Genomics in Health, Environment, and the Economy: Opportunities and Challenges

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Former Director, Leukemia/BMT Program of BC
Board of Directors, Genome British Columbia

Kelowna: June 27, 2014
Diclosures

- No commercial or other conflicts

- I have borrowed liberally (with permission) from friends and colleagues and while I will try to acknowledge them as the talk goes on, thanks to all of them for their generosity

- I was going to try not to focus on just cancer—there are too many other areas of great interest to discuss
  - But cancer is way way ahead!
Definition of genomics (WHO)

Genomics is defined as the study of genes and their functions, and related techniques.

Differs from “genetics” in that the latter studies the structure and function of a single gene while the former is concerned with the inter-relationships of the entire genome of the organism.

Numerous subdefinitions which are beyond the scope of this presentation (for example proteomics, meta-genomics, epi-genomics, etc.)
Rapidly evolving area

First human genome sequence was reported in 2003 at a cost of 3 billion US dollars.

Even as this was happening, competing technologies were published suggesting that a genome could be sequenced for 300 million dollars.

Now an individual human genome can be sequenced by many research and some commercial enterprises for about 2500 dollars!

(so Moore’s Law does not just apply to computer chips!)
Title
The era of “big sequence”
Genomics is the “fuel” of Personalized Medicine

- Allows the “stratification” of diseases that appear identical
- Stratification leads to improved outcomes: examples
  - Cancer
    - Breast/HER2
    - Oncotype Dx
    - CML/Gleevec
  - Cystic fibrosis
  - HIV
Genomic Medicine = Personalized Medicine
Pertinent to all areas of medicine

- Oncology
- Microbiology
- Pharmacology
- Neonatology
- Perinatology

- Emergency medicine
- Public Health
- Neurology
- Newborn screening
Personalized Medicine

Spectrum of Genetic/Genomic Contribution to Disease

Very rare single gene disorders

- Cystic Fibrosis
- Hemophilia
- Huntington’s Disease
- Muscular Dystrophy

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

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
Personalized Medicine: a New Paradigm

“One-size-fits-all” paradigm:

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>Prevention</th>
<th>Targeted Monitoring</th>
<th>Diagnosis</th>
<th>Therapy</th>
<th>Response Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Detection Testing</td>
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Same frequency of testing for large population (e.g. mammograms)  
Symptom-driven diagnosis  
Therapy based on clinical symptoms  
Monitoring based on clinical symptoms

Personalized medicine paradigm:

<table>
<thead>
<tr>
<th>Test for markers that ↑ risk (e.g. genetic variants in cancer)</th>
<th>Focused prevention efforts in people with ↑ risk</th>
<th>Focused monitoring in people with ↑ risk</th>
<th>Molecular monitoring for disease subtypes</th>
<th>Targeted therapy based on disease subtype, risk of adverse response</th>
<th>Molecular monitoring for response to therapy</th>
</tr>
</thead>
</table>

Source: Personalized Medicine Coalition
Support for Personalized Medicine in British Columbia

**Personalized Medicine Program (Genome BC)**
- investigator-driven
- outcomes are ready for clinic use and/or uptake into the health system within 3 years of launch
- Must demonstrate the support from the payer (e.g. a regional health authority) & the potential cost-effectiveness of the translation of the proposed research to the healthcare system
- project budget up to $3 million

**Genomics and Personalized Health (Genome Canada)**
- in partnership with Canadian Institutes of Health Research (CIHR),
- deliverables clinical utility and/or practical applicability
- project budget $10 million
GPH Program fully underway in 2014

## Genomics and Personalized Health – New Projects

<table>
<thead>
<tr>
<th>Project Leader(s)</th>
<th>Project Title</th>
<th>Total budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joseph Connors</td>
<td>Personalized Treatment of Lymphoid Cancer: British Columbia as Model Province</td>
<td>$10M</td>
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<tr>
<td>Marco Marra</td>
<td></td>
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<tr>
<td>Randy Gascoyne</td>
<td></td>
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<tr>
<td>Richard Harrigan</td>
<td>Viral and Human Genetic Predictors of Response to HIV Therapies</td>
<td>$4.9M</td>
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<tr>
<td>Julio Montaner</td>
<td></td>
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<tr>
<td>Andrew Penn</td>
<td>Reducing Stroke Burden with Hospital-Ready Biomarker Test for Rapid TIA Triage</td>
<td>$9.8M</td>
</tr>
<tr>
<td>Christoph Borchers</td>
<td></td>
<td></td>
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<tr>
<td>Shelagh Coutts</td>
<td></td>
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<tr>
<td>Don Sin</td>
<td>Clinical Implementation and Outcomes Evaluation of Blood-Based Biomarkers for COPD Management</td>
<td>$7.2M</td>
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<tr>
<td>Raymond Ng</td>
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</table>
A 67-year-old Asian lifelong never-smoker male was diagnosed with metastatic NSCLC (T2N3M1b). ALK IHC was equivocal, subsequent FISH analysis (Vysis probes) was negative for ALK rearrangement. He showed disease progression. He consented to participate in the personalized oncogenomics pilot study.

