequencing can provide additional important clues about the etiology of cancer. In particular, they highlight that (i) most cancers have evidence of multiple mutational signatures although their cause is usually unknown, and (ii) international comparisons can highlight important differences between populations and provide evidence of new causes of cancer. One aim of ICGCmed studies will be to understand the reason why specific mutation signatures occur, and what they can tell us about the primary causes of different types of cancer in various populations, and prompt greater primary prevention efforts.

Cancers that should be prioritized for such studies include those with large international or regional differences in incidence (frequently more than an order of magnitude) that are unexplained or only partially explained by known risk factors. Cancer types where incidence has increased substantially in recent decades, although again for unclear reasons (e.g., lymphomas, testicular cancer, renal cancers), or with important differences linked to ethnicity could also be a focus. The selection of cancer cases for sequencing could also oversampled based on potentially important exposures. Such studies could generate further information about specific mutational signatures and their links. It will be important that within such studies, additional clinical and phenotype data will need to be collected in a comprehensive and accurate fashion through standardized epidemiological questionnaires and ideally with trained interviewers. In summary, the next generation of ICGCmed studies will likely contribute to identifying novel causes of cancer, and therefore be important for cancer prevention choices and efforts. Careful planning of these studies will help to ensure their incredible potential is maximized.

Germline and pharmacogenomics subgroup: Germline analysis was not a top priority for ICGC. Today, including clinical data such as adverse events and drug efficacy in large series of patients with germline diversity will enable the consortium to identify novel, clinically relevant germline variations associated with clinical response and toxicities to therapies. These analyses will benefit greatly from cross tumor comparisons, since therapeutic measures are often similar in different tumor types. This is not only true for current chemo- and radiotherapies, but also for tailored therapies when the same biochemical pathways are targeted. Such “pancancer” approaches underline the need for optimal standardization of clinical data collection.

Molecular pharmacology subgroup: A goal of this subgroup will be to identify mechanisms of resistance or unusual sensitivity to therapies. Data generated on relapsed samples will be encouraged.

Based on emerging knowledge of current trials, guidelines will be developed to identify druggable targets keeping in mind the levels of omics data required, that is:

- Exome or whole genome data to identify targetable new altered proteins, transcriptome data for the identification of fusion genes to target, methylome data to refine the classification of tumors and role of aberrant protein expression to target;
- The level of omics data is also relevant to prioritize genomic alterations to be targeted by a drug; and
- Recommendations will be formulated for appropriate monitoring of patients that include repeated genetic analyses to detect the emergence of drug resistance and/or tumor recurrence.

Clinical trials methodology subgroup: In order to maximize data collection from clinical trials based on genomic analysis, two approaches are being considered:

1. ICGCmed will list specific criteria allowing the consortium to identify clinical trials, which could benefit from a genomic perspective: Such trials, by definition, are not driven by a genomic design or a genomic hypothesis, but could represent a real opportunity if a genomic question presents itself. Take the example of large randomized adjuvant trials enrolling over 1,000 patients that are anticipated for resected NSCLC, which will test the added value of anti-PD1 or anti-PDL1 therapy. Such trials could be a key opportunity to validate mutational load and immunogenic peptides as predictors of immune-checkpoint blockade efficacy.
2. ICGCmed will foster the implementation of prospective genomic-driven clinical trials that foresee:
 - Engagement with pharmaceutical and biotechnology companies to increase access to matched targeted therapies, as appropriate in local jurisdictions;
 - When possible, randomization to demonstrate the superiority of the genomic-oriented therapy vs the standard of care;
 - Defining the best patient populations to enroll (first diagnostic, refractory, sensitive...) to answer clinically important questions; and
 - New generation trials needed to integrate intra-tumour heterogeneity as well as immune-markers for the stratification of patients. Indeed, actionable mutations will be enriched with new dimensions such as immunogenicity and clonal architecture.

