Personalized Medicine: A Hospital Perspective

Elizabeth G. Nabel, M.D.
President, Brigham and Women’s and Faulkner Hospitals
Professor of Medicine, Harvard Medical School

October 20, 2010
Personalized Medicine and Patient Care

- Crimson
- i2b2
- Partners Center for Personalized Genetic Medicine
- Center for Advanced Molecular Diagnostics
- Our Genes, Our Health, Our Community
- Personalized Cancer Medicine Partnership

Acknowledgements: >1000 individuals contributed to these efforts!
Crimson: The Basic Premise

The average Clinical Laboratory/Pathology Department discards thousands of samples daily.

These materials represent the entirety of the human condition, in health and disease.
Crimson and i2b2: The Basic Premise

Timely Clinical Data:
Lab/Pathology Samples, Other

Consented samples

Samples
(Consented, De-Identified or Anon)
Crimson and i2b2: Infrastructure to Support a Research Enterprise

**Clinical/Phenotypic Data**

- CDR (RPDR/i2b2) + NLP tools
  - Clinical Data Repository is the basis for cohort generation + datasets.
  - Need NLP to get predictive values >95% for cohorts and to enrich datasets.
  - In existence for 12 years at Partners
  - High hundreds of requests/year
  - ~100M in grants supported.

(Shawn Murphy, Zak Kohane)
Crimson and i2b2: Infrastructure to Support a Research Enterprise

Samples
Crimson
(Lynn Bry, Neil Herring)
- In existence for 3 yrs
- Mid-tens requests/year
- ~30M in grants supported

Clinical/Phenotypic Data
CDR (RPDR/i2b2) + NLP tools
(Shawn Murphy, Zak Kohane)
- In existence for 12 years at Partners
- High hundreds of requests/year
- ~100M in grants supported.

~20% of studies requesting samples use cohorts and/or data from a CDR (RPDR, i2b2, APLIS or other system).
Crimson and i2b2: Infrastructure to Support a Research Enterprise

High-throughput ‘omics studies
- Scalable infrastructure in place for 3 yrs
- 3-4 new studies/year
- ~15M in grants supported.

Samples
Crimson
(Lynn Bry, Neil Herring)
- In existence for 3 yrs
- Mid-tens requests/year
- ~30M in grants supported

Clinical/Phenotypic Data
CDR (RPDR/i2b2) + NLP tools
(Shawn Murphy, Zak Kohane)
- In existence for 12 years at Partners
- High hundreds of requests/year
- ~100M in grants supported.
## Multiple Use Cases: High Throughput Collection

<table>
<thead>
<tr>
<th>Cases</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consented - Dedicated Collection</td>
<td>Consent patients for designated research samples</td>
</tr>
<tr>
<td>Consented - Discarded Collection</td>
<td>Consent patients for collection of discarded samples.</td>
</tr>
<tr>
<td>Time-Limited-Link</td>
<td>Link to PHI for IRB-defined period - used for (1) clinical escrow, (2) await final results/data, (3) chart review and annotation by honest broker, or (4) approach patients for consent.</td>
</tr>
<tr>
<td>De-identified</td>
<td>Sample linked to de-ID dataset (various flavors).</td>
</tr>
<tr>
<td>Anonymous</td>
<td>Sample linked to very limited dataset</td>
</tr>
</tbody>
</table>
i2b2: Free and Open Source Translational Toolkit - Implementations

- Project Management
- Natural Language Processing
- De-Identification of Data
- Workflow Framework
- VisualTerm Mapping
- File Repository
- Correlation Analysis
- Ontology Management
- Identity Management
- Data Repository (CRC)
- Data Visualization
- Annotating Genomic Data
- Data Queries
Diabetes Drug Maker Hid Test Data, Files Indicate

by GARDNER HARRIS
Published: July 12, 2010

In the fall of 1999, the drug giant SmithKline Beecham secretly began a study to find out if its diabetes medicine, Avandia, was safer for the heart than a competing pill, Actos, made by Takeda.

Avandia’s success was crucial to SmithKline, whose labs were otherwise all but barren of new products. But the study’s results, completed that same year, were disastrous. Not only was Avandia no better than Actos, but the study also provided clear signs that it was riskier to the heart.

