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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

UNIVERSITY of WASHINGTON

bhi Biomedical and Health Informatics

cser Clinical Sequencing Exploratory Research

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GENETICS IN MEDICINE | ORIGINAL RESEARCH ARTICLE

A survey of informatics approaches to whole-exome and whole-genome clinical reporting in the electronic health record

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Genetics in Medicine **15** 824-32 (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

Clinical Sequencing Exploratory Research

Moving the Genome Into the Clinic

377 Researchers
21 Institutions
1 Consortium

Purpose & Structure

- Explore, within an active clinical setting, the application of genomic sequence data to the care of patients.
  1. Generation of genomic sequence data,
  2. Interpretation and translation of data for the physician
  3. Communication to the patient

- Three (3) Project Teams per Site
  1. Practice: clinical setting being studied and what medical outcomes measured
  2. Lab: sequencing and reporting of genome-scale results to clinicians/EMR
  3. ELSI: ethical and psychosocial implications of bringing broad genomic data into the clinic

Plon: Overview of CSER, Fall 2012

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

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)

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

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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

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Clinical Sequencing Exploratory Research

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Working Groups & Steering Committees	Leadership	
CSER Steering Committee	Ian Krantz	
CSER Coordinating Center	Gail Jarvik	
ELSI Steering Committee	Steven Joffe	
Actionable Variants & ROR	Laura Amendola	Wendy Chung
Electronic Medical Records	Peter Tarzcy-Hornoch	Brian Shirts
Genetic Counselors	Denise Lautenbach	Sarah Scollon
Informed Consent & Governance	Paul Appelbaum	Joon Ho-Yu
Pediatrics	Kyle Brothers	Ben Wilfond
Analysis & Phenotype Measures	Ian Krantz	Peter White
Outcomes & Measures	Stacy Gray	Christine Rini
Sequencing Standards	Nick Wagle	Donna Muzny
Cancer	Will Parsons	TBD

As of 12/10/2013

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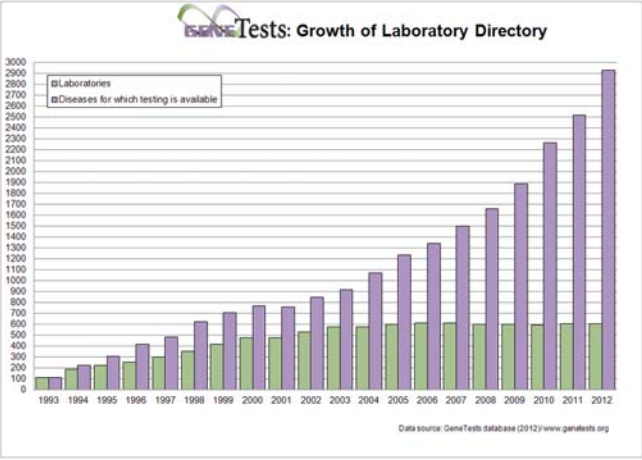
CSER Electronic Health Record (EHR) Working Group

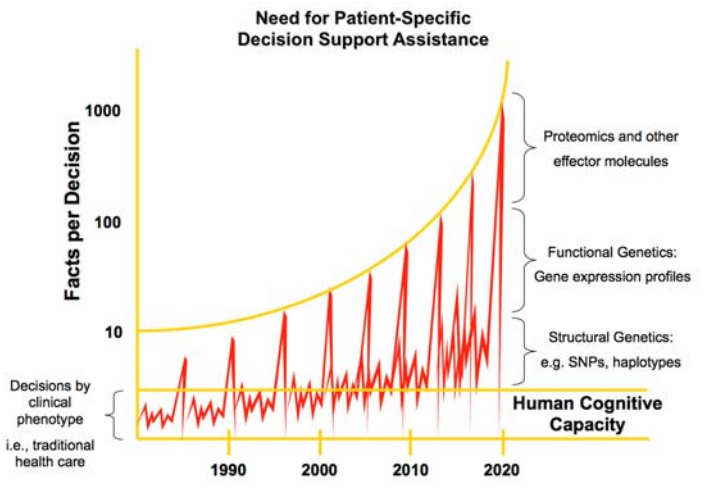
- Mission:
  - Understand and facilitate cross site collaboration nationally around informatics work as related to a) integration into **electronic health (medical) record**, b) integration into **decision support**, and c) linkage to **variant databases/knowledge bases (VDBKB)**
- Membership
  - Multiple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