Building on the work of the subgroups described above, the Clinical Data Coordination Committee will determine the clinical parameters that need to be annotated (see Annotations, below). Despite considerable effort being expended defining the “must be provided” and “nice to have” categories of clinical data for ICGC, very little clinical information was actually submitted to the Data Coordinating Centre. This information, however, will be mandatory for ICGCmed. In addition, data requirements for those studies that also consider epidemiological parameters, such as geographic or ethnic parameters (by the epidemiology and signatures subgroup) also need to be well defined, including the specific data requirements for the detection of drug sensitivity or adverse effects due to a patient’s genetic constitution. These steps will be essential if ICGCmed is to provide guidelines for the selection of drugs/therapies based on ‘omics data and clinical follow-up.

ANNOTATIONS

The mandatory elements below constitute a minimal set of information. These might need to be expanded for a given tumour entity or scientific questions of a trial. All samples will have to be reviewed by two or more reference pathologists. This assessment will need to be performed on stained sections of the very same tissue piece from which biomolecules will be purified. Histological examination has to be documented and respective optical images have to be stored and made available to those studying the given samples and on a dedicated web page.

PATIENT (DONOR)

Patient Identifier

- Patient sex
- Age at diagnosis (in years)
- Date of diagnosis (to calculate overall survival or progression free survival)
- Cancer type (WHO ICD-10)

Therapy

- Chemotherapy – single agent
- Chemotherapy – multi agent
- Cryotherapy
- Hormonal therapy
- Other targeted molecular therapy
- Immunotherapy
- Radiation – external
- Radiation – internal
- Surgical resection
- Bone marrow transplant
- No treatment
- Other

Patient Vital Status

- Alive
- Died of cancer
- Died of other reasons
- Unknown

Therapy Response

- Complete remission
- Partial remission
- Disease progression
- Relapse
- Stable disease
- Unknown

Disease Status

- Progression – yes/no
- Progression status (determined by imaging etc)

Treatment Protocol

- Chemotherapy protocol – drug name(s)
- Chemotherapy protocol – cumulative dose
- Radiation therapy protocol – dosage
- Radiation therapy protocol – fractions
- Radiation therapy protocol – modality

SAMPLES

Specimen ID and Type

- Primary tumour
- Relapsed tumour
- Metastatic tumour
- Tumour xenograft

Related Samples

- Adjacent normal tissue
- Lymph node(s)
- Buffy coat
- Whole blood
- Plasma
- Serum
- Urine
- Other (please specify)

TISSUE ANALYSIS

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- | | |
|--|--|
| <ul style="list-style-type: none"> • Tumour histological type (http://codes.iarc.fr/codegroup/2) • Anatomic location • Number of regional lymph nodes positive (x from n examined nodes) • Central pathology confirmed, yes/no • Tumor grade (all tumours) at time of sample acquisition (surgery, biopsy) • TNM stage (carcinomas) at time of sample acquisition | <ul style="list-style-type: none"> • TNM stage (carcinomas) at time of recurrence • Tissue analysis, percentage of tumor cells • Tissue analysis, percentage of proliferating cells (Ki67, if available) • Tissue analysis, percentage of inflammatory tissue • Tissue analysis, percentage of stromal cells • Tissue analysis, percentage of necrosis |
|--|--|
-

PHARMACOGENOMICS AND GERMLINE ANALYSIS

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- | | |
|--|---|
| <ul style="list-style-type: none"> • Known cancer predisposition – yes/no • Prior malignancy – yes/no • Cancer type of prior malignancy | <ul style="list-style-type: none"> • Family history of cancer • Cancer history first degree relative • Side effects (neutropenia, etc) |
|--|---|
-

EPIDEMIOLOGY AND SIGNATURES

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- | | |
|---|---|
| <ul style="list-style-type: none"> • Ethnicity – classification schemes vary tremendously between continents/countries | <ul style="list-style-type: none"> • Exposure to risk factors – tobacco, alcohol, others |
|---|---|
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ETHICS AND POLICY

A key question will be how ICGCmed will address the growing consensus in the research community that, in addition to general research results, research findings obtained using patient's data should be shared with them if those findings are analytically valid, indicative of a serious disease or health condition, have clinical utility, and if a proven beneficial intervention is available. This is also an important issue in the pediatric context. Choosing whether or not to receive results unrelated to the study may not be open to parents when such results are clinically actionable during childhood and disclosure is considered to be in the best interest of the child. Like other issues, such positions are based on cultural norms as well as practicalities and have implications for the availability of healthcare resources and reimbursement for genetic services.