But instead of publishing the results, the company spent the next 11 years...
i2b2: Oral Hypoglycemic Agents

- Rosiglitazone vs Pioglitazone
- Rosiglitazone vs Metformin
- Rosiglitazone vs Sulfonylurea

Relative risk of myocardial infarction

Year:
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
i2b2: SHRINE – Distributed Multiinstitutional Query across Hospitals
i2b2: Catalyst and SHRINE Network

[Diagram showing connectivity between various datasets and institutions]

- **SHRINE Adaptor**
- **Local Databases**
- **Source Institution**

Institutions and Data Sources:
- **BIDMC**
- **DFCI**
- **CHB**
- **PHS**
- **GIGPAD**
- **RPDR**
- **SPIN VSL**
- **SPL Martinos**
- **Harvard Dental**
- **MGH Oral & Maxillofacial Surgery**
- **Forsyth Institute**

Data Sources and Aggregates:
- **GCRC Data**
- **Crimson**
- **MR Images**
- **Genomics Center**
- **Genomics Center**
- **CHQuery**
- **Remote CTSC**
- **Remote CTSC**
Partners Center for Personalized Genomic Medicine

- 100 faculty and staff of MGH/BWH/Partners Healthcare
- Mission: Advance translational genetics and genomics and its application to the clinical care of patients across the Partners HealthCare System and in healthcare nationally and globally
Partners Center for Personalized Genetic Medicine: Vision for an Academic System

- Integrated genomic and phenotypic data repository
- Hypothesis and Non-hypothesis-driven research
- Pre & post symptomatic disease management
- Drug Discoveries
- Diagnostics Discoveries
- Improved Personalized Medicine
- Information Technology Advances

Translational Research

Diagnostics

Drug Discoveries
Synergistic and Interdependent Research and Clinical Visions

Researchers

- Provide the tools and data needed to produce genomic discoveries
- Supply cases and samples

Clinicians

- Clinically validate discoveries and rapidly integrate them into routine care
- Improve patient care by enabling effectively use of increasing amounts of genetic data and knowledge
Partners Personalized Medicine Infrastructure

Research
- I2B2 (HIVE/RelNet/Pharmacologic Surveillance)
- Computational Cluster and Storage Resources

Clinical
- Clinical Decision Support Rules Engine
- Electronic Health Record (EHR)
- Genomic Variant Interpretation Engine (GVIE)

Support
- Consent Tracking System (CTS)
- Genomic Knowledge Base (GenelInsight)
- Enterprise LIMS Superstructure (Inventory Management/GIGPAD/PowerPah)
- Research Patient Data Registry (RPDR)
Partners Center for Personalized Genomic Medicine: Accomplishments

Research/Clinical Accomplishments:

- First genetic laboratory test for EGFR (2004)
- First genetic laboratory test for Hypertrophic Cardiomyopathy (2007)
- First use of microarray technology for genetic testing (2008)
- Pharmacogenomics studies (2000-present)
- i2b2 project first bench to bedside use of EHR for genomics research (2005)

Delivered the first:

- Integration of fully structured genetic results into an EHR (2005)
- Pharmacogenomic clinical decision support rule through an EHR (2006)
- Interorganizational transfer of fully structured, standards compliant genetic results (2009)
- System capable of delivering electronic alerts when new knowledge is learned about a variant previously identified in their patient population (2010)

- Drove the creation of a standard for integrating genetic results into the electronic medical record

- Other organizations look to us for leadership in this area
Clinical Implementation – Center for Advanced Molecular Diagnostics (CAMD)
CAMD: Clinical Implementation
CAMD: Clinical Implementation
Operational Challenges

- **IS**
  - New databases and new ways of accessing databases are being created

- **Communications**
  - Personalized medicine efforts have to be publicized to attract donor funds and to position DF/BWCC in comparison to its competition
  - Ongoing tension between the need to publicize and the need to create realistic expectations based on what has actually been accomplished to date
  - Critically important to coordinate this with BWH

- **Reimbursement**
  - Some of the genotyping tests are likely to be reimbursed by 3rd party payers
  - Need to continually analyze our position and attempt to capture whatever charges we can
Personalized Cancer Medicine at Dana Farber/Brigham and Women’s Cancer Center
Rationale for Personalized Cancer Medicine Partnership

- In most of the cancers we understand, the disease is caused by mutations in genes that control cell proliferation.
- Drugs that specifically block the effects of the proteins produced by those mutated genes may halt tumor growth and, in some cases, lead to tumor cell death.
  - Side effects should be minimized because the ideal drugs would be targeted specifically against a mutated, altered protein.
- Knowing the mutation that drives a patient’s cancer could lead to providing the therapy that specifically targets that mutation.

