Implementing Genomic Medicine Programs: The Laboratory Perspective

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Assistant Professor of Pathology, Harvard Medical School, Brigham & Women’s Hospital, Massachusetts General Hospital
Genomic Medicine at PCPGM

- Case selection
- PHS Genetics visit required initially
- Consent process

Whole Genome and Exome Sequencing

- Variant annotation
- Variant filtration
- Evidence-based variant assessment

BWH and MGH Clinics
(Personal Genome Consultation Service)

Patient Workup, Consent and Test Order

- Genetic EHR
- Longitudinal patient support

Data Analysis

- Orthogonal confirmation
- Report structure and content
  - Disease-Specific Reports
  - General Genome Report

GeneInsight

Initially Outsource and LMM

GeneInsight

 Interpretation and Reporting

MedSeq™
Challenges for the Clinical Implementation of WES/WGS

• Sequencing technologies are changing rapidly
• Computational requirements are unprecedented
• Result confirmation with orthogonal methods: Sanger, independent NGS platform, genotyping, MLPA, FISH, CMA
• WES/WGS vs. Disease Panels: WES/WGS have reduced analytic performance
• Return secondary findings
• Updating results over time
• Human variation is enormous and rare; phenotype and genotype data sharing will be critical
Indications for Testing
Diagnostic:
- No tests available, prior tests negative, testing likely to be lengthy/costly/low yield
Screening:
- Preconception but not prenatal or newborn; healthy if high threshold for results return

Pre-test Considerations
- Counseling and consent
- Secondary findings
- Clinical vs. research (VUSs -> research)

Clinical Testing and Results Reporting
- CLIA labs with boarded geneticists
- Test results can include: known genes, novel genes, secondary findings
- Labs should have policies on the return of secondary findings and be given the option to not receive secondary findings
- Clinical geneticist involved in results return
- Labs should share genotypic data from WGS/WES in public databases

ACMG Workgroups
- Secondary Findings (Co-Chairs: Robert Green and Les Biesecker)
- NGS/WES/WGS Laboratory Standards (Co-Chairs: Heidi Rehm and Pinar Bayrak-Toydemir)
Sporadic disorders: Sequence parents/child trio and examine de novo variants (1-2 per exome, ~175/genome)


Recessive disorders: Examine genes with biallelic mutations (prioritize those with truncating variants)

Power increased with multiple sibs

Consanguineous families: Search for homozygous rare variants

Dominant disorders: Examine multiple distantly affected family members and select for shared variants

Can perform linkage to identify candidate genomic regions to analyze

Cancer: Compare somatic and germline results

Identify variants sporadically occurring in tumor
Approaches to improve WES and WGS Data

Supplement WGS with WES
• Improves coverage of exonic sequences for which data analysis is primarily targeted

Supplement WES with Clinical Exome
• Improves analysis of genes with known association to disease

Analyze genome/exome with multiple technologies
• Some errors are platform-specific
Supplemental and Confirmatory Testing by Sanger

- For targeted tests, missing data is added by Sanger
- Even for WES/WGS there may be critical content that must be covered
- Adding custom design of confirmatory assays from WES/WGS is a significant added challenge
## Average Time to Assess a Variant

### ~300 NVAs/month

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<th>NVA Type</th>
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<td>NVA with dbSNP/ESP data only</td>
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<tr>
<td>NVA with publications</td>
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### NVA includes:

- Searches (Google, PubMed, Variant Databases)
- Assessment of data from literature and databases
- *In silico* assessments (PolyPhen, alignments, splicing, etc)
- Segregation studies with family members
- Evidence-based classification

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The image contains a flowchart that outlines the process of NVAs, with NVAs, Draft Reports, Genetic Counselors, Signout Geneticists, and Clinical Correlation Pathologists. The flowchart highlights the involvement of various roles in the assessment process, including NVAs for Fellows/Residents, Draft Reports for Genetic Counselors, Signout for Geneticists, and Clinical Correlation for Pathologists. Additionally, there is a note indicating the assessment of somatic cancer, with an estimate of 300 NVAs per month.
HCM Gene Mutations – 3000 cases tested

>500 clinically significant mutations identified

66% of clinically significant mutations are seen in only one family

Number of variants

Number of probands

MYBPC3  E258K  MYH7  R663H  MYBPC3  W792fs  R502W
81% (423/523) of clinically significant variants have been seen in only one family. 
46% (423/910) of hearing loss gene variation is unique.
dbSNP contains lots of data but is mostly un-annotated

Most annotated publically available variant data comes from initial research studies with small control populations.