www.genetests.org

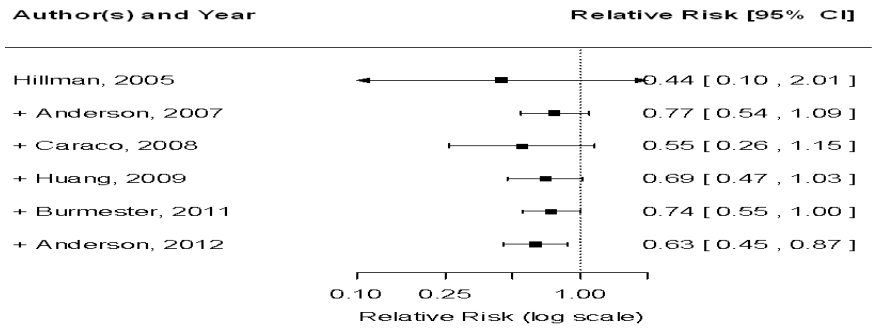
Next generation sequencing moves from daunting to beyond cognitive capacity requiring **decision support**



Masys, 2012

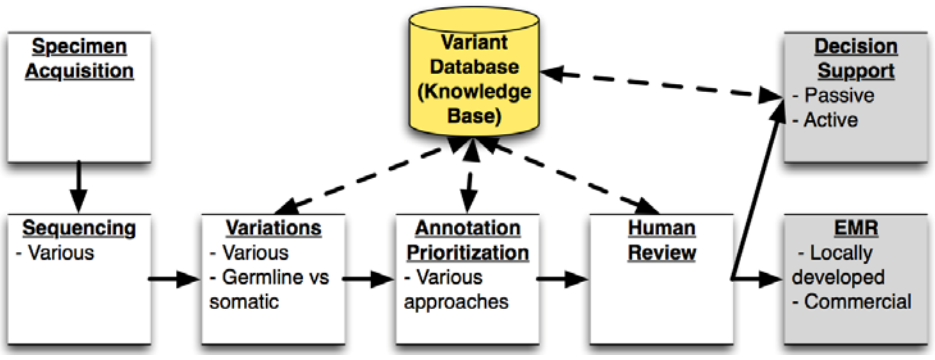
As genomic knowledge evolves what care providers do with next gen sequencing (NGS) data changes

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



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



NIH NHGRI Clinical Sequencing Exploratory Research Electronic Health (Medical) Record Working Group (Chair: Tarczy-Hornoch)

Outline

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52 Element Survey of CSER Sites Using Framework

Area of Survey	Characteristics
Context	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 "binning" of results, and nature of the study population
Variant Databases - Knowledge Bases	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
Reporting of Results into the EHR	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.
Communication of Results to Providers	Whether consultation regarding NGS results is provided and if so by whom, length of consultation, and current capacity to scale up
Handling of Changing Variant/Annotation Information	Content included in the consent process, whether reports are updated subsequent to receiving new information, and if so, how this is achieved
Clinical Decision Support	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

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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

Example: NEXT U01 Genes to Return

Colorectal cancer and/or polyps

Return:
a. Known disease causing variants
b. Variants of uncertain significance

Usual:		Other Disease with CRCP Research:	CRCP only Research:
APC	POLD1	CDH1*	MLH3
BMPR1A	POLE	FLCN*	PMS1
EPCAM (del)	PTEN*	PTCH1*	
GREM1	SMAD4	RET*	
MLH1	SCG5	TGFBR2*	
MSH2	STK11		
MSH6	TP53*		
MUTYH			

