Approaches to Integrating Next Generation Sequencing into the Electronic Health Record

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On behalf of the Clinical Sequencing Exploratory Research Electronic Health Records Working Group

Work Presented Today Published in:
Genetics in Medicine 15 824-32 (Sept 26, 2013)
Objective

- To understand how reports are/will be integrated into the electronic health record in ways that will allow updating and genomic clinical decision support

Outline

- Background
- Methods
- Results
- Conclusions
Example: The NEXT U01 (Seattle) Projects (I)

- **Project 1 (Practice):** Evaluate the comparative outcomes of whole exome sequencing versus usual care in patients with familial colorectal cancer/polyposis (CRCP) syndromes in a randomized controlled trial (Jarvik, Veenstra, Patrick, Regier, Heagerty, Hisama)

- **Project 2.1 (Lab)** Perform comprehensive exome sequencing and variant detection on samples randomized from the University of Washington (UW) colon cancer patient set (Nickerson)

- **Project 2.2 (Lab)** Reporting of incidental findings to clinicians and patients (Tarczy-Hornoch, Amendola)
Example: The NEXT U01 (Seattle) Projects (II)

- **Project 3.1 (ELSI)** Characterize patients’ and referring providers’ attitudes and preferences regarding the return of exome sequencing results (Burke, Fullerton, Trinidad)
- **Project 3.2 (ELSI)** Explore patients’ views and experiences of receiving genetic test findings generated from exome sequencing (Burke, Fullerton, Trinidad)
- **Project 3.3: (ELSI)** Legal analysis of the regulatory requirement of CLIA compliance as a precondition to returning results from genomic research studies, and attendant normative implications (Burke, Fullerton, Trinidad)

Currently there are 9 CSER sites (6 in paper)

<table>
<thead>
<tr>
<th>Institution</th>
<th>PI (ELSI lead)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dana Farber Cancer Institute</td>
<td>Garraway (Joffe)</td>
<td>The Use of Whole-Exome Sequencing to Guide the Care of Cancer Patients</td>
</tr>
<tr>
<td>Brigham and Women’s Hospital</td>
<td>Green (McGuire)</td>
<td>Integration of Whole Genome Sequencing into Clinical Medicine</td>
</tr>
<tr>
<td>University of Washington</td>
<td>Jarvik (Burke, Fullerton)</td>
<td>Clinical sequencing in cancer: Clinical, ethical, and technological studies</td>
</tr>
<tr>
<td>Children’s Hospital of Philadelphia</td>
<td>Krantz (Bernhardt)</td>
<td>Applying Genomic Sequencing in Pediatrics</td>
</tr>
<tr>
<td>Baylor College of Medicine</td>
<td>Plon, Parsons (McCullough, Street)</td>
<td>Incorporation of Genomic Sequencing into Pediatric Cancer Care</td>
</tr>
<tr>
<td>University of Michigan at Ann Arbor</td>
<td>Chinnaiyan</td>
<td>Exploring Precision Cancer Medicine for Sarcoma and Rare Cancers</td>
</tr>
<tr>
<td>Kaiser Foundation Research Institute</td>
<td>Goddard</td>
<td>Clinical Implementation of Carrier Testing Using Next Generation Sequencing</td>
</tr>
<tr>
<td>Hudson-Alpha Institute for Biotechnology</td>
<td>Myers</td>
<td>Genomic Diagnosis in Children with Developmental Delay</td>
</tr>
</tbody>
</table>
Clinical Sequencing Exploratory Research
Moving the Genome into the Clinic

The Big Questions

- What are the best practices in moving whole genome sequencing, using Next Generation technologies, from medical science to the clinical practice?
- What are the patient characteristics that signal potential utility (or lack thereof) for applying genome-scale sequencing?
- What are the best approaches to analyzing data?
- Are there special considerations in different populations?
- How should relevant information be best represented in the EMR?
- What criteria are most useful in guiding which results should be returned (and how) to the patient and physician?
- How should we deal with the plethora of highly heterogeneous “non-target” data generated when performing sequencing?

Evans: Overview of CSER, Fall 2013 and NHGRI staff

www.genome.gov/CSER
www.cserv-consortium.org

Clinical Sequencing Exploratory Research
Moving the Genome into the Clinic

Working Groups & Steering Committees
- CSER Steering Committee
- CSER Coordinating Center
- ELSI Steering Committee
- Actionable Variants & ROR

Leadership
- Ian Krantz
- Gail Jarvik
- Steven Joffe
- Laura Amendola
- Wendy Chung

Electronic Medical Records
- Peter Tarzy-Hornoch
- Brian Shirts
- Denise Lautenbach
- Sarah Scollon
- Paul Appelbaum
- Joon Ho-Yu
- Kyle Brothers
- Renn Wilford
- Ian Krantz
- Peter White
- Stacy Gray
- Christine Rini
- Nick Wagle
- Donna Muzny
- Will Parsons
- TBD

