David M. Margulies, M.D.

Executive Director, Gene Partnership, CHB

Faculties of Center for Biomedical Informatics, Genetics, Genomics, Developmental Medicine, Harvard Medical School

November 17, 2011
• Emerging Medical Genomics
• Children’s Hospital Gene Partnership Project
• Gene Partnership
  • Inputs: consents + specimens + phenotypes + genomic measurements + prevalence and annotation data
  • Outputs: the correlation between a genotype and a phenotype
**D'où Venons Nous? Que Sommes Nous? Où Allons Nous?**
Where do we come from? what are we? where are we going?

Genetics + human genetics + molecular biology (recently, DNA/RNA editing) + biotechnology + nucleic acid chemistry + microelectronics + computer sciences + informatics + fiber optics + robotics + nanotechnology + systems biology + stem cell biology + ...
Extensive Sequencing to Diagnose Rare Disorders

• 1902 – disorder in the metabolism of phenylalanine and tyrosine
  • Disorder of joints and heart valves with curious darkening of urine
  • Treatment with dietary restriction
Exome sequencing for known genes:
-- Sequence an exome
-- Interpret a ‘region of interest’
Sequencing to Diagnose Rare Disorders

Exome (or genome sequencing) for unknown diseases

Exome sequencing identifies the cause of a mendelian disorder

Sarah B Ng, Kati J Buckingham, Choli Lee, Abigail W Bigham, Holly K Tabor, Karin M Dent, Chad D Huff, Paul T Shannon, Ethylin Wang Jabs, Deborah A Nickerson, Jay Shendure & Michael J Bamshad

Affiliations | Contributions | Corresponding authors

Nature Genetics 42, 30–35 (2010) | doi:10.1038/ng.499
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New exome sequencing data → that a disease causing sequence variation or chromosomal structural abnormality can be identified in 68-82% of XLID cases.
• Approval of bone marrow transplant (BMT)
• Choice NOT to use BMT in a leukemic patient
• Genome sequencing $\rightarrow$ therapy
Individualizing Cancer Treatment

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

Steven JM Jones,1 Janessa Laskin,2 Yvonne Y Li,1 Obi L Griffith,1 Jiehong An,1 Mikhail Bilenky,1 Yaron S Butterfield,1 Timothee Cezeard,1 Eric Chuah,1 Richard Corbett,1 Anthony P Fejes,1 Malachi Griffith,1 John Yoo,3 Montgomery Martin,2 Michael Mayo,1 Nataliya Mlynky,4 Ryan D Morin,1 Trevor J Pugh,1 Tesa Severson,1 Sohrab P Shah,1,5 Margaret Sutcliffe,2 Angola Tam,1 Jefferson Terry,4 Nina Thiessen,1 Thomas Thomson,2 Richard Varhol,1 Thomas Zeng,1 Yongjun Zhao,1 Richard A Moore,1 David G Huntsman,3 Inanc Birol,1 Martin Hirst,1 Robert A Holt,1 and Marco A Marra1

1Genome Sciences Centre, British Columbia Cancer Agency, 570 West 7th Avenue, Vancouver, BC, V5Z 4S6, Canada
2British Columbia Cancer Agency, 600 West 10th Avenue, Vancouver, BC, V5Z 4E6, Canada
3Vancouver General Hospital, 2021 Burrard Street, Vancouver, BC, V5Z 1M9, Canada
4Centre for Translational and Applied Genomics of British Columbia Cancer Agency and the Provincial Health Services Authority, Laboratories, 600 West 10th Avenue, Vancouver, V5Z 4E8, BC, Canada
5Molecular Oncology, BC Cancer Research Centre, 601 West 10th Avenue, Vancouver, BC, V5Z 1L3, Canada
RCorresponding author.

