Whole Genome Sequencing at The Partners HealthCare System (PHS)

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Outline

- Components of the Partners Center For Personalized Genetic Medicine
- Laboratory for Molecular Medicine (LMM)
- Whole Genome Sequencing for clinical use
- GeneInsight Lab and Clinic
- Acknowledgements
How PCPGM Components Links to Each One

Research Cores
- Sequencing
- Genotyping
- Microarray
- RNA Seq.

CLIA Lab / LMM
- Sanger Sequencing
- Microarray
- Targeted Next Gen. Seq.
- Whole Genome Seq. (WGS)

Biorepository / PBMD
- 200,000 Blood / Samples
- DNA

RPDR / EMR
- 4 Million
- Partners Patients

Information Technology (IT) Infrastructure and Bioinformatics Support

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Laboratory for Molecular Medicine (LMM)

- CLIA certified lab licensed through Massachusetts General Hospital, opened in Nov 2003
- Offers high complexity Genetic tests (LDTs – laboratory developed tests)
  - Exempt from FDA approval but require validation of performance characteristics by the lab
  - Main testing platforms are capillary and array-based sequencing
  - Launched Next Gen Sequencing Tests for Cardiomyopathy in July 2011
- 200 genes, >4000 tests/year

Testing Areas at the LMM:
- Cardiomyopathy
- Marfan
- Noonan
- Hearing Loss
- Cancer
- GEM
Predicting Treatment Response Lung Cancer

May 20/June 4, 2004

The NEW ENGLAND JOURNAL of MEDICINE

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Study by Massachusetts General Hospital

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

Study by Dana Farber Cancer Institute

Test available to patients

Science, August 27, 2004

Cancer Sharpshooters Rely on DNA Tests for a Better Aim

Without further ado, two diagnostic labs have launched a genetic test to guide doctors treating a common and deadly form of lung cancer. Despite lingering questions about whether the test is comprehensive, physicians think this approach could herald a new generation of gene-based methods of tailoring cancer treatments.

Designed to prepare patients who might be helped by the drug, Iressa, the new test hunts for mutations in a gene called epidermal growth factor receptor (EGFR), whose protein targets the tumor. People who test positive are thought to benefit more from the therapy, which has in the past been the only treatments for the notoriously hard-to-treat non–small cell lung cancer—often in a small fraction of cases. If screening tests are even that effective, the roughly 10% of patients, but better group the impact was dramatic. Researchers concluded that the drug worked best in those with EGFR-dependent tumors, but there was no way to check.

Discovery

Merge Molecular, Clinical Data

Clinical Validation

Patient
Context: Evolution of Clinical Genetic Testing

Approximate Numbers of Structured Results Per Test

- Targeted Genotyping Test
- 1 or 2 Gene Sequencing Test
- 10-20 Gene Sequencing Test
- “Category” Tests 20-200 Genes
- Whole Genome Sequencing

Assumes Deltas from Reference Sequences Stored for Sequencing Tests

- Warfarin, Sickle cell
- BRCA1/2, Cystic fibrosis
- HCM CardioChip, OtoChip
- CardioScan, MR Panels

First 2 insurance reimbursements have occurred

Just Entering Use
We Anticipate WGS Will Render Targeted NGS Obsolete In About 4 Years

Percentage of LMM Tests Involving > 10 Genes

Microarray | Targeted NGS | WGS

% of LMM Volume

Pre-NGS Launch | Post-NGS Launch
BWH and MGH Clinics

Patient Workup, Consent and Test Order

Whole Genome Sequencing

Data Analysis

Interpretation and Reporting

Whole Genome Sequencing Process

Existing Infrastructure at LMM

Initially Outsource To CLIA WGS sites

Under Development at the LMM, PCPGM
Context: The Clinician’s Perspective

- Whole genome sequencing will generate 2-5 million variants per patient tested
- New information can emerge on any variant at any time
- New forms of support are already needed to stay up to date on the limited number of variants identified by today’s category tests
- Infrastructure dependent clinical processes need to be established to:
  - Enable clinicians to receive and manage genetic results
  - Link clinicians to experts capable of determining the implications of each patient’s genetic profile
  - Keep the up to date

This Creates Significant Opportunities Along Multiple Dimensions for PHS
A Key Challenge in Personalized Medicine

Constant Flow of Cases

Geneticist Constantly Signs out Cases

Leveraged and maintained as each case is signed out

Evolving Knowledgebase

Treating Clinicians Consume Reports

Case History Continuously Grows

Updating Reports When New Information Emerges on a Variant is Critical ... But Unreimbursed
Driving Cost Out of the System

Geneticist Constantly Signs out Cases

- New Variant Assessments and Knowledge Base Updates
- Occurs Automatically on Knowledgebase Update
- No Case Level Work Required
- GeneInsight
  - Report Generation Engine
  - Knowledgebase

Treating Clinician Consumes Reports

Case History Continuously Grows
GenelInsight Clinic

- Enables management of patient genetic profiles
- Delivers alerts as new variant information emerges

Provides Direct and Indirect Links to Clinician Desktops
Thereby Creating a Very Powerful Distribution Channel
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