24 genes

* *Also on incidental finding list*
x *Not detectable by WXS*

Incidental findings

Return: known disease causing variants and truncations

Dominant					X-Linked
ACTA2	GCH1	PLN	TGFBR1	F5	DMD
ACTC1	HMB2	PRKAG2	TGGBR2	GAA	EMD
ACVRL1	KCNE1	PRKAR1A	TMEM43	HAMP	GLA
BRCA1	KCNE2	PROC	TNNI3	HFE	OTC
BRCA2	KCNH2	PROS1	TNNT2	HFE2	
CACNA1C	KCNJ2	PTCH1	TP53	IDUA	
CACNA1S	KCNQ1	PTEN	TPM1	LDLRAP1	Pharmaco
CACNB2	KIT	RBM20	TSC1	PAH	COMTx
CDC73	LDLR	RET	TSC2	PCBD1	CYP2C9
CDH1	LMNA	RYR1	TTN	PTS	CYP2C19
CNBPx	MEN1	RYR2	VHL	QDPR	CYP2D6x
COL3A1	MET	SCN5A		SERPINA1	CYP3A5x
DMPKx	MYBPC3	SDHAF2	Recessive	SLC25A13	CYP4F2
DSC2	MYH11	SDHB	ATP7B	SLC37A4	DPYD
DSG2	MYH7	SDHC	BCHE	SLC7A9	FLOT1x
DSP	MYLK	SDHD	BLM		SLCO1B1
ENG	MYL2	SERPINC1	CASQ2		TPMT
FBN1	MYL3	SGCD	CFTR		UTG1A1
FH	NF2	SMAD3	COQ2		VKOR1x
FLCN	PDGFRA	SMARB1	COQ9		
	PKP2	TGFB3	CPT2		

114 genes

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

Gene	Variant(s)[a, b]	Clinical Significance	Recommendation
CYP2C19	p.Pro227= (*2) p.Trp212Stop (*3) -806C>T (*17)	Clopidogrel, impaired responsiveness (http://www.ncbi.nlm.nih.gov/pubmed/21716271)	Consideration of Prasugrel or other alternative therapy (if no contraindication). Contact a pharmacist for more information.
CYP2C9	p.Arg144Cys (*2) p.Ile359Leu (*3)	Warfarin sensitivity (http://www.ncbi.nlm.nih.gov/pubmed/21900891)	Consideration of reduced doses of warfarin (Coumadin). Contact a pharmacist for more information.
VKORC1	-1639GA	Warfarin sensitivity (http://www.ncbi.nlm.nih.gov/pubmed/21900891)	Consideration of reduced doses of warfarin (Coumadin). Contact a pharmacist for more information.
CYP4F2	p.Val433Met	Warfarin sensitivity (http://www.ncbi.nlm.nih.gov/pubmed/23132553)	Consideration of reduced doses of warfarin (Coumadin). Contact a pharmacist for more information.
DPYD	IVS14 + 1G>A	5-fluorouracil toxicity; Dihydropyrimidine dehydrogenase deficiency (http://www.ncbi.nlm.nih.gov/pubmed/21412232)	Consideration of reduced doses of fluoropyrimidine drugs or alternative drug selection. Contact a pharmacist for more information.
TPMT	c.6261G>A p.Ala154Thr p.Tyr240Cys p.Ala80Pro	6-mercaptopurine sensitivity;Azathioprine sensitivity (http://www.ncbi.nlm.nih.gov/pubmed/21270794)	Consideration of reduced doses of Thipurine drugs. Contact a pharmacist for more information.
UGT1A1	(TA)7 promoter insertion *homozygotes	Irinotecan sensitivity (http://www.ncbi.nlm.nih.gov/pubmed/18253145)	Consideration of reduced doses of irinotecan. Contact a pharmacist for more information.
SCLO1B1	p.Val174Ala	Statin induced myopathy (http://www.ncbi.nlm.nih.gov/pubmed/22617227)	Consideration of reduced doses of simvastatin or alternative statin selection. Contact a pharmacist for more information.

Example: Selected UW Non-Pharmacogenetic CDS

Gene	Variant(s)	Clinical Significance	Recommendation
HFE ***homozygotes OR compound heterozygotes**	p.C282Y p. H63D	HFE-Associated Hemochromatosis (http://www.ncbi.nlm.nih.gov/books/NBK1440/)	Consider routine monitoring of serum ferritin concentration. 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 ***homozygotes**	Arg506Gln	Factor V Leiden Thrombophilia (http://www.ncbi.nlm.nih.gov/books/NBK1368/)	Consider long term oral anticoagulation. Avoid oral contraceptives and HRT. [5]. 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 (http://www.ncbi.nlm.nih.gov/books/NBK1146/)	Consider avoidance of potent volatile anesthetic agents and succinylcholine. Avoid extremes of heat. Calcium channel blockers should not be given together with dantrolene [4]. Contact an anesthesiologist of 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

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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

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- 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