During the last eight years, the ICGC Ethics and Policy Committee has actively revisited, discussed and examined the operation of the overarching ethical and governing principles guiding the ICGC policy framework that has ultimately proved successful. Entering the clinical domain may amplify existing ethical, political, and legal issues and raise new ones. ICGCmed will face new issues because of the increased use of medical records, discussions related to cloud computing safety, return of results to the patients and the public, incidental findings, privacy legislation, data access regulation, intellectual property (patents, authorship policy and benefit sharing), patient access to genomic and clinical data and patient rights.

The Ethics and Governance Committee: The principles and approaches developed by the Ethics and Policy Committee for the first phase of ICGC are being updated for ICGCmed through the work of the new Ethics and Governance Committee and will reflect the new aims and goals that will guide ICGCmed in its future activities. Sharing international data will follow agreed international standards and best practices that take into account the rights and expectations of the individuals involved, while reflecting the right to share in scientific progress. ICGCmed has adopted the GA4GH Framework for Responsible Sharing of Genomic and Health-Related Data, on which the effective and responsible sharing of genomic and clinical data can be built. One of the flagship projects of this organization is the BRCA Challenge which is pooling data on BRCA genetic variants (e.g., sequence variation, phenotype and scientific evidence) from around the world for shared analysis. ICGCmed will liaise with such projects to learn from their experience and integrate appropriate measures into its own policies and procedures.

The EGC will also track and address as needed research and policy regulation on the issues of identification, security and efficiency of international data sharing, intellectual property (patents, authorship policy and benefit sharing), and barriers to providing data, such as institutional or national regulations, or the lack of (or ambiguity of) consent language.

The Data Access Compliance Office (DACO), hosted by the Public Population Project in Genomics and Society (P3G) at McGill University will be responsible for overseeing access to controlled data of ICGCmed. It is already providing access to over a thousand registered users of ICGC controlled data and its role will likely expand given the additional clinical information to be collected.

COMMUNICATIONS AND OUTREACH

Examples from the literature and from public-led initiatives such as PatientsLikeMe or the Genetic Alliance, show that patients want to be involved and are happy to give consent for their data to be used to advance research and benefit health, but this may not always be possible for technical reasons or institutional rules, or the reluctance to participate, among some practitioners and data stewards. Health care institutions are exploring mechanisms to allow patients to access their own data.

Communications Committee: A new autonomous Communication Committee has been formed to focus on communication and engaging health professionals, patients and the greater public so as to increase the visibility and accessibility of ICGCmed research. The ICGCmed Communications Committee will inform and involve participants and practitioners, creating opportunities where such issues may be raised, discussed, and acted upon. A topic of interest will be the growing interest in the return of patient-specific genomic, clinical and other data. Cancer survivors and/or advocates will be consulted through the Communication Committee to ensure that public communication regarding ICGCmed is developed to give hope, without excessive hype. The Communication Committee will also work to share information with a wide audience, including patients and the public, funding institutions, and other partners in order to disseminate aims and findings.

ADDITIONAL GUIDELINES

PUBLICATION

Individual research groups in ICGCmed will be free to publish the results of their own efforts in independent publications at any time (subject, of course, to any policies affecting ongoing collaborations). ICGCmed will adopt rapid data release policies to accelerate the dissemination of datasets that will precede publication of any global analyses of ICGC datasets, to promote maximum use of the data. ICGCmed members will inform users about ICGCmed member publication plans (including publication moratoriums), which shall not exceed one year from the first deposit of the data.

INTELLECTUAL PROPERTY

ICGCmed members agree not to make proprietary claims on ICGCmed primary data (including somatic mutations) and to not pursue IP protection that would prevent or block access to or use of any element of ICGC data or conclusions drawn directly from it.