Whole genome sequencing identified an atypical EML4-ALK fusion oncogene that was expressed in the tumor, evident from the transcriptome. Complex structural rearrangements around this well-characterized oncogene (Figure) likely interfered with the binding of FISH probes leading to negative test results. Administration of crizotinib following this study resulted in dramatic and rapid tumor shrinkage.
Bioinformatic Analyses Approaches for Personalized Oncogenomics

Katayoon Kasaian, Yaoqing Shen, Sreeja Leelakumari, Peter Eirew, Yvonne Li, Erin Pleasance, Richard Corbett, Karen Mungall, Jacquie Schein, Andrew Mungall, Yongjun Zhao, Richard Moore, Stephen Yip, Karen Gelmon, Howard Lim, Daniel Renouf, Robyn Roscoe, Yussanne Ma, Marco Marra, Janessa Laskin, Steven Jones

Background & Rationale

The personalized oncogenomics initiative at the British Columbia Cancer Agency aims to identify tumor-specific therapeutic targets in cancer patients with late stage disease who have failed standard therapy. Comprehensive profiling of individual patients’ tumor(s) at the DNA and RNA level allows for characterization of altered pathways and hence identification of therapeutics designed to specifically target them.

Bioinformatic Analysis Pipeline

50 patients with various cancer types have entered the program over the past 18 months. The average time from the acquisition of tissue biopsy to the delivery of final report is 37 days.

Various bioinformatic analyses are run concurrently by different, color-coded, production pipelines. Results of all analyses runs are integrated into a unified pathway diagram demonstrating the altered networks and putative oncogenic events; potential therapeutic options are flagged. Comparison of metastatic/recurrent and primary genomes reveals the evolution of the tumor over time and in response to previous therapies. A standard report describing in great detail the bioinformatic analysis tools and parameters and the results are prepared and presented to the clinical oncology team.

Case Study #1, SCC

A 59-year-old Caucasian man presented with squamous cell carcinoma; two prominent tumors were present, one on the chest and one by the left ear. Whole genome and transcriptome data of the two tumors showed very divergent tumors, requiring different therapies.

Pathway Analysis

Cancer pathways with acquired somatic mutations and altered copy number and expression levels guide therapy decision making.

Case Study #2, NSCLC

A 67-year-old Asian lifelong never-smoker male was diagnosed with metastatic NSCLC (T2N3M1b). ALK IHC was equivocal, subsequent FISH analysis (Vysis probes) was negative for ALK rearrangement. He showed disease progression. He consented to participate in the personalized oncogenomics pilot study.

Future Directions

Study biopsies will be collected at the time of initial diagnosis, enabling the administration of targeted therapies earlier in the course of disease.

Acknowledgements

We are greatly indebted to the patients for their participation in this study. This work has been made possible by the generous financial support of the British Columbia Cancer Foundation.
Practical applications now reported almost daily!

Proteomic Signature for EGFR Inhibitor Therapy Predicts Survival Benefit of Second-Line Chemotherapy vs Erlotinib in NSCLC

Plenary Paper

LYMPHOID NEOPLASIA

Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma

Joaquin Martinez-Lopez,1 Juan J. Lahuerta,1 François Pepin,2 Marcos González,3 Santiago Barrio,1 Rosa Ayala,1 Noemí Puig,3 María A. Montalban,1 Bruno Paiva,4 Li Weng,2 Cristina Jiménez,3 María Sopena,1 Martín Moorhead,2 Teresa Cedena,1 Immaculada Rapado,1 María Victoria Mateos,3 Laura Rosiñol,5 Albert Oriol,6 María J. Blanchard,7 Rafael Martínez,8 Joan Bladé,5 Jesús San Miguel,4 Malek Faham,2 and Ramón García-Sanz3
Assessment of survival in myeloma by MRD

- Among patients in complete response, MRD assessment by sequencing enables identification of 2 distinct subgroups with different TTP.

