Translating cancer genomes into personalized health and disease management

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Cancer statistics

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>New cases</td>
<td>6,629,112</td>
<td>1,529,560</td>
<td>173,800</td>
</tr>
<tr>
<td>Deaths</td>
<td>4,225,662</td>
<td>562,875</td>
<td>76,200</td>
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- 40% of Canadian women and 45% of men will develop cancer during their lifetimes.
- 1 out of every 4 Canadians are expected to die from cancer.
- Cancer is the leading cause of premature death in Canada. This represents 32% of the potential years of life lost resulting from all causes of death.

Source: GLOBOCAN 2008/IARC; American Cancer Society; Canadian Cancer Society.

Promises of cancer genome research to patients, healthcare providers and payers

- Genetic information will be used to predict risk, optimize screening programs, identify tumors at early stages when disease is more often curable, save health care costs;
- Cancer diagnosis will be more precise, will provide more accurate prognostic information and allow optimization of treatment interventions;
- New therapies will be developed that target specific alterations in cancer cells, reducing the need for highly toxic chemotherapies.

Current status: A few successes – potential far from being realized.

Outline

- Genome technologies
- Inherited genomic variation and cancer
  - Genetic predisposition to colon cancer
- Acquired (somatic) variation and cancer
  - Pancreatic Cancer Genome Project
- Concepts of personalized medicine
  - Implementation by the Ontario Institute for Cancer Research

Sequencing Evolution

- ~ 1,000 bases per day
- >10,000 bases per day
- >1,000,000 bases per day
- >200,000,000 bases per day

Sequencing Revolution

- Human Genome Project

Pacific Biosciences RS

- Single molecule, Simple sample prep
- Long reads (>10kb)
- 2010: ~50 Mb, 0.5 hour, $99
- ~2015; Complete genomes, 15 minutes, < $1000
Sequencing adapted to study DNA, RNA, methylation and chromatin

- **SNP/indel discovery**
  - Targeted genomic sequencing: exome
- **Structural variation**
  - Rearrangements, large indel, copy number
- **Whole transcriptome sequencing**
  - mRNA and miRNA
- **Copy number variation**
  - Sequence, Microarray and Beadstation
- **Small RNA discovery/sequencing**
- **Whole genome sequencing**
- **Epigenomics**
  - Chromatin IP transcription factor binding (ChIP-seq)
  - Methylation/Methylome

Blood and Tissues

Cumulative pace of disease gene discovery

Most of these discoveries were for rare genetic disorders

- Describe the common patterns of sequence variation in the human genome
- Include multiple populations with ancestry from parts of Africa, Asia and Europe
- Make this information freely available in the public domain
- Provide tools to aid discovery of genetic variants that affect common disease in association studies.

Gene discoveries for common complex diseases

- **Genes identified before 2005** (Pre-HapMap)
  - Breast Cancer Genes
  - Alzheimer’s Disease
  - Colon Cancer
- **Loci identified since 2005** (HapMap and GWAS)
  - Macular Degeneration
  - Type 2 Diabetes
  - Prostate Cancer
  - Lupus
  - Myocardial Infarction
  - Inflammatory Bowel Disease
  - Colon Cancer

> 2000 other loci!
THE ARCTIC PROJECT
Assessment of Risk of Colorectal Tumors in Canada

Design:
• 1200 Cases (Ontario)
• 1200 Controls (Ontario)
• 1.4 billion genetic tests

Output:
• Predictors of Disease
• Disease prevention
• ARCTIC kits

rs10505477 (8q24 locus)
First genetic marker validated in > 10,000 subjects

<table>
<thead>
<tr>
<th>Population</th>
<th>OR</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontario</td>
<td>1.22</td>
<td>0.058</td>
</tr>
<tr>
<td>Quebec/Newfoundland</td>
<td>1.11</td>
<td>0.087</td>
</tr>
<tr>
<td>Scotland</td>
<td>1.16</td>
<td>0.046</td>
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<tr>
<td>France/Nantes</td>
<td>1.13</td>
<td>0.060</td>
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<tr>
<td>France/Familial</td>
<td>1.28</td>
<td>0.099</td>
</tr>
<tr>
<td>EPIC</td>
<td>1.13</td>
<td>0.072</td>
</tr>
<tr>
<td>Summary All</td>
<td>1.17</td>
<td>0.024</td>
</tr>
<tr>
<td>French/EPIC only</td>
<td>1.16</td>
<td>0.042</td>
</tr>
</tbody>
</table>

OR = Odds ratio; SE = Standard error

Risk versus CRC-allele Count
Houlston et al, Nat Genet, 2008

Published GWAS for CRC with n>10,000

• Zanke et al, Nat Genet, 2007
• Tomlinson et al, Nat Genet, 2007
• Broderick et al, Nat Genet, 2007
• Jaeger et al, Nat Genet, 2008
• Tenesa et al, Nat Genet, 2008
• Tomlinson et al, Nat Genet, 2008
• Houlston et al, Nat Genet, 2008

Cancer
A disease of the genome

Lessons learned from cancer genome research:
• Heterogeneity within and across tumour types;
• High rate of abnormalities (driver vs. passenger);
• Sample quality matters.

Challenge in treating cancer:
• Every tumour is different;
• Every cancer patient is different.
International Cancer Genomics Strategy Meeting
October 1–2, 2007 Toronto (Canada)

22 countries represented
120 participants
- 34 genome or cancer centre directors;
- 24 representatives from funding agencies;
- 62 scientists selected to represent ethics, technologies, statistics, informatics, pathology, clinical oncology and cancer biology.