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PMCID: PMC2945784

Children's Hospital Boston
Figure 4 PET-CT scans of the patient. (a) 1 October 2008, 1 month before sunitinib initiation. (b) 29 October 2008, baseline before sunitinib initiation on 30 October 2008. (c) 9 December 2008, 4 weeks on sunitinib.
BRAF Inhibitor Shrinks Metastatic Melanoma

BRAF Inhibitor Prolongs Survival in Patients with Metastatic Melanoma

But ONLY in patients whose tumors have the BRAF mutation

Potential for Personalized Cancer Medicine in Pediatrics

- Somatic targetable cancer promoting mutations in pediatric malignancies
  - Neuroblastoma
    - ALK
  - Low grade gliomas
    - BRAF, EGFR, PDGFR, PIK3CA
  - Langerhan’s Cell Histiocytosis
    - BRAF, MET
  - There are likely to be more

Activating mutations in ALK provide a therapeutic target in neuroblastoma


NATURE Vol 455 | 16 October 2008

Profiling Critical Cancer Gene Mutations in Clinical Tumor Samples


Recurrent BRAF mutations in Langerhans cell histiocytosis

Gayane Badalian-Very, Jo-Anne Vergilio, Barbara A. Degar, Laura E. MacConaill, Barbara Brandner, Monica L. Calicchio, Frank C. Kuo, Azra H. Ligon, Kristen E. Stevenson, Sarah M. Kehoe, Levi A. Garraway, William C. Hahn, Matthew Meyerson, Mark D. Fleming, and Barrett J. Rollins

BLOOD, 16 SEPTEMBER 2010 • VOLUME 116, NUMBER 11
Predicting Relapse in Patients With Medulloblastoma by Integrating Evidence From Clinical and Genomic Features

Pablo Tamayo, Yoon-Jae Cho, Avid Tsherniak, Heidi Greulich, Lauren Ambrogi, Netteke Schouten-van Meeteren, Tianni Zhou, Allen Buxton, Marcel Kool, Matthew Meyerson, Scott L. Pomeroy, and Jill P. Mesirov

See accompanying editorial on page 1395 and articles on pages 1400, 1408, and 1424

ABSTRACT

Purpose
Despite significant progress in the molecular understanding of medulloblastoma, stratification of risk in patients remains a challenge. Focus has shifted from clinical parameters to molecular markers, such as expression of specific genes and selected genomic abnormalities, to improve accuracy of treatment outcome prediction. Here, we show how integration of high-level clinical and genomic features or risk factors, including disease subtype, can yield more comprehensive, accurate, and biologically interpretable prediction models for relapse versus no-relapse classification. We also introduce a novel Bayesian nomogram indicating the amount of evidence that each feature contributes on a patient-by-patient basis.

Patients and Methods
A Bayesian cumulative log-odds model of outcome was developed from a training cohort of 96 children treated for medulloblastoma, starting with the evidence provided by clinical features of metastasis and histology (model A) and incrementally adding the evidence from gene-expression-derived features representing disease subtype-independent (model B) and...
Future State

Cho Y et al. JCO 2011;29:1424-1430

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In Kirby-Bauer testing, white wafers containing antibiotics are placed on a plate of bacteria. Circles of poor bacterial growth surround some wafers indicating susceptibility to the antibiotic.
AmpliChip CYP450 Test: Case study
Enabling right drug, at right dose

62 yr patient treated with codeine. On day 4 found to be unresponsive and transferred to intensive care

- CYP2D6 genotyping showed mutations causing ultra-rapid metabolism → hugely increased levels of active compound
- Treatment altered and patient recovered

→ additional CHF 13’000 unnecessary costs incurred

Genotyping CYP450 has potential to improve efficacy of 10–20% of all drug therapy and reduce incidence of ADRs by 10–15%

Source: Trends in Pharmacological Sciences, April 2004, p198
Diagnostics value proposition
Tailoring medicine for efficient healthcare

- In the US over 2 million adverse drug reactions (ADRs) per year
- AmpliChip CYP450 could cut costs in 44% of cases
- US health spending forecast growth 7.3% per annum
- US health care system could potentially save $21 bn by 2020

Potential ADR Savings

USD bn
25
20
15
10
5
0
2005 2010 2015 2020

$7  $10  $15  $21

Calculation:
Total ADEs
ADEs associated with drug metabolized CYP450 Enzyme (75% of 59% x total ADEs)
Cost per ADE (from above)