MRD+. When stratifying patients by different levels of MRD, the respective TTP medians were: MRD $\geq 10^{-3}$ 27 months, MRD $10^{-3}$ to $10^{-5}$ 48 months, and MRD $<10^{-5}$ 80 months. GPR patients were MRD+. In complete response patients, the TTP remained significantly longer for MRD− compared with MRD+ patients (131 vs 35 months; $P = .0009$). (Blood. 2014;123(20):3073-3079)
Making Genotyping routine for Advanced Malignancies: proposal for the BCCA OncoPanel

Hagen Kennecke MD MHA FRCPC on behalf of Vancouver Centre, BCCA and Aly Karsan MD FRCPC, Head, Center for Clinical Genomics
WHY THE BCCA?

1,100 per year

Leverage existing outcomes database

We have the capacity, capability, and it will make a clinical difference!
HOW DO WE INCORPORATE CANCER GENOTYPING INTO ROUTINE CARE?

- What clinically validated assay?
- Can we test non-validated markers? What if we uncover familial syndromes?
- KRAS $500, EGFR $500, BRAF $500, ALK…..
- What tissue, when, turn-around time?
ALL METASTATIC CRC REferred TO BCCA: 2009

Any chemo, median survival = 22.3 months

Reference: M Ho GI ASCO 2013
CURRENT STATE: VERY LIMITED, VERY LATE GENOTYPING

Median Survival = 22.3 months
ROUTINE GENOTYPING MODEL

Median Survival = 22.3 months
**REQUIREMENTS**

**Large Volume, Low Cost:**
- Many mutations rare <10%
- 1000+ patients/year: CRC, Lung, Melanoma

**Clinically validated, or need to repeat:**
- Standard and non-standard mutations

**Short turnaround: 1-2 weeks**

**Models: MD Anderson? PMH? MGH/Dana Farber**
Why does this have so much promise in cancer?

- As shorter turnaround times become reality, can be used to make therapeutic decisions in real time
- Both genetics and biomarkers may predict response to therapy or guide therapy
  - Avoid costly drugs which won’t be of benefit
  - Potentially allow use of cheap drugs for some disorders
  - Select patients for clinical trials or for more aggressive therapy based on genetic signature of tumour
- Note that this is not just an add-on cost—some of these ideas will potentially reduce costs!
The applications of genomics in cancer are here now!

**FDA Approves Panitumumab Plus FOLFOX for Wild-Type KRAS Metastatic Colorectal Cancer**

By The ASCO Post

Posted: 5/27/2014 2:01:32 PM
Last Updated: 5/27/2014 2:01:32 PM

**Key Points:**

- The FDA approved panitumumab in combination with FOLFOX as first-line treatment in patients with wild-type KRAS (exon 2) metastatic colorectal cancer.

- The approval is based on results from the PRIME and ASPECTT phase III clinical trials.

- Therascreen KRAS test, a companion diagnostic, was also approved to guide use of panitumumab in the treatment of metastatic colorectal cancer.

The U.S. Food and Drug Administration (FDA) has approved panitumumab (Vectibix) for use in combination with FOLFOX (fluorouracil, leucovorin, oxaliplatin) as first-line treatment in patients with wild-type KRAS (exon 2) metastatic colorectal cancer.

This approval converts the accelerated monotherapy approval granted in 2006 to a full approval. Panitumumab was previously approved by the FDA as a monotherapy for patients with EGFR-expressing metastatic colorectal cancer after disease progression and prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy. The agent is not indicated for the treatment of patients with KRAS-mutant metastatic colorectal cancer or for whom KRAS mutation status is unknown.

The FDA also approved the therascreen KRAS test as a companion diagnostic to guide use of panitumumab in the treatment of metastatic colorectal cancer.
Molecular Profiles of Cytogenetically Normal AML

<table>
<thead>
<tr>
<th>RISK STATUS</th>
<th>CYTOGENETICS</th>
<th>MOLECULAR ABNORMALITIES</th>
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</table>
| Better-risk  | \(\text{inv}(16)^{2,3}\) or \(\text{t}(16;16)^2\)  \
|              | \(\text{t}(8;21)^2\)            | Normal cytogenetics:  \
|              | \(\text{t}(15;17)\)            | \(\text{NPM1}\) mutation in the absence of \(\text{FLT3-ITD}\)  \
|              |                                      | or isolated biallelic \(\text{CEBPA}\) mutation |
| Intermediate-risk | Normal cytogenetics  \
|                | +8 alone                        | \(\text{t}(8;21), \text{inv}(16), \text{t}(16;16)\):  \
|                | \(\text{t}(9;11)\)           | with \(\text{c-KIT}\) mutation |
|                | Other non-defined                |                         |
| Poor-risk     | Complex (\(\geq3\) clonal chromosomal abnormalities)  \
|                | Monosomai karyotype \
|                | \(-5, 5q-, -7, 7q-\)       | Normal cytogenetics:  \
|                | \(11q23 - \text{non t}(9;11)\) | with \(\text{FLT3-ITD}\) mutation^6 |
|                | \(\text{inv}(3), \text{t}(3;3)\) |                         |
|                | \(\text{t}(6;9)\)           |                         |
|                | \(\text{t}(9;22)\)^4         |                         |
Where else is genomics being used/studied?