As of 12/10/2013

www.genome.gov/CSER
www.cserv-consortium.org
CSER Electronic Health Record (EHR) Working Group

Mission:
- Understand and facilitate cross site collaboration nationally around informatics work as related to a) integration into electronic health (medical) record, b) integration into decision support, and c) linkage to variant databases/knowledge bases (VDBKB)

Membership
- Multiple representatives from each site
- NIH representatives
- eMERGE network liaisons

The number of individual genetic tests is daunting and requires creation of variant data/knowledge bases

[Graph showing growth of laboratory directory over time]

www.genetests.org
Next generation sequencing moves from daunting to beyond cognitive capacity requiring **decision support**

As genomic knowledge evolves what care providers do with next gen sequencing (NGS) data changes

Cumulative meta-analysis of sequential studies over time: Relative Risk (RR) of Warfarin adverse effects using a pharmacogenomics guided dosing algorithm

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillman, 2005</td>
<td>0.44 [0.10, 2.01]</td>
</tr>
<tr>
<td>+ Anderson, 2007</td>
<td>0.77 [0.54, 1.09]</td>
</tr>
<tr>
<td>+ Caraco, 2008</td>
<td>0.65 [0.28, 1.15]</td>
</tr>
<tr>
<td>+ Huang, 2009</td>
<td>0.69 [0.47, 1.03]</td>
</tr>
<tr>
<td>+ Burmester, 2011</td>
<td>0.74 [0.55, 1.00]</td>
</tr>
<tr>
<td>+ Anderson, 2012</td>
<td>0.63 [0.45, 0.87]</td>
</tr>
</tbody>
</table>

Adapted from C. Lee PhC General Exam
Source: Shojannia KG, AHRQ Publication, 2007
CSER EHR working framework to characterize integration of knowledge bases, EHR, decision support

Outline

- Background
- Methods
- Results
- Conclusions
52 Element Survey of CSER Sites Using Framework

<table>
<thead>
<tr>
<th>Area of Survey</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Context</td>
<td>Germline versus somatic sequencing of tumors, sequencing platform, sequencing laboratory, approach to CLIA certification, data sources used for annotation and referenced in reports, approach to “blending” of results, and nature of the study population</td>
</tr>
<tr>
<td>Variant Databases - Knowledge Bases</td>
<td>What databases are used to curate variants and annotations, how these databases are integrated with clinical workflow, how variants are presented to molecular diagnostic staff for interpretation and sign out, how databases assist with report writing and/or rule generation, and linkages between variant databases and EHR decision support tools</td>
</tr>
<tr>
<td>Reporting of Results into the EHR</td>
<td>What EHR(s) are used, if the NGS/EHR process is generalized or specific to the site’s CSER, systems currently used for EHR report generation, NGS laboratory information management systems (LIMS) used, interfaces to the EHR for reporting, structure of reports, report generation processes, customization of reports by the audience, routing of results, and reporting tools external to the EHR being utilized</td>
</tr>
<tr>
<td>Communication of Results to Providers</td>
<td>Whether consultation regarding NGS results is provided and if so by whom, length of consultation, and current capacity to scale up</td>
</tr>
<tr>
<td>Handling of Changing Variant/Annotation Information</td>
<td>Content included in the consent process, whether reports are updated subsequent to receiving new information, and if so, how this is achieved</td>
</tr>
<tr>
<td>Clinical Decision Support</td>
<td>Type of decision support (passive versus active), mechanisms to ensure that all providers can view key content, which subset of results are used for decision support, and further characterization of active decision support systems and of how these systems operate</td>
</tr>
</tbody>
</table>

Genetics in Medicine 15 824-32 (2013)

Outline

- Background
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Annotating Variants: Sources and Knowledge Bases

- **Common Sources:** HGMD (all), 1000 Genomes (4/6), ESP (4/6)
- **Other Sources (<50%):** Local variant DB, PolyPhen, ClinVar, dbSNP, PubMed, Alamut, SIFT, COSMIV, SNPedia, RefSeq, etc.

