Genomics and Health Information Technology Systems: Exploring the Issues

Challenges in Standards Development

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Molecular Pathologist Perspective

• Genomics
• Information Technology
• Quality
Genomics

• Past
  – Single gene tests for single gene genetic disease & cancer

• Present
  – Single gene, gene panel, gene expression, CNVs for genetics & cancer

• Future (very near!) = Genomics
  – Large gene sets, whole exome, genome, transcriptome, microbiome for most disease states
  – Driven by lower cost of sequencing, but IT lags
Genomics

- Every person has a unique genome
- Each patient’s genomic sequence will be a new test interpretation: never seen before
- This will not change with more research
- Requires significant molecular genetic expertise
- Requires as much information as possible to interpret individual genomes (Software & Variant Database)
  - Significance analysis of variants
  - Previous knowledge of sequence variants and phenotype
  - Clinical information on individual
Genomics & Evidence

• Evidentiary standards currently very high
  – USPSTF, EGAPP, AHRQ, etc
  – Population-based evidence
  – Not many molecular tests found useful

• How apply evidence standards to individual unique patient genome interpretation?
  – Single gene variations with known phenotypes →
  – Complexity of an entire genome (pathways, modifiers, etc)
Genomics Testing Process

• Informed consent (extent of interpretation, database entry, reinterpretation)
• Sequence data generation & analysis
  – Quality assessment of sequence data (coverage, variant frequency, etc)
  – Alignment to reference sequence
  – Variant calling compared to reference sequence
• Variant Interpretation
  – Comparison to databases (OMIM, COSMIC, dbSNP, 1000 Genomes, ENCODE, etc.)
  – Evolutionary conservancy analysis
  – Protein structural analysis
  – Pathway analysis
  – Integration with clinical, phenotype & family data
• Report in Laboratory Information System
• Transfer report from LIS to EHR and PHR for genomics reports
• Store sequence/variants & reinterpret VS sequence again with new technology

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National/International Variant Database

• Define inclusion criteria
  – Informed consent
  – Quality of sequence (coverage, %, etc)
  – Genotype-phenotype data

• Curation of database
  – Assure quality of sequence and phenotype
  – Assign level of evidence (pathogenic, probably pathogenic, non-pathogenic, etc)
  – Update based on new knowledge

• Accessibility & interoperability

• Public engagement
Genomic Testing & Quality

• Sequence Quality
  – Standards will vary by purpose of test
  – Capture, coverage of genome, coverage of sequence, variant frequency, error rate
## Constitutional vs Cancer

<table>
<thead>
<tr>
<th>Constitutional</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood or buccal specimen</td>
<td>Tissue (handling &amp; selection)</td>
</tr>
<tr>
<td>Sequence does not change for person but can by tissue</td>
<td>Repeat sequence with relapse</td>
</tr>
<tr>
<td>Lower coverage (30X)</td>
<td>Higher coverage (&gt;500X)</td>
</tr>
</tbody>
</table>
# Cancer Sequencing

<table>
<thead>
<tr>
<th>Cancer Sequencing</th>
<th>Coverage Handicap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial depth of sequencing coverage</td>
<td>100X (1)</td>
</tr>
<tr>
<td>Heterozygous mutation</td>
<td>50X (0.5)</td>
</tr>
<tr>
<td>Tumor cellularity</td>
<td>100% (best possible, e.g. blood): 50X (0.5)</td>
</tr>
<tr>
<td></td>
<td>20% (conservative): 10X (0.1)</td>
</tr>
<tr>
<td>Tumor heterogeneity</td>
<td>Only 1 clone (best possible): 10X (0.1)</td>
</tr>
<tr>
<td></td>
<td>3 clones (low estimate): 3.3X (0.033)</td>
</tr>
<tr>
<td></td>
<td>10 clones (conservative estimate): 1X</td>
</tr>
</tbody>
</table>

Cancer sequencing requires 500X coverage for 97% confidence

John Pfeifer, MD, PhD, Washington University
Genomic Testing & Quality

• **Sequence Quality**
  – Standards will vary by purpose of test
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• **Bioinformatics Quality**
  – Different algorithms gives different results
  – Validate, but how know what gives the “right” answer?
  – Version documentation
Genomic Testing & Quality

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• Phenotype Quality (EHR)
  – Race & ethnicity: reported or based on genome?
  – Family history standards
  – Disease definition standards
  – Environmental exposures
  – Formatted EHRs, not free text
Clinical Use of Sequence Results

• Clinical Decision Support Tools
  – Given complexity of genome interpretation, where deliver clinical usefulness information: report vs clinical information system vs physician knowledge?
  – Each patient’s genome is unique, so can MDs act on non-population based evidence?
  – Even if agree on Decision Support Tools that are clinically valid, how implement in all clinical IT systems?

• Personal Health Record Support Tools
  – How communicate results at 6th grade level?
Genomics & Information Technology

• Interoperability essential
  – Genomic testing
  – Results to EHR/PHR
  – Data to National Variant Database

• Formatted data in EHRs

• Standard gene nomenclature

• Documentation of software & database versions used for interpretation, as knowledge changes
"Genomics" IT System

LIS
- Instruments → Sequence Data
- Alignment & Analysis Software & Database(s)
- Interpretation & Report

EHR
- Clinical Usefulness Software & Database → Patient Management

PHR
- Patient & Family Support Tools

Clinical Quality Standards & Interoperability

National Variant Database
Other Issues

• Informed consent
  – Extent of genome interpretation, retention, re-interpretation

• Record retention
  – Store raw sequence data, all variants or reported variants?
  – Cost of sequence data storage vs resequence with improved technology in future

• Payment
  – No FDA approved tests; performed in CLIA-certified labs
  – No CPT codes for technical or interpretive components of testing OR for reinterpretation, if store sequence
  – Third party payer reimbursement?

• Public engagement AND family engagement issues