- **Infectious diseases**
  - Outbreak tracking
  - Resistance monitoring
  - Environmental assessment (water and food safety)

- **Virology**
  - Ability to predict response to therapies for chronic viral diseases such as HIV and HCV

- **Detection of rare diseases**
  - Potential of whole genome sequencing for newborns to diagnose rare disorders early and avoid devastating complications
Where else is genomics being used/studied?

- Large number of studies of biomarkers (in many areas) to predict outcome and response to therapy
  - At presentation, may allow tailored therapy to risk
  - At earlier assessment may allow better prognostication
  - During therapy, may be able to predict response early and avoid costly or toxic therapies
What areas are currently under-represented? (IMO)

- **Metabolic diseases and syndromes**
  - Why do some diabetics develop complications and some not?

- **Heart disease**
  - Can we predict which patients with CHF will respond to which drug?

- **Mental health**
  - Huge potential to understand multifactorial causes of MH disorders
  - (NB Globe article June 21, 2014 re autism)

- **Drug/genome interactions**
  - Covered yesterday

- **Environmental/occupational predispositions or effects on disease**
Controlling the mosquito menace

John J. Coirssen and Henry I. Miller

Mosquito-borne diseases kill millions of people annually, and cause suffering for many more. In 2012, there were an estimated 207 million cases of malaria, leading to some 627,000 deaths. Dengue fever is a leading cause of illness and death in the tropics and subtropics, with as many as 100 million people infected each year. And there are an estimated 200,000 cases of yellow fever annually, leading to 30,000 deaths worldwide.

It takes only one bite from a disease-carrying mosquito to transmit a debilitating or deadly infection. Male mosquitoes do not bite, so their release presents no health risk, and, because their progeny die, no genetically engineered mosquitoes persist in the environment.

Male mosquitoes are bred in the laboratory with a specific genetic mutation. As a result, their offspring produce high levels of a protein that prevents their cells from functioning normally, causing them to die before reaching maturity. Male mosquitoes do not bite, so their release presents no health risk, and, because their progeny die, no genetically engineered mosquitoes persist in the environment.

If the males are released over a period of several months, this would, in theory, result in a marked reduction in the mosquito population.

As a result, research and development in genetic engineering is more expensive, discouraging investment and hampering innovation.

This is all the more problematic in the case of mosquito control, given the urgency of the problem. The World Health Organization's Special Program for Research and Training in Tropical Diseases has called upon regulatory agencies to emphasize "science-based, case-by-case targeted requirements with a de-
Why BC is ideally suited to lead

- World class institutions devoted to life sciences research
  - Universities
  - Health authorities
  - Research networks within the above
- Funding agencies who “get it”
  - Genome British Columbia
  - Michael Smith Foundation for Health Research
  - Provincial and federal agencies in health, industry, agriculture, forestry, and fisheries
- Strong government structures for things such as intellectual property, commercialization, etc
BC has a vibrant biotech industry!

- 310 Life Science Organizations
- Total estimated annual expenditures around $1 Billion
- Total estimated employment – 8,500 FTEs and 5,500 indirect FTEs
- Total estimated wages & salaries - $600 million
- Average industry wage - $68,000
- Total estimated life sciences research funding - $424 million
- 26 publicly traded companies with total market value of $1.1 billion

Courtesy Jeremy Webster, GBC Forum May 2014
Background

- Co-founded by the late Dr. Michael Smith, Nobel Laureate, Genome British Columbia was formed in July 2000.

- The initial strategic plan covered the period 2001 through 2005, with a $69M program.

- Genome BC has successfully implemented its second strategic plan (2005-2010) and exceeded the $300M research program.

- Genome BC has initiated its third strategic plan (2010-2015) and currently is executing a $340M research program.