Curating Variants and Bioinformatics Workflow

- NGS Bioinformatics pipeline unique to each site
  - Goal: going from all variants to relevant subset
- Ditto NGS Variant Databases/Knowledge Bases
  - Goal: reuse of annotations across patients

Categorizing and Reporting Variants

- All sites have indication specific and some form of incidental finding report for NGS
  - **BUT** site specific lists of indication specific reportable genes & reportable incidental findings
- **Common Categorizations**
  - Indication (phenotype), medically actionable incidental, other reportable incidental (carrier status, pharamcogenomic)
- Reports include external links (but Δ by site)
  - E.g. OMIM, PubMed, RefSeq, dbSNP, GeneTests, GeneReviews, PharmGKB
Colorectal cancer and/or polyps

Return:
- Known disease causing variants
- Variants of uncertain significance

<table>
<thead>
<tr>
<th>Usual Genes</th>
<th>Other Disease Genes</th>
<th>CRCP only Genes</th>
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<tbody>
<tr>
<td>BMPR1A</td>
<td></td>
<td></td>
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<tr>
<td>EPAC1</td>
<td></td>
<td></td>
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<tr>
<td>GREM1</td>
<td></td>
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<tr>
<td>MLH1</td>
<td></td>
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<tr>
<td>MSN2</td>
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<tr>
<td>MSH6</td>
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<tr>
<td>MUTYH</td>
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<tr>
<td>PMS2</td>
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<tr>
<td>POLE</td>
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<tr>
<td>POLD1</td>
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<td>PTEN*</td>
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<td>SMAD4</td>
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<tr>
<td>STK11</td>
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<tr>
<td>TP53*</td>
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<tr>
<td>Unusual Genes</td>
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<tr>
<td>BMPR1A</td>
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<tr>
<td>EPCAM (del)</td>
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<tr>
<td>GREM1</td>
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<tr>
<td>MLH1</td>
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Incidental findings

Return: known disease causing variants and truncations

 Dominant | X-Linked
---------|----------
 ACTA2 | DMD
 ACTC1 | DMD
 ACVRL1 | DMD
 BRCA2 | DMD
 CACNA1C | DMD
 CACNA1S | DMD
 CACNB2 | DMD
 CDC73 | DMD
 CDH1 | DMD
 CNBP | DMD
 COL3A1 | DMD
 DMPK | DMD
 ENG | DMD
 FBN1 | DMD
 FH | DMD
 F5 | DMD
 F8 | DMD
 F9 | DMD
 F10 | DMD
 FGFR1 | DMD
 LMNA | DMD
 MEN1 | DMD
 MET | DMD
 MLH3 | DMD
 PMS1 | DMD
 POLD1 | DMD
 PTEN* | DMD
 STK11 | DMD
 TP53 | DMD

 Incidental Genes

 Dominant | X-Linked
---------|----------
 ACTA2 | X-Linked
 ACTC1 | X-Linked
 ACVRL1 | X-Linked
 BRCA2 | X-Linked
 CACNA1C | X-Linked
 CACNA1S | X-Linked
 CACNB2 | X-Linked
 CDC73 | X-Linked
 CDH1 | X-Linked
 CNBP | X-Linked
 COL3A1 | X-Linked
 DMPK | X-Linked
 ENG | X-Linked
 FBN1 | X-Linked
 FH | X-Linked
 F5 | X-Linked
 F8 | X-Linked
 F9 | X-Linked
 F10 | X-Linked
 FGFR1 | X-Linked
 LMNA | X-Linked
 MEN1 | X-Linked
 MET | X-Linked
 MLH3 | X-Linked
 PMS1 | X-Linked
 POLD1 | X-Linked
 PTEN* | X-Linked
 STK11 | X-Linked
 TP53 | X-Linked

* Also on incidental finding list
X Not detectable by WXS

Example: NEXT
U01
Genes to Return

Reporting of Results into the EMR

- NGS clinical reports semi-automatically (5) or manually (1) generated from VDBKB using local bioinformatics workflow
  - Different sources, bioinformatics workflow, VDBKB and reportable genes result in heterogeneity in what is reported and how
  - All (6) have final stage of manual review
- EMRs: 3 custom, 3 Epic, 1 Sorian, 1 Cerner
- Upstream variability => Same: PDFs in EHR
  - Structured reports
  - Human but not machine/computer readable
Desiderata: machine/computer readable reports

- Barriers to standard machine readable reports
  - No standards for content, structure
  - No standards for coding variants/actionability
  - No EHR standards (yet) for coded NGS results
- Three sites have machine readable reports
  - Brigham and Womens, Dana Farber, U of Wash.
  - Each uses their own approach
  - E.g. UW codes a subset of actionable NGS finding as a series of single gene tests inside lab system

