Challenges in translating genomics technologies to the clinic

Irish Biomarkers Network
Dublin Castle, Ireland
May 2\textsuperscript{nd}, 2012

\textit{Pierre Meulien, President and CEO, Genome Canada}
Presentation Today

• Introduction to the Canadian environment
  • Healthcare and Genomics
• Some examples of low hanging fruit
  ➢ Rare diseases
  ➢ Cancer
• New program design in Canada for large program in Personalized Health (launched in January 2012)
• Some conclusions and looking ahead
Canadian Environment

● Publically funded health care system
● Provincially delivered (Regional Health Authorities)
● Costs the country around $140 Billion per year
● Growth in cost is around 5-7% annually (NOT sustainable)
● Biomedical research very strong in Canada
● Canada spends about 2% of government funded global research but produces 3% of the highest impact factor publications
● Strong clinical networks across the country and - for some diseases - has among the best outcomes in the world
● However our ability to move the latest technology into healthcare delivery is low and the way technology is assessed across the country is very heterogeneous
● New technologies are often seen as just an added cost and economic analyses performed are not convincing enough for the payers
Vision

Harness the transformative power of genomics to deliver benefits to Canadians.
Canada’s Genomics Enterprise

6 Regional Genome Centres

Over 160 projects –
$2 Billion investment over 10 years
7 key areas – Agriculture, Fish & Aquaculture, Forestry, Environment, Mining, Energy and Human Health

5 Science and Technology Innovation Centres

U. Vic./Genome BC Proteomics Centre
Proteomics (Christoph Borchers)

McGill University & Genome Quebec Innovation Centre
Genomic Analysis (Mark Lathrop)

The Metabolomics Innovation Centre
Metabolomics (David Wishart & Christoph Borchers)

The Centre for Applied Genomics
Genomic Analysis (Stephen Scherer)

Genomics Innovation Centre at the BCCA GSC
Genomic Analysis (Marco Marra, Steven Jones & Robert Holt)

Ontario

Québec

Prairie

Genome Canada

Atlantic

Alberta

B.C.

B.C.

Vancouver

Montreal

Toronto

Edmonton

Victoria

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**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.
Molecular Medicine Continuum

Health Maintenance and Disease Prevention

Early Detection

Treatment of Disease

Increasing Knowledge of Underlying Disease Mechanisms

Environment

Behaviour

Lifestyle
Personalized Medicine

Spectrum of Genetic Contribution to Disease

Very rare single gene disorders
- CF
- Hemophilia
- MD
- HD

More common single gene disorders

Disorders with prominent genetic contribution
- Childhood cancer
- BRCA 1/2 Breast cancer
- Some forms of autism spectrum disorders
- Adverse Drug Reactions

Genetic susceptibility to certain common diseases
- Colon cancer
- Certain cardiovascular diseases
- Certain forms of Alzheimer

Most common chronic diseases with many genetic factors but also major environmental factors contributing to disease onset
Impact on Human Health

Canadian Examples

Nursing Mothers and use of Codeine
- Genome wide studies across the country on infant sudden death has resulted in the discovery of genotypes associated with fast metabolizers of codeine (into morphine)
- FDA and Health Canada labelling change

Atlantic Medical Genetics and Genomics Initiative
- Genome wide study in Newfoundland discovering a gene responsible for sudden death from heart failure in young men.
- These families are now screened for the gene and those affected are fitted with defibrillators that can be automatically activated in a crisis situation

World class groups in Canada working on Cancer, Stem Cells, Autism, Transplantation, Infection and Immunity, Diabetes, Neuro-psychiatric diseases and Genomics and Society
So how do we translate when we need to consider a lot of complex issues?

- How good is the technology? (clinical validation)
- In a fast moving field, when do we decide that “now is the time for transfer”
- Is it easy to adapt existing clinical laboratory structures?
- Who will be making these decisions? (and based on what criteria?)
  - Technology assessment based on sound economics and clinical benefit?
- Who will pay?
Dramatic decreases in sequencing costs have resulted in rapid increases in genetic data.