- 2015-2020 strategic plan being completed.
Genome BC funding and objectives

**Investment Sources**
- Federal: 45%
- International, Industry & Institutional: 30%
- Provincial: 25%

**Research Investment Objectives**
- Match BC’s key economic concerns.
- Leverage contributions from other organizations.
- Maintain partnerships with a broad cross-section of provincial institutions, and locations.
Title

2000-2005 Plan
Building the
Foundation

2005-2010 Plan
International
Recognition for
Excellence

2010-2015 Plan
Strategic
Investment for
Applications

2015-2020 Plan
Sector-driven
User Co-investment

- Discovery
- Applied
- Translation

<table>
<thead>
<tr>
<th>Year</th>
<th>Discovery</th>
<th>Applied</th>
<th>Translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-2005 Plan</td>
<td>90%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>2005-2010 Plan</td>
<td>63%</td>
<td>30%</td>
<td>7%</td>
</tr>
<tr>
<td>2010-2015 Plan</td>
<td>41%</td>
<td>37%</td>
<td>22%</td>
</tr>
<tr>
<td>2015-2020 Plan</td>
<td>36%</td>
<td>36%</td>
<td>28%</td>
</tr>
</tbody>
</table>
Title
Where/what are the challenges?

- We don’t know what we don’t know until we find it
  - Although the human genome consists of over 3 billion base pairs, there are estimated to be only 20,000 protein coding genes (<1.5% of total genome)
  - In early studies, accusations were made about “fishing expeditions” but in fact these were not valid

- We need to look at both the input and output data of genomic studies of populations and patients
  - BC is ideally suited to this because we have a single payer system with good (and getting better) electronic records and outcomes analysis, particularly in some fields

- Consumer driven knowledge will be both an asset and a problem
genomics in colon cancer

Targeted Cancer Therapy - perthera.com
Find the Right Treatment for YOU With Perthera's Molecular Analysis
For Physicians Patient Information
Personalized Approach

Stage 4 Colorectal Cancer - scienceofcrc.org
Treatment Information For Stage 4 Resources For Metastatic Patients

Colon Cancer Awareness - colorectal-cancer.ca
Find all the facts you need: Prevention, treatment & support
Colon Cancer Symptoms - Local Support Groups - Treatment Options

Systematic genomic identification of colorectal cancer gene...
www.biomedcentral.com/1755-8794/6/54
by HJ Lee - 2013 - Cited by 2 - Related articles
Dec 5, 2013 - While the genomic and genetic basis of colorectal cancer has been elucidated to some degree, less is known about the identity of specific...
Abstract - Background - Methods - Results

Molecular Profiling of Colorectal Cancer - My Cancer Genome
www.mycancergenome.org/content/disease/colorectal-cancer
Colorectal cancer is the second leading cause of cancer related mortality in the United States, with an estimated 136,830 new cases and 50,310 deaths...
Where/what are the challenges?

Public consumer initiated testing may result in downstream tests/costs which are not necessarily indicated

- Some “mutations” represent genetically selected balanced polymorphisms
- Physicians/HCP may not have the ability to interpret results and thus further drive costs through referrals or supplementary testing (same as for “big data”)
Figure 4. Distribution of Genome BC's Investment by Sector.
Genomics is NOT just for health!

2. Reverse the neglect of agriculture and industrial biotechnologies

The bioeconomy will be global, with heavy involvement from both OECD and non-OECD countries, especially in agricultural and industrial applications. Approximately 75 percent of the future economic contribution of biotechnology and large environmental benefits are likely to come from these two areas. Yet, over 80 percent of research investments in biotechnology by the private and public sectors go to health applications.

1. Boost research in agricultural and industrial biotechnologies by increasing public research investment, reducing regulatory burdens and encouraging private-public partnerships.

2. Encourage the use of biotechnology to address global environmental issues (e.g. climate change and fishery depletion) by supporting international agreements to create and sustain markets for environmentally sustainable biotechnology products.

Source: The bioeconomy to 2030. OECD 2009
Interrelationships between health and other areas

- Environmental/climate change
- Industrial remediation
- Food safety and security
- Bioeconomy of forests, oceans, and agriculture
Conclusions

- Genomic research and knowledge offers huge promise for the diagnosis, prognosis, and therapy of human diseases

- At the current moment, our understanding of how this will all fit together remains (somewhat) rudimentary
  - Population based research will likely be key and BC is well positioned to carry this out

- A recurrent theme at genomic meetings is the need for analytical power/people to match the rapidly evolving power of the sequencing machines

- We as health professionals need to understand the interrelationships with other areas where genomic research will also be of fundamental importance
Thank You!

GENOMICS AS A CATALYST

GENOMICS IS UNLOCKING POTENTIAL IN BC'S STRATEGIC GROWTH SECTORS.

LEARN HOW.