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

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

Constitutional	Cancer
Blood or buccal specimen	Tissue (handling & selection)
Sequence does not change for person but can by tissue	Repeat sequence with relapse
Lower coverage (30X)	Higher coverage (>500X)

Cancer Sequencing

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

Cancer sequencing requires 500X coverage for 97% confidence

John Pfeifer, MD, PhD, Washington University

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- Bioinformatics Quality
  - Different algorithms gives different results
  - Validate, but how know what gives the “right” answer?
  - Version documentation

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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

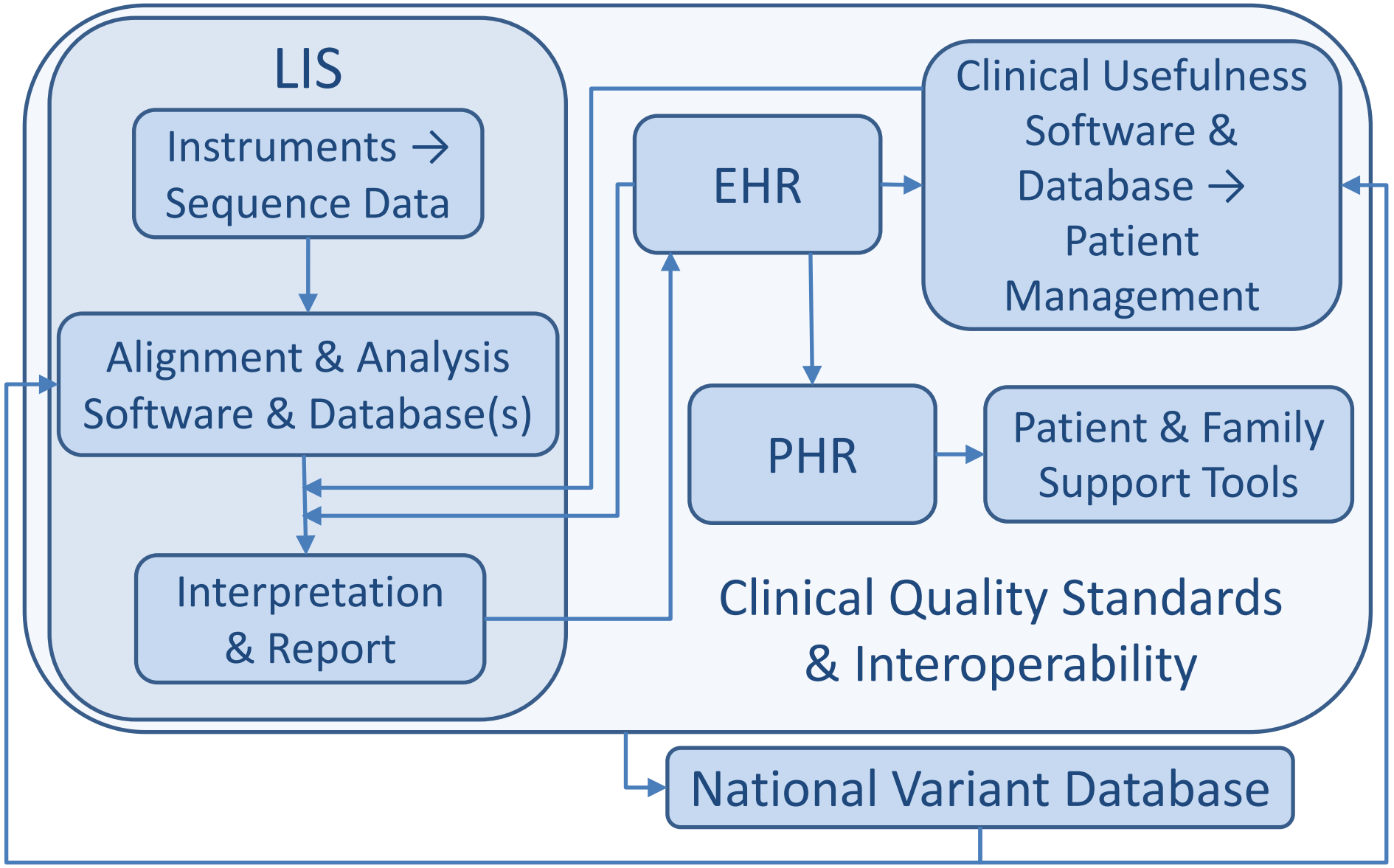
Clinical Use of Sequence Results

- 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?
  - What level of evidence needed to change patient care management? USPSTF? EGAPP? AHRQ? Medical science?
  - 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



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