**Personalized Cancer Medicine:** Providing a molecular profile of the cancer of every patient who comes to DF/BWCC in order to support therapeutic decisions now or in the future.

But, we can’t always predict the mutation that might be driving an individual’s cancer.
Targeted Treatments Require Knowledge of the Mutation – Personalized Medicine

**Patient A**
- **Mutation A**
- **Drug A**
- Malignant Cell Growth

**Patient B**
- **Mutation B**
- **Drug B**
- Malignant Cell Growth

**Patient C**
- **Mutation C**
- **Drug C**
- Malignant Cell Growth
Dramatic Clinical Responses to Drugs Targeting BRAF

- only in patients with the BRAF mutation!

Baseline

Day 15

Flaherty et al., ASCO 2009 (abstract #9000)
Reasons for Rapid Implementation of Personalized Cancer Medicine

- **Important treatment opportunities for our patients**
  - Availability of targeted therapies is increasing (Gleevec, Tarceva, Herceptin, …)
  - Providing tumor genotyping as a clinical test for all of our patients will let providers identify patients who will benefit from approved targeted therapies

- **Important clinical research opportunities for investigators & patients who want to participate in research**
  - Permits variety of genotype/phenotype studies in cancer
  - Substantial pipeline of new targeted therapies awaits testing
  - Tumor genotyping on all patients would provide database for identifying subjects for trials enriched for patients with specific target abnormalities
    - Speeds the clinical assessment of new agents
    - Makes this a very attractive testing site for developers of new, targeted agents

- **Important translational research opportunity**
  - Only a handful of genomic abnormalities are known to be unambiguous drivers of cancer
  - Full realization of personalized medicine requires the identification of all abnormalities
  - We have a large cohort of well characterized patients in which a non-biased genotyping study may help accomplish this
OncoMap to be Implemented First

- “OncoMap” identified as a robust genotyping technology for FFPE material
  - Center for Cancer Genome Discovery at DFCI adapted mass spectrometry-based Sequenom platform for identifying SNPs in archived, FFPE material
    - Levi Garraway led development team for OncoMap
  - Detection performance is nearly identical for FFPE and fresh frozen material
  - Highly amenable to multiplexing & therefore to being useful as a high-throughput clinical test
  - Most recent version measures >1000 cancer-related SNPs in 140 genes
  - PCMP implemented version will measure 495 cancer-related alterations in 38 genes
    - Weighted toward “actionable” mutations – mutations for which drugs exist or mutations that provide important clinical information

- OncoMap’s drawback: not an unbiased test
  - OncoMap only measures what it measures; a limited discovery tool
  - PCMP’s goal is to create an infrastructure that is independent of any specific technology
  - New assays may be added as they become validated, old assays may be swapped out on the way to whole genome sequencing
  - Already working on next generation genotyping that will allow analysis of copy number alterations and some unbiased mutation detection
## Clinical Implementation – PCMP OncoMap