Decision Support

- Passive
  - Requires provider to act (e.g. read the PDF report)
  - All (6) sites implement this
- Active
  - Context triggers an alert automatically (e.g. ordering a drug in presence of a mutation in the gene metabolizing that drug triggers pop up alert)
  - Two sites implementing active decision support
- Other
  - Custom iPad app with clickable links (1 site), PDF reports with clickable links (2 sites)
### Example: Selected UW NEXT U01 Pharmacogenetics CDS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant(s)</th>
<th>Clinical Significance</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| CYP2C19    | p.Pro227= (*2) | Clopidogrel, impaired responsiveness
|            |            |                                                           | Contact a pharmacist for more information.                                    |
|            | p.Ile359Leu (*3) |                                                           |                                                                               |
| CYP2C9     | p.Arg144Cys (*2) | Warfarin sensitivity
| VKORC1     | -1639GA    | Warfarin sensitivity
| CYP4F2     | p.Val433Met | Warfarin sensitivity
| DPYD       | IVS14 + 1G>A | 5-fluorouracil toxicity,
|            |                                                           | Dihydropyrimidine dehydrogenase deficiency
| TPM1       | c.6261G>A  | 6-mercaptopurine sensitivity
|            | p.Ala154Thr | Azathioprine sensitivity
|            | p.Ala80Pro |                                                           |                                                                               |
| UGT1A1     | (TA)7 promoter insertion
|            | *homozygotes | Intoxin sensitivity
| SCLO1B1    | p.Val174Ala | Statin induced myopathy
| HFE        | p.C282Y    | HFE-Associated Hemochromatosis
|            | *homozygote s OR compound heterozygotes | (http://www.ncbi.nlm.nih.gov/books/NBK1440/)            | Consider routine monitoring of serum ferritin concentration.
|            | p. H63D    |                                                           | Avoid medicinal iron, mineral supplements, excess vitamin C, and uncooked seafood.
|            |            |                                                           | Consideration of vaccination against hepatitis A and B 6.
|            |            |                                                           | Contact a hematologist for more information.                                      |
| F5         | Arg506Gln  | Factor V Leiden Thrombophilia
|            |            |                                                           | Contact a hematologist for more information.                                      |
| RYR1       | *31 established pathogenic mutations from European Malignant Hyperthermia Group (http://www.emhg.org/genetics/mutations-in-ryr1/) | Malignant Hyperthermia Susceptibility
|            |            |                                                           | Contact an anesthesiologist for more information.                                      |
Approaches to New Genomic Information

- When new genomic information changes the interpretation of a variant:
  - All (6) sites update their variant DB/KB
  - Subsequent reports reflect the new information

- Propagating new information to old reports
  - Ultimately for clinical use of NGS this is needed
  - 2/6 sites opt to not update reports in the CSER research study (included as part of consenting process)
  - 4/6 sites opt to update reports if logistically feasible
    - 1/6 dynamically (next talk)
    - 1/6 semiannually
    - 2/6 as determined by the lab

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Acknowledgements

- Clinical Sequencing Exploratory Research Consortium (cserv-consortium.org)
- NIH extramural projects U01HG006507, U01HG00637, U01HG006500, U01HG006492, U01HG006487, U01HG006485, U01HG006546, KG100355, RC1LM010526, UL1RR02574, UL1TR000423, U01HL098188, 275200800001C-2-0-1; the Susan G Komen, WA State Life Sciences Discovery Fund, Northwest Institute for Genetic Medicine, Dana-Farber Cancer Institute Leadership Council.

Conclusions (CSER WG)

- Commonalities
  - Starting point: Illumina HiSeq
  - Ending point: passive decision support (PDF)
- Differences
  - Intermediate steps!
- Gaps (& Future Work)
  - Lack of standards for a) variant DB/KB, b) representing NGS in EMR and b) linking VDBKB/EMR
- Challenges (& Future Work)
  - Same genome => different interpretations due to differences in annotation sources, bioinformatics tools, lists of reportable variants
  - Propagating changes in knowledge to EHR
Recommendations (PTH)

- Annotating Variants
  - Use common sources & for now develop custom tools
  - NHGRI/NCBI focusing on revamping ClinVar

- Reporting Variants
  - Build on recommendations by ACGME, FDA and variant lists from CSER and eMERGE sites (using custom tools)

- Reporting Results into EMR/Decision Support
  - Aim for structured coded data in addition to PDFs
  - Leverage EMR CDS infrastructure
  - Monitor work by EMR vendors and CSER/eMERGE

- Handling New Genomic Information
  - In clinical use (non research, non CSER) must have mechanism to propagate new information to old reports

Follow on study (CSER/eMERGE)

- Background:
  - Many categories of genetic findings
  - Handled by different clinical providers in different ways
  - No fixed location in the EMR for genetic results

- Goals:
  - Determine current practice about how and where genetic information is displayed in EMRs **(not just whole exome)**
  - Envision how this genetic information might be optimally used
  - Propose and develop consensus around best practices about where different types of genetic information would logically reside in the EMR
**Conclusions ➔ Questions**

- **Commonalities**
  - Starting point: Illumina HiSeq
  - Ending point: passive decision support (PDF)

- **Differences**
  - Intermediate steps!

- **Gaps (& Future Work)**
  - Lack of standards for a) variant DB/KB, b) representing NGS in EMR and b) linking VDBKB/EMR

- **Challenges (& Future Work)**
  - Same genome => different interpretations due to differences in annotation sources, bioinformatics tools, lists of reportable variants
  - Propagating changes in knowledge to EHR