- 27% (122 of 460) of literature-cited disease mutations were judged to be common polymorphisms, sequencing errors or had a lack of evidence of pathogenicity. (Bell et al., 2011)

Subsequent data sits in the clinical labs and is not well published or available.
Variant Curation Standards and Data Dictionary Developed

Phenotyping Approaches and Data Collection Forms Defined

Variant Classification and Curation Standards Approved
Data Sharing Models (De-identified, Opt-out, Consented) Approved
Sustainability Models Developed

Variant Workgroups

Phenotyping Workgroup

Policies, Standards and Sustainability Workgroup

Variant Curation Standards and Data Dictionary Developed
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Curated Clinical Lab Data
Curated LSDBs/OMIM Data
Uncurated Population Data

Aim 1

Aim 2

QC

Aim 3

ClinVar

Curated Data
Uncurated Data
Expert Curation

Clinical Grade Variant Database

Engagement, Education, and Access Workgroup
Facilitate access to the resource by the community
Overview of Data Flows and Systems

Genotype and Phenotype Data Submission (Genomic Case Data)
- WES
- WGS
- CMA

Genotype and Phenotype Data Submission (Variant /Case Observations)
- Variant QC check
- Retrieve variant accessions

Vendor Supported or Direct Submission
- MutaDATABASE
- OMIM
- GeneReviews
- LSDBs/HVP

Overview of Data Flows and Systems

NCBI Controlled Access Archive
- Data aggregation
- dbGAP

NCBI Public Reference Archives
- Register new variants
- Retrieve variant accessions
- dbSNP < 50 bps
- dbVar > 50 bps

Data Curation
- Lab A
- Lab B
- Lab C
- Lab D

Expert Curators

OMIM
GeneReviews
LSDBs/HVP
The ISCA Consortium

- Established in 2007
- Over 160 institutional members worldwide
- Over 1,200 registered individual members
- The ISCA Consortium database now includes CNV data on ~30,000 postnatal clinical cases
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**Cases Per Disease Area**

| Cases Per Disease Area | 8918 | 7672 | 34205 | 3242 | 23911 | 728 | 4732 | 234 | 77208 | 160850 |
How do we update reported variant knowledge?

ACMG 2007 Guidelines: The testing laboratory…should make an effort to contact physicians of previously tested patients in the event that new information changes the initial clinical interpretation of their sequence variant.
Variant Classification Changes – HCM Data

Benign
Likely Benign
Unknown Significance
Likely Pathogenic
Pathogenic

~300 category changes over 5 year (~4% of reports/yr)

GeneInsight Clinic℠ Interface

Registered with FDA as a Class I Exempt Medical Device
Updated Variant Information

Individual Reported Variant Interpretation History (Variant 1 of 1)
Warning: This page only lists information on a single variant. This is outside of the patient report context and may be insufficient for re-interpretation of the patient report.

Heterozygous c.1030C>T (p.His344Tyr), Exon 9, PRKAG2 (Germline)
Report (FINAL, 04/05/2010 01:17 PM), HCM CardioChip (11 Genes Sequenced), Sequence Confirmation Test
Patient George, Curious 678345 (DEMOA-MRN) 05/01/1991 (19) Male
Current Category* Pathogenic (Reported: Unknown Significance)
Counts Reports (1), Families (1)

Alerts

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<th>Status</th>
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<td>Unreviewed</td>
<td>04/06/2010 10:27 AM</td>
<td>Non- incidental Level Change</td>
<td>The category for the PRKAG2 c.1030C&gt;T (p.His344Tyr) association to HCM changed from Unknown Significance to Pathogenic.</td>
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Mark Reviewed

