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Clinical Sequencing Exploratory Research

CSER: *VENI, VIDI*, AND A ROADMAP TO *VICI*

Integrating Genomic Sequencing into Clinical Care: CSER and Beyond

September 28, 2015

WHAT IS CSER?

CSER Consortium

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Clinical Sequencing Exploratory Research

Clinical Sequencing Exploratory Research
*Moving the **Genome** Into the **Clinic***

Range of Issues:

- **Technology**: Generate and interpret genomic sequence data in a variety of clinical contexts
- **Clinical Care**: Study the challenges of integrating comprehensive sequence data into patient care
- **Outcomes & ELSI**: examine the implications of bringing genomic sequence data into the clinic

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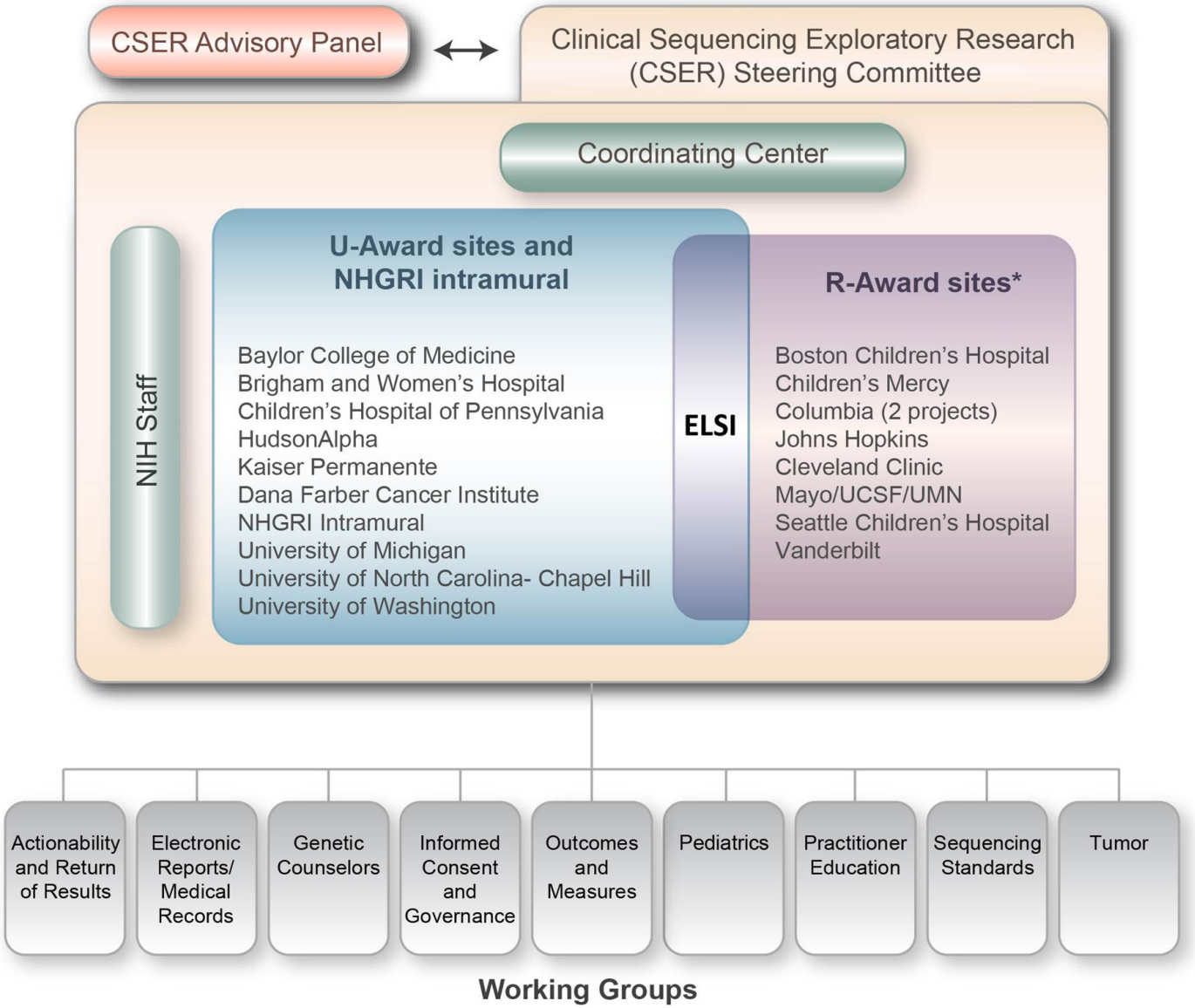
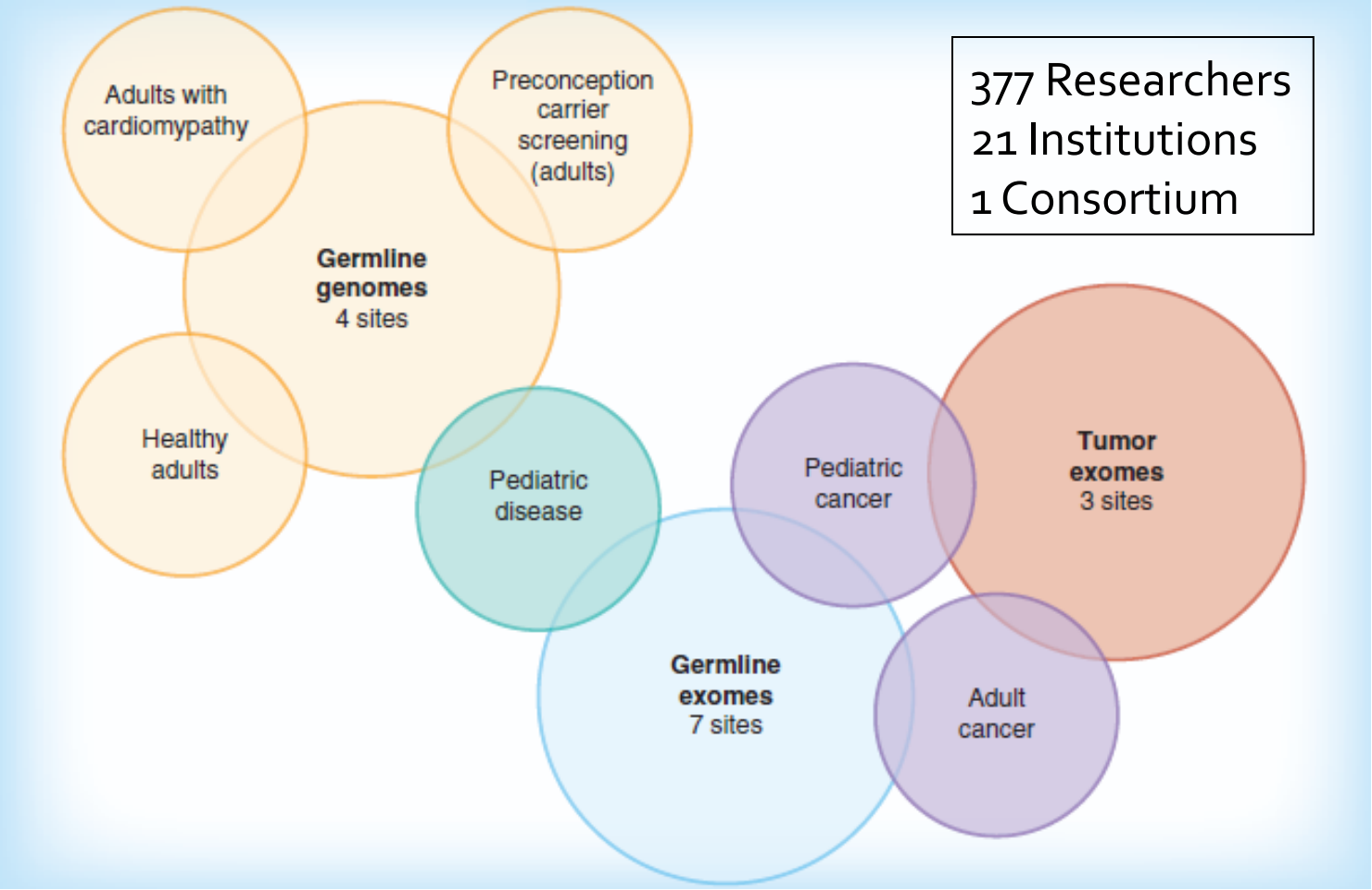
www.genome.gov/CSER
www.cser-consortium.org

Consortium Organization



CSER Study Populations



Amendola et al. *Per. Med.* (2015) 12(3):283-295

Study Diversity

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Observational (Cases Only) vs. Randomized Trial (Cases & Controls)

Adult vs. Pediatric

Participants/Patients vs. Clinicians

Individuals vs. Families/Trios

Germline Only vs. Germline + Tumor

Exome vs. Genome

List-Guided (Candidate) Approach vs. Unguided (Agnostic) Approach

Genetics experts return results vs. Non-experts return results

WHAT HAS CSER LEARNED SO FAR?