**Cost and Growth of Bases**

- **Cost per million base pairs of sequence (log scale)**
- **GenBank**

**Sources:**
- NCBI

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Dramatic decreases in sequencing costs have resulted in rapid increases in genetic data. The graph illustrates the reduction in cost per million base pairs over time, with significant decreases in cost from $10,000 to $100, and further to $1, reflecting a substantial growth in the number of base pairs available. The data is sourced from NCBI.
What we need now

• Demonstrations that the technology can deliver real value to patients

• Demonstrations that integrating the technology within the healthcare system will be cost effective
Some Examples

✓ Very Rare Mendelian Inherited Disorders

✓ Cancer
A nation-wide effort to identify genes causing rare pediatric disorders

Kym Boycott, PhD, MD, FRCPC, FCCMG

Clinical Geneticist, Department of Genetics
Investigator, Children’s Hospital of Eastern Ontario Research Institute
Associate Professor, Department of Pediatrics, University of Ottawa
Rare Genetic Disorders in Canada

- **Definition**
  - Affects fewer than 1:2000 individuals

- **As a group, rare disease is not rare**
  - 1:12 Canadians are affected
  - **500,000 children**

- **Impact**
  - Individual, family, healthcare, society
FORGE Canada Consortium

Objectives

- Rapidly identify genes for rare pediatric single-gene disorders
  - 2 years
  - April 2011 to March 2013

- Establish a sustainable national Consortium focused on rare disorders
International Collaborators
How many human single gene disorders remain to be discovered?

*Single-gene disorders*

- gene known: ~2900
- gene unknown: ~3600
- suspected single gene disorders: ~4500

300 Disorders Proposed
1-2% of the entire human genome but contains all of the human genes.
1 Story... Undiagnosed Neurodegeneration

http://www.ottawacitizen.com/technology
December 4, 2011
A Diagnosis…..

- Exome sequencing
  - Both boys
  - 50 Mb Agilent SureSelect
  - Illumina HiSeq
- Compound heterozygous mutations in *HSD17B4* identified

- c.101C>T; p.A34V
- c.1547T>C; p.I516T
Expansion of Genotype-Phenotype

- Classic D-bifunctional protein deficiency is a severe life-limiting congenital disorder
- Usually associated with the most severe peroxisomal disorder
- Hypomorphic mutations
- Treatment??
  - Stabilize protein
  - Upregulate transcript

HSD17B4

3-hydroxyacyl-CoA dehydrogenase

2-enoxy-co-A hydratase

324

596

735 aa

A34V

cleavage

I516T

peroxisomal targeting sequence

HSD17B4
FORGE Progress – 12 months

- ACTH Resistance
- Hermansky-Pudlak like
- Hawk Junction Microcephaly
- Perrault-Syndrome
- Severe Combined Immunodeficiency
- AD Retinitis Pigmentosa
- Hadju-Cheney Syndrome
- Metaphyseal dysplasia, maxillary hypoplasia
- Leber Congenital Amaurosis
- Floating Harbor syndrome
- French Canadian Joubert syndrome
- Chudley McCullough syndrome
- Weaver syndrome
- Hyper IgM
- Megalencephaly Capillary Malformation
- Nager syndrome
- Microcephaly Capillary Malformation
- Mandibulofacial dysostosis with Microcephaly
- Jeune-Joubert syndrome
- Short stature, cataracts, peripheral neuropathy
- Intestinal pseudo-obstruction with sick sinus
Impact on Care

“What if there is an intervention?”
“Will this happen again”?

- Less invasive diagnostic testing
- Earlier and more precise diagnosis
- Accurate genetic counseling
- Tailored therapy
CANCER

Slides kindly provided by Tom Hudson- OICR
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.
Personalized medicine has started

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

<table>
<thead>
<tr>
<th>Her2 test for breast cancer</th>
<th>Herceptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>Adjuvant chemotherapy for breast cancer</td>
</tr>
<tr>
<td>K-RAS mutations</td>
<td>EGFR inhibitors for colon cancer</td>
</tr>
<tr>
<td>Many more coming...</td>
<td>Many more coming...</td>
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International Cancer Genome Consortium

- Collect ~500 tumor/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.

Identify genome changes
Successful Targeted Drug Development

Rapid identification of potential targets

For “druggable” targets
Interval from target to clinical candidate is shorter

For clinically important targets
Interval from FIH to drug approval is short

Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors

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For all author emails, please log on.
How are we currently using genomics in patient management

Single Gene Alteration

- Already incorporated in patient management;
- Impacts the following decisions:
  - Selection of agents:
    - Positive effect;
    - Negative effect.
  - Prediction of toxicity;
  - Treatment changes in case of resistance.