2'000'000
865'000
54'685
Lazarou et al.
Phillips et al.
Classen et al.
Future State

- Reverse blindness? [LCA – replacement of RPE65 gene by viral vector]
- Direct DNA editing?
- Define cancer therapy based on dynamic tumor genomics?
- Comprehensive pharmacogenomic surveillance?
- Prevention sudden cardiac death?
Future State

- Define mechanisms of ASD and specify treatments
- Reverse intellectual impairment?!?!
The telescope first appeared in the Netherlands. In October 1608, the national government in The Hague discussed a patent application for a device that aided "seeing faraway things as though nearby." It consisted of a convex and concave lens in a tube. The combination magnified objects three or four times. The government of the Netherlands approved the patent for this device and granted it to a group of astronomers in the Netherlands. The group included Galileo Galilei, who was funded by the government for further research. Galileo's work led to the development of the telescope and its use for astronomical observation. The telescope allowed astronomers to observe the moon, sunspots, and other celestial objects in greater detail than ever before. The telescope also played a key role in the development of modern astronomy and the understanding of the universe.
Creating a “Macroscope”? 

- TGP is the blueprint for a system (of instruments, methods, data, software, and people) which:
  - Measures the gene sequence and gene expression of an individual or a population.
  - Correlates these measurements with individual or population phenotype information.
  - Associates these measures with all available existing data and heuristics about the meaning of gene sequence variation.

- Macroscope: [mak-ruh-skohp]
  - A macroscope is the fundamental instrument of systems biology (“macrobiology”).
  - Its purpose is to measure the correlation between genotypes and observed properties of cells, tissues and individuals.
TGP's Activities

1. **Collect & Bank Samples, and Extract DNA**
   - Features:
     - Centralized patient acquisition
     - Easily understood informed consent
     - Sample collection procedures

2. **Sequence DNA and aggregate data with clinical data**
   - Features:
     - CLIA next-gen sequencing facility
     - I2b2 connected across locations with the ability to incorporate genomic data

3. **Perform Research on Genomic & Clinical Data**
   - Features:
     - Genomic data from CLIA Lab
     - Clinical data from CHB
     - Tools to mine data and find new correlations

4. **Return Research Results**
   - Features:
     - Research results generated both at and outside CHB
     - Scientific Advisory Board and ICOB evaluation

5. **Maintain Ongoing Condition Updates**
   - Features:
     - Research results converted into rules, with patient messaging
     - Rule-based “Safe Genes” DB to become de facto industry standard for genomic medicine

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**Genetic Counseling Services**

Children's Hospital Boston
Using a “Macroscope”

- **Characterize** *(people, disorders, tissues)*
  - One gene, many phenotypes AND one phenotype, many genes
  - Absent proper categorization/mechanism, rational therapy impossible

- **Hypothesize**
  - This gene $\rightarrow$ this pathway $\rightarrow$ this compound
    - Marfan’s trial
    - Fragile X

- **Categorize**
  - Patient stratification in trials
  - Patients in clinical cohort
    - PGx responsiveness
  - Tumors

- **Discover**
  - Standardized observations $\rightarrow$ new insights
  - GEO
    - Ontology
    - Expression arrays
Marfan’s Syndrome

Dominantly inherited systemic connective tissue disorder characterized by multiple variable abnormalities of the skeletal, ocular, cardiovascular, pulmonary, skin, and nervous systems.

Arachnodactyly

- Tall, thin stature
- Long arms,
- Cubitus valgus,
- Pectus carinatum
- Myopia

Images from John C.S. Dean. Heart 2002;88:97-103
Marfan’s Syndrome (MFS) Leads to Aortic Dilation and Dissection

The clinically most severe complications of MFS are aortic dilation and dissection, which typically begin at the aortic root and can remain isolated or propagate along the descending aorta.

Aortic dilation can be slowed through timely pharmacologic treatment, and aortic dissection can be prevented by prophylactic aortic root replacement surgery.