Major Accomplishments

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- Generating new evidence for the Evidence Base:
  - Analytic validity
  - Clinical validity
  - Clinical utility
  - Ethical, legal, regulatory & social issues
- Contributions to Professional Guidelines
- Development of infrastructure, methods, resources & tools

Major Accomplishments

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Clinical Sequencing Exploratory Research

✓Generating new evidence for the Evidence Base:

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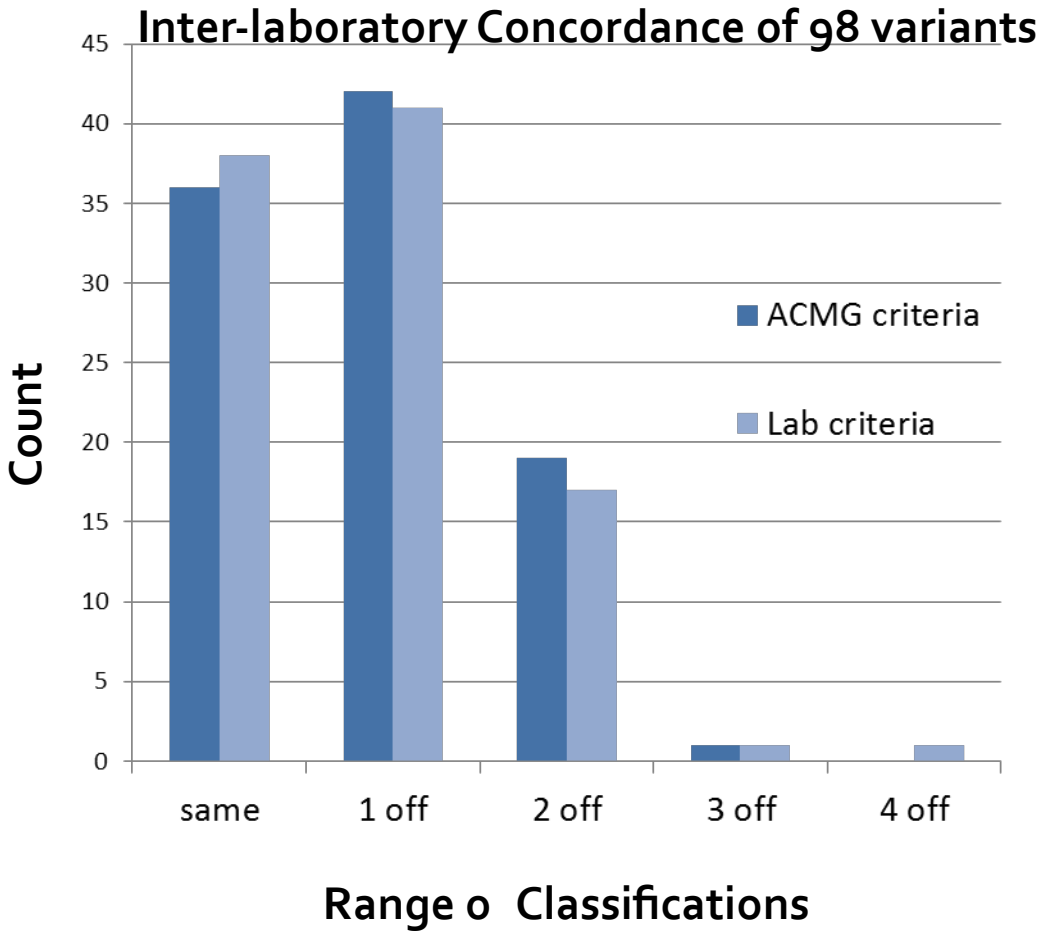
- Contributions to Professional Guidelines

- Development of infrastructure, methods, resources & tools

2015 CSER Variant "bake-off"



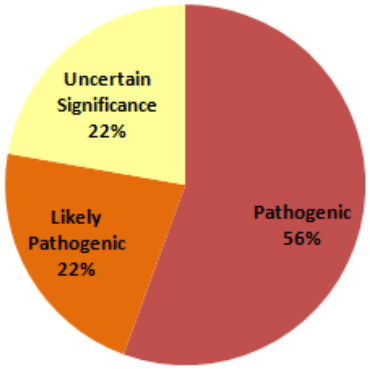
Jarvik et al. ASHG 2015 Poster #1896F

Actionability & Return of Results WG