Multiple gene alterations

- Under investigation at many institutions;
- Should it be incorporated in routine care or remain a research tool?
- Is it practical?
- What is the cost/benefit?
Surveys of mutation databases indicate that most mutations are found in many tumour types

Sanger Institute: http://www.sanger.ac.uk/cosmic, COSMIC v54 Release (Forbes et al., 2011).
Key questions regarding the implementation of cancer sequencing in the clinic

1. Is technology ready and reliable?
2. Can FFPE replace fresh tumour biopsies?
3. What are the differences between primary and metastatic sites?
4. Is turnaround of results acceptable for clinical use?
5. How to interpret and report the data?
6. Do we have enough targeted agents available?
7. How to design clinical trials to prove benefits?
8. How to handle incidental findings (heritable risks)?
Genome Canada- CIHR

2012 Large Scale Applied Research Competition

Personalised Health
New Program Design - Role of Funders

- How do we encourage...

- The right team formation
- The right types of deliverable are achieved
- That true demonstrations of value are obtained
Program partnered with the Canadian Institute for Health Research

Raised $65 Million which will be doubled by others to deliver a $130 Million program

Requires teams to provide an economic analysis and rationale for why their particular application will demonstrate value to the health system

Requires relevant Economic, Environmental, Ethical, Legal and Social (GE³LS) research

Teams must provide detailed development plan for integration into the HC system

Teams must have buy-in from the payer and clinicians and must have considered the regulatory frameworks existing in Canada

Around 13 projects will be funded at around $10M each
Molecular Medicine Continuum

- Health Maintenance and Disease Prevention
- Early Detection
- Treatment of Disease

Increasing Knowledge of Underlying Disease Mechanisms

- Environment
- Behaviour
- Lifestyle
Potential Outcomes

Development of:

- Diagnostic tools for screening programs for diseases
- Molecular markers to monitor disease progression and/or response to treatment
- Biomarker panels to stratify patients so that more targeted treatments can be offered
- Computational methods that will enable translation of genomic discoveries to the clinic
- Pharmacogenomic approaches to improve the safety and efficacy of existing drugs
- Molecular markers that can inform dietary or behavioural choices in disease prevention strategies

GE³LS studies, such as:

- Economic modelling to inform provincial health authorities
- Assessment of the social and economic benefits derived from genomics research and its integration into the health care system
Conclusions - the way forward
Integration of Genomics into the Healthcare System

• Develop receptor capacity for technology pull (capacity for clinical and translational research)
• Involvement of the private sector
• Educate and train healthcare professionals to be proficient users of the technology
• Ensure information systems are modern and harmonize e-patient records
• Role of patients and advocacy groups in demanding evidence based medicine
• Robust technology assessments focused on improvement on clinical outcomes and economic benefit analyses
• More balance between prevention and treatment
• Legislation to “encourage” behaviour change in the younger population
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• **Lead**
  - Kym Boycott, University of Ottawa

• **Co-Leads**
  - Jan Friedman, University of British Columbia
  - Jacques Michaud, Université de Montréal

• **Steering Committee**

  ![Francois Bernier](image1)
  - University of Calgary

  ![Mike Brudno](image2)
  - University of Toronto

  ![Bridget Fernandez](image3)
  - Memorial University

  ![Bartha Knoppers](image4)
  - McGill University

  ![Mark Samuels](image5)
  - Université de Montréal

  ![Steve Scherer](image6)
  - University of Toronto

  ![Jacques Michaud](image7)
  - Université de Montréal

  ![Janet Marcadier](image8)

  ![Chandree Beaulieu](image9)

• **Clinical Co-ordinator:** Janet Marcadier

• **Project Manager:** Chandree Beaulieu

• **FORGE Membership**

• **International Collaborators**

  - Bridget Fernandez
  - Memoria University

  - Bartha Knoppers
  - McGill University

  - Mark Samuels
  - Université de Montréal

  - Steve Scherer
  - University of Toronto
The Genetic Basis for Cancer Treatment Decisions

Tom Hudson, MD
President and Scientific Director
Ontario Institute for Cancer Research