<table>
<thead>
<tr>
<th>Gene</th>
<th># Mutations</th>
<th>Disease Center</th>
<th>Tumor Type (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>14</td>
<td>Thoracic, leukemia</td>
<td>leukemia</td>
</tr>
<tr>
<td>AKT1</td>
<td>1</td>
<td>Breast, GI, thoracic, GU, Gyn</td>
<td>breast, colon, lung, bladder, ovary, endometrial</td>
</tr>
<tr>
<td>AKT2</td>
<td>2</td>
<td>Breast, GI, thoracic, GU</td>
<td>breast, colon, lung, bladder</td>
</tr>
<tr>
<td>APC</td>
<td>15</td>
<td>GI, thoracic</td>
<td>colon, lung</td>
</tr>
<tr>
<td>BRAF</td>
<td>47</td>
<td>Phase 1, cutaneous, Gyn</td>
<td>Melanoma, colon, RCC, ovary</td>
</tr>
<tr>
<td>CDK4</td>
<td>1</td>
<td>Phase 1, cutaneous</td>
<td>Melanoma</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>15</td>
<td>Cutaneous, GI, Gyn</td>
<td>melanoma, pancreatic, cervix</td>
</tr>
<tr>
<td>CSF1R</td>
<td>7</td>
<td>Thoracic</td>
<td>lung</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>37</td>
<td>GI, thoracic</td>
<td>hepatocellular, lung</td>
</tr>
<tr>
<td>EGFR</td>
<td>52</td>
<td>Phase 1, Chemistry</td>
<td>Lung cancer, RCC</td>
</tr>
<tr>
<td>ERBB2</td>
<td>7</td>
<td>Phase 1, GU</td>
<td>Breast, lung (phase 1), RCC</td>
</tr>
<tr>
<td>FGFR1</td>
<td>2</td>
<td>Chemistry, GU</td>
<td>Breast, bladder, endometrial</td>
</tr>
<tr>
<td>FGFR2</td>
<td>7</td>
<td>Chemistry, GU</td>
<td>breast, ovarian, endometrial</td>
</tr>
<tr>
<td>FGFR3</td>
<td>11</td>
<td>GU, Chemistry</td>
<td>Breast, bladder, endometrial</td>
</tr>
<tr>
<td>FLT3</td>
<td>10</td>
<td>Leukemia</td>
<td>leukemia</td>
</tr>
<tr>
<td>GNAQ</td>
<td>2</td>
<td>Cutaneous</td>
<td>melanoma</td>
</tr>
<tr>
<td>GNAS</td>
<td>3</td>
<td>GI</td>
<td>colon</td>
</tr>
<tr>
<td>HRAS</td>
<td>18</td>
<td>Phase 1, GU</td>
<td>lung, GI, bladder</td>
</tr>
<tr>
<td>IDH1</td>
<td>3</td>
<td>Leukemia, Neuro-Onc</td>
<td>AML, MPD, glioma</td>
</tr>
<tr>
<td>IDH2</td>
<td>2</td>
<td>Leukemia, Neuro-Onc</td>
<td>AML, MPD, glioma</td>
</tr>
<tr>
<td>JAK2</td>
<td>2</td>
<td>Leukemia</td>
<td>MPD</td>
</tr>
<tr>
<td>JAK3</td>
<td>3</td>
<td>Leukemia, Gyn</td>
<td>leukemia, ovary</td>
</tr>
<tr>
<td>KIT</td>
<td>30</td>
<td>Leukemia, sarcoma, cutaneous, Gyn</td>
<td>leukemia, GIST, ovary</td>
</tr>
<tr>
<td>KRAS</td>
<td>45</td>
<td>Cutaneous, lung, GI, Phase 1, GU, Gyn</td>
<td>endometrial, leukemias, colon, lung , GI (phase 1), bladder, ovary</td>
</tr>
<tr>
<td>MEK1</td>
<td>5</td>
<td>Cutaneous, thoracic</td>
<td>melanoma, lung</td>
</tr>
<tr>
<td>MET</td>
<td>6</td>
<td>Phase 1, GU, Gyn</td>
<td>renal, SCLC, RCC, bladder, ovary</td>
</tr>
<tr>
<td>MLH1</td>
<td>1</td>
<td>GI</td>
<td>colon</td>
</tr>
<tr>
<td>MYC</td>
<td>6</td>
<td>Multiple</td>
<td>multiple</td>
</tr>
<tr>
<td>NRAS</td>
<td>30</td>
<td>Phase 1, ovary cutaneous, Gyn</td>
<td>lung, GI, bladder, melanoma, ovary</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>21</td>
<td>Sarcoma, Gyn</td>
<td>GIST, ovary</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>22</td>
<td>Phase 1, GU, Gyn</td>
<td>colon, breast, lung, RCC, ovary, endometrial, cervix</td>
</tr>
<tr>
<td>PTEN</td>
<td>14</td>
<td>Cutaneous, Neuro-Onc, GU, Gyn</td>
<td>melanoma, glioma, prostate, RCC, ovary</td>
</tr>
<tr>
<td>RB1</td>
<td>12</td>
<td>Multiple</td>
<td>multiple</td>
</tr>
<tr>
<td>RET</td>
<td>15</td>
<td>Leukemia</td>
<td>thyroid</td>
</tr>
<tr>
<td>SRC1</td>
<td>1</td>
<td>GI, Gyn</td>
<td>colon, ovary</td>
</tr>
<tr>
<td>STK11</td>
<td>12</td>
<td>Thoracic, GI</td>
<td>lung, GI</td>
</tr>
<tr>
<td>TP53</td>
<td>7</td>
<td>Phase 1, GU, Gyn</td>
<td>multiple</td>
</tr>
<tr>
<td>VHL</td>
<td>7</td>
<td>GU, Chemistry</td>
<td>renal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total (Gene)</th>
<th>Total (Mutations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>495</td>
</tr>
</tbody>
</table>
CAMD Sequenom: Clinical Implementation
Clinical Implementation – CAMD Reporting

Oversight in concert with PCMP Clinical Research Executive Committee

Tier 1:
Validated, FDA approved and actionable genetic test

Tier 2:
Either non-validated or non-FDA approved but potentially actionable

Tier 3:
All other genotyping data
Our Genes
Our Health
Our Community

Christine E. Seidman, MD and Elizabeth W. Karlson, MD
OurGenes, OurHealth, OurCommunity

- Patients come to BWH for exceptional patient care at a hospital where physician-scientists perform cutting edge research.

- OurGenes, OurHealth, OurCommunity can enhance this mission by discovering how genetic, environmental and lifestyle factors impact human health.

- OurGenes will develop a biorepository with consented blood samples linked to personal health information from every BWH patient over 18 years old.

At BWH Science is Part of the Cure
OurGenes, OurHealth, OurCommunity

OurGenes will provide all BWH researchers with

- **Samples**: Consented for broad-based genetics/biomarker research
- **Data linked to samples**: Longitudinal medical record, Family history, Lifestyle/Environment
- **Recontact**: Optional for subjects
- **Access**: Available to all BWH researchers with IRB approved projects
- **Genetic data**: Researchers required to return genetic data to bank

*OurGenes = An Expanding Resource*
# OurGenes, OurHealth, OurCommunity

## Core Variables in OurGenes Information Repository

### Family History
Surgeon General’s Family Health Portrait

<table>
<thead>
<tr>
<th><strong>Electronic Medical Record</strong></th>
<th><strong>Health Questionnaire</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal identifiers</td>
<td>Birth place; residence at 15, 30 yrs</td>
</tr>
<tr>
<td>Medical record number</td>
<td>Marital status</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td>Height/weight</td>
</tr>
<tr>
<td>ICD codes</td>
<td>Education/occupation</td>
</tr>
<tr>
<td>Prescription medications</td>
<td>Smoking/alcohol</td>
</tr>
<tr>
<td>Screening history</td>
<td>Sun exposure</td>
</tr>
<tr>
<td>Medical history</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Over the counter medicines</td>
<td>Falls and fractures</td>
</tr>
<tr>
<td></td>
<td>Vitamins, dietary supplements</td>
</tr>
<tr>
<td></td>
<td>Reproductive history</td>
</tr>
</tbody>
</table>
OurGenes, OurHealth, OurCommunity

Added Opportunities from OurGenes

- Establish at BWH *culture of collaboration* where patients, physicians & researchers promote discoveries to improve human health

- Enhance *BWH leadership* as shaping the future of clinical care

- Establish BWH as *premier educator* of clinicians and biomedical researchers
  - Genomic Medicine Leadership Program
The BWH Biomedical Research Institute (BRI) and Center for Faculty Development and Diversity (CFDD) are launching a Genomic Medicine Leadership Program to help familiarize physicians with current genomic technologies and the relevance of their application/interpretation in patient care.

The GMLP is an interactive six week course that will cover clinical and educational aspects of genomics, next generation sequencing, genetic counseling and risk assessment.

Participating physicians will have the option to take advantage of genomic analysis provided by a leading direct to consumer company and thus experience the course material as it relates to their own personal genome.
BW/F, Partners Healthcare, and DF/BWCC Commitment to Personalized Medicine