International Cancer Genome Consortium

- Collect ~500 tumour/normal pairs from each of 50 different major cancer types;
- Comprehensive genome analysis of each pair: genome, transcriptome & methylome;
- Make the data available to the research community & public.

Rationale for an international consortium

- The scope is huge, such that no country can do it all;
- Coordinated cancer genome initiatives will reduce duplication of effort for common tumours and ensure complete studies for many less frequent forms of cancer;
- Standardization and uniform quality measures across studies will enable the merging of datasets, increasing power to detect additional targets;
- The spectrum of many cancers varies across the world for many tumour types;
- The ICGC will accelerate the dissemination of genomic and analytical methods across participating sites and the user community.

International network of cancer genome projects

This International Cancer Genome Consortium (ICGC) was launched to coordinate large-scale cancer genome studies in tumours from 50 different cancer types and/or subtypes that are of clinical and societal importance across the globe.

Systematic studies of over 30,000 cancer genomes at the genomic, epigenomic and transcriptomic levels will reveal the complete genome landscapes, cancer foci of the epigenetic differences, define clinically relevant subtypes for prognostic and therapeutic assignment, and enable the development of new cancer therapies.

Nature 464, 993-998 (15 April 2010)

ICGC Partners:
12 countries, 38 projects
Commitments for > 10,000 cancer genomes

Pancreatic tumour sequencing at OICR

Sample collection: ~75/year

Blood: germline DNA

Primary tumour

Cell lines

Xenograft

Structural variants
Copy number
Exome
Epigenetics

Structural variants
Copy number
Transcriptome

Heidi Ledford, Nature, 2010
Pancreatic sample acquisition (2009-10)

OICR Cancer Genomics Platform:
~5,000 Gb/mo (1500 raw genomes)

- 7 GAIIx
- 3 HiSeq 2000
- 5 SOLiDv3/4
- 1 Pacific Biosciences RS
- 3 PB storage
- 3,600 cores

ICGC data is distributed, but is accessible through a common portal

Submissions to DCC as of September 2010

- Cancer types: 8 (from 8 centres, including TCGA)
- Donors: 1,474
  - Simple somatic mutations: 107,478
  - Copy number mutations: 23,302
  - Structural rearrangements: 4,562
  - Genes affected by simple somatic mutations: 18,201
  - Genes affected by copy number mutations: 12,407
  - Genes affected by structural rearrangements: 815
- Only open tier data currently available

ICGC web portal

DACO Application Form
What is personalized medicine?

“It’s no longer one size fits all. Your therapy may be different from mine, even though we have the same disease, because of differences in genetic makeup, lifestyle, health history and other factors”.

Diana Bartlett, Keck Graduate Institute

Definitions

Personalized Medicine (NCI): A form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose and treat disease.

Biomarker (NIH): A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biological Target (Wiki): A protein or nucleic acid (DNA or RNA) whose activity can be modified by an external stimulus.

Personalized medicine has started

Examples of validated diagnostic tests that can be used to select cancer therapies

- Her2 test for breast cancer
- Oncotype DX
- K-RAS mutations
- Many more coming…

Challenges and Opportunities

Translating cancer genomes into personalized health and disease management at the Ontario Institute for Cancer Research

- Develop translation paths from discovery to impact cancer (reduce incidence, morbidity and mortality);
- Prioritize resources on problems that matter most to clinicians
- Develop partnerships in Ontario, Canada and internationally.

The Canadian Partnership for Tomorrow Project
Goals

- to enrol 300,000 Canadians aged 35-69 years into a cohort study (‘population laboratory’)
- to follow cohort participants for up to 50 years, periodically collecting health related information and biological samples
- to build up layers of information and biological samples over time, eventually leading to in-depth study of why some people in the cohort develop cancer, or other chronic diseases, and others do not

Federated model

Cohorts
- Alberta (The Tomorrow Project)
- Atlantic Canada (Partnership for Tomorrow’s Health)
- British Columbia (BC Generations Project)
- Ontario (Ontario Health Study)
- Quebec (MARGINE)

Task Forces & Working groups
- ELSI and Privacy TF
- Information Technology TF
- Harmonization TF
- Environment & Occupation Advisory Group
- Physical measures working group
- Biological samples working group

Canadian Partnership for Tomorrow Project

Power enhanced by P3G

PIG OBSERVATORY (www.p3gobservatory.org)
- 159 large population-based studies (>10,000 healthy participants)
- (P3G members and non-members)
- Over 10 millions participants

OICR partnerships in the target-to-drug pipeline

Adoption of more Personalized Medicine for Cancer

- OICR/PMH Initiative
- Collaboration with other provincial initiatives

MOH:TC
- develop policy for pharmacogenetics testing
CGO
- develop guidelines for implementation of pharmacogenetics tests
Digital environment needed to support clinical decisions in a personalized medicine world

Requirements for personalized medicine in Canada
- Maintain leadership in fundamental sciences that lead to better understanding of the molecular basis of disease;
- Establish translational research programs that have clinical endpoints that address important clinical problems;
- Support translational research platforms such as cohorts, clinical trials, that can validate biomarkers, imaging probes and targeted agents as tools for clinical management;
- Support health services research via linked-databases;
- Develop partnerships between academia, health care providers, regulatory agencies, and industry.

Outcomes of Personalized Medicine
- More effective and safer therapies, increased survival, improved quality of life, stronger economy.

International Cancer Genome Consortium
Madrid, Spain – March 2010

OICR Leaders

Sponsors
- Ontario
- GenomeCanada
- GenomeQuebec
- GenomeOntario