Images from http://www.massgeneral.org/loc/patients/diseases.asp?id=a_dissection and John C.S. Dean. Heart 2002;88;97-103
Genetic Diagnosis of Marfan’s Syndrome Can Guide Therapy

- *FBN1* codes for fibrillin, which assembles into microfibrils involved in:
  - Conferring elasticity to connective tissue
  - Regulating bioavailability of TGFβ and, indirectly, activation of Smad transcription factors.

- Loss-of-function mutations in *FBN1* increase TGFβ bioavailability and thus Smad activity

- Angiotensin II increases Smad activity independently of TGFβ

- Angiotensin II receptor blockers likely to ameliorate effects of *FBN1* mutations

Losartan prevents aortic aneurysm in mice. Representative mouse ascending aortas (arrowheads) are shown after latex injection. (A) Wild-type mouse. (B–F) Mice heterozygous for Fbn1 mutation (C1039G), treated with placebo (B), propranolol (C), or losartan (D–F). Scale bars: 4 mm. (Habashi et al. 2006. Science 312:117–21)
Angiotensin II Type 2 Receptor Signaling Attenuates Aortic Aneurysm in Mice Through ERK Antagonism

Jennifer P. Habashi,1,2* Jefferson J. Doyle,1* Tammy M. Holm,1 Hamza Aziz,1 Florian Schoenhoff,1 Djahida Bedja,3 YiChun Chen,1 Alexandra N. Modiri,1 Daniel P. Judge,4 Harry C. Dietz1,2,4†

Losartan Shows Promise in Preventing Aortic Aneurysm – Here’s How
Mean Annual Rate of Change in Absolute and Normalized Aortic Diameters before and after Initiation of Therapy with an Angiotensin II–Receptor Blocker (ARB).

## Selected Children’s Projects and Current State

<table>
<thead>
<tr>
<th>Category</th>
<th>Children’s project</th>
<th>Consent</th>
<th>Curate</th>
<th>Phenotype</th>
<th>Sequence</th>
<th>Analyze</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine mechanism of disease in a patient</td>
<td><em>Manton Center, Genetics and Genomics</em></td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Characterize evolving neoplasm</td>
<td><em>Somatic sequencing of tumors</em></td>
<td>✓ ✓ ✓</td>
<td></td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Determine suitability of intervention for patient</td>
<td><em>Screening for known drug/genetic interactions</em></td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Define pathways implicated in disease</td>
<td><em>Autism Spectrum disorders, Cardiology, Hematology, etc.</em></td>
<td>✓ ✓ ✓</td>
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</tr>
<tr>
<td>Stratify patients for trials</td>
<td><em>Autism Spectrum Disorder</em></td>
<td>✓ ✓ ✓</td>
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</tbody>
</table>
Space, the Final Frontier?

“The whole enterprise will cost Mr. Yerkes certainly half a million dollars. He is red hot and does not hesitate...It is a pleasure to do business with such a man.”
—William R. Harper, 1892

Hale set himself to organizing what would become Yerkes Observatory. He knew that Alvan Clark & Sons had a partly finished lens, 40 inches in diameter, left over from another telescope project that never materialized. A few days after the visit to Yerkes, Alvan Graham Clark arrived in Chicago and agreed to finish the 40-inch lens for the new observatory. The noted instrument firm Warner and Swasey would make the telescope mount.

Alvan Clark & Sons finished the lens (actually an achromatic pair, one lens of crown glass and one of flint glass) in October 1895. It weighed 500 pounds and had a focal length of 62 feet. In 1897, the lens was shipped to Williams Bay, Wisconsin, the chosen site of the new observatory. The telescope with its moving parts and counterweights weighed over 20 tons, yet it was so well-balanced that small motors could easily move it to point at any part of the sky. As at Lick, astronomers could raise and lower the entire floor of the observatory in order to reach the eyepiece. Astronomers who used the new telescope were delighted with its quality.
• Redefine research compact...
  – IRB ✓
  – ICOB ✓
• Store tissues
  – Biorepository ready in spring, 2012 ✓
• Genomic measurements ✓
Approach and Status?

- Define infostructure
  - EMR (Cerner and EPIC) links – underway
  - i2B2/SHRINE – underway
  - CBI – underway
- Define clinical, research pilots
  - Clinical pilots defined – Q1/2 2012 start
  - First research pilot defined; specimens on hand
- Collaborative outreach
  - Underway -- many roups involved: genetics, genomics, neurology, developmental medicine, psychiatry, cardiology, orthopedics, hematology, GI, immunology, oncology, endocrinology, ...
A Pipeline is Key...
Next Generation Platforms
Descriptions

Run (load)
Gross yields, by lanes, tiles. Read error rates, filters. Other instrument activity and run logs

Sample libraries
De-multiplexed reads by sample libraries. Yields and errors by sample library.

Assay (primary)
Align to field of view (FOV). Alignment yield, fragment performance (unique, pair coherence, sizing). Yield and assay effectiveness in area of focus (AF).

Target (secondary)
Substitutions, indels in regions of interest (ROI)

Quality
Depth of coverage (illumination) across FOV, ROI. Quality of genotyping, of analyses.

Interpretation of variation
Naming, classification, annotation, review, assessment. Scoring (scored, un-scored, new, novel). Advanced, in context of related data (family, time series, germline)

Technical performance (validation)
Sensitivity, false detection, by segments in ROI

Clinical performance
Sensitivity by genes, relationship with clinical explanatory power, critical segments.

Test metrics (QA assessment)
Variant, interpretation, specimen, runs and segment quality relative to validation standards. Confirmations.

Clinical reporting
Interpreted findings and recommendations for physician and patient.

Technical (quality)reporting
Supporting data and documentation
Clinical reports are comprehensive, yet simple:

**Front page:**
*Who the report is about, the essence, a focus on significant findings and links to further information*

**Starting with following page:**
*A gene-by-gene detailed positive findings with references and authority*

**Then:**
*Technical specification and results*

**And finally:**
*Representations and signatures*
Variant Analysis Algorithm

Sequence variant

- Found only in affected population
- No or insufficient information on variant occurrence
- Found in general population

Functional effect shown in experimental system

- yes
- unclear
- no

Predicted to impair structure and/or function of gene product based on:
- Nature of change in gene product
- Location of change in gene product (conserved/non-conserved region)

- Truncation, splice-site mutation
- Missense mutation
- Intrinsic mutation
- Silent (exonic)

Associated
- probably associated
- possibly associated
- unknown significance
- unlikely to be associated
- very unlikely to be associated
- not associated

-3 to +3 scale

Children's Hospital Boston
GP Opportunities with Pharma R&D

• CHB is an efficient partner for stratified clinical trials
  – Large cohort (over time, most/all CHB) who are consented and phenotyped
    • Many will have been sequenced (DNA and RNA)
    • Tissue specimens in our biorepository
    • Receptive to trial invitations
    • Pipeline sits atop NCBI, Broad, ‘ROW’ data and analytic methods

  – Multi-institution query capabilities to expand the cohort

• CHB is an efficient partner for study of monogenic, penetrant disorders with known targetable mechanism of disease and a reasonable outcome measure or biomarker.

• By combining phenotype, genotype and tissue, CHB can help move well stratified clinical trials back to the bench
Challenges:

- The “Incidentalome”
- Clinical utility and cost impact of new testing
- Attainment of CLIA standards for new testing
- Data integration is complex
  - Genes
  - Expression
  - Pathways
  - Phenotypes
- Pace and complexity of projects
- ...

Children's Hospital Boston
Conclusions

• Great hope that we’ll come to see transformative changes in the understanding and care of patients with devastating disorders
• Genome-derived knowledge may allow a safer transit for many through the clinical interactions in their lives
• We may attain a clearer understanding of some of the fundamental processes of human biology
• Excellence in genomic research and medical genetics is a ‘natural franchise’ for CHB and HMS. With focus and strong collaboration, this will be a wonderful decade.