Current Knowledge** Approved 04/05/2010 01:22 PM by Matthew Varugheese

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<th>Diseases/Drugs</th>
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<td>HCM</td>
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<td>The His344Tyr variant has not been reported in the literature nor previously identified in our laboratory. The His344 residue is well conserved from fruitfly to mammals, and the His344Tyr variant occurs within the CBS domain region where all pathogenic PRKAG2 variants have been identified to date. In addition, the presence of concentric HCM and Wolff-Parkinson-White syndrome in the first proband identified with this mutation, which are clinical features consistent with PRKAG2 mutations, as well as follow-up testing showing that the variant arose de novo, provide strong support for this variant being pathogenic.</td>
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* The current category field displays the variant significance only within the diseases/drugs that have been interpreted on each report, primarily defined by the ordered test. Additional interpretations, if present, outside these diseases/drugs are not considered.

** The Current Knowledge only includes the following Diseases/Drugs Interpreted on Report: HCM, DCM, LVNC, ROM, Danon disease, myopathy, Fabry disease, ARVD/C, Barth syndrome

Data in this slide should not be used for any clinical purpose.
### Software Usability Assessment

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<td><strong>Task 9 – Locate all of a patient’s variants. Locate reviewed variants info.</strong></td>
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<td>B+</td>
<td>42.9%</td>
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<td>B+/B</td>
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<td><strong>Task 12 – Conduct a search for patients with unreviewed information</strong></td>
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<td><strong>Task 14 – Review GIC Alert Summary Email</strong></td>
<td>100%</td>
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As reports scale in content, alerting process will adapt to clinical decision support paradigms

Up-to-date data is available when physician looks at a patient record

Genetic data is accessed in real-time using CDS rules as needed (drug dosing, etc)

We may use infrastructure for clinical trial notification
GeneInsight Laboratory Data Sharing Network

Clinical Laboratories using GeneInsight Lab:
- LMM
- ARUP
- MGH Mol Path
- Bioreference Lab

Future Knowledge Providers:
- ClinVar?
- My Cancer Genome?
- PharmGKB?
- Specialized Consult Services

GeneInsight Network Hub

Patient Care Providers using GeneInsight Clinic:
- Brigham & Women’s Hospital
- Mass. General Hospital
- University Michigan
- Toronto, Canada
- Intermountain Health
- Others
- Others

GeneInsight Lab

GeneInsight Clinic
Shared Variant Knowledge and Interpretations

**Variant Details: EGFR c.2369C>T (p.Thr790Met)**

- **Gene:** EGFR (NSCLC)
- **Transcript:** NM_005228.3 [28 Exons, Coding 1..28]
- **Variant:** c.2369C>T (p.Thr790Met)

### Full Details

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<th>AA</th>
<th>Region</th>
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<th>AA Type</th>
<th>Interp</th>
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### LABX Information

- **# Reports:** 37
- **# Families:** 36

**Category/Inher./Excl.**

- Resistant

**Diseases/Drugs**

- Non-Small Cell Lung Cancer

**Variant Interpretation**

The T790M mutation in combination with other EGFR kinase domain mutations has previously been described in individuals with acquired resistance to EGFR-tyrosine kinase inhibitors (TKIs, Pao 2005). This mutation has been seen in tumors from patients who have been treated with TKIs and whose tumors also harbor a TKI susceptibility mutation.

**References**

<table>
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<th>Source</th>
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<th>Year</th>
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<tr>
<td>PUBMED 15728811</td>
<td>Kobayashi S, Boggon TJ, Dayaram T, Janns PA, Koch...</td>
<td>EGFR mutation and resistance of non-small-cell lung cancer to gef...</td>
<td>2005</td>
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</table>
### Shared Case Histories

#### Report Search
- **Source Instance**: equals Local and Remote
- **Date: Sign Out**: equals 08/30/2010 or 02/09/2012 or 01/31/2012
- **Test Code**: contains SNaPshot or ImEGFR-a_L or ImOto-pniA_L

#### Matching Reports
- **List Variants for Currently Displayed Columns** | **Run Autodraft Analysis** | **Variant Column Help**

**Note**: reports that are not FINAL or not CLINICAL are highlighted in red.

#### Table

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<th>Actions</th>
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<th>KRAS c.181C&gt;T Path</th>
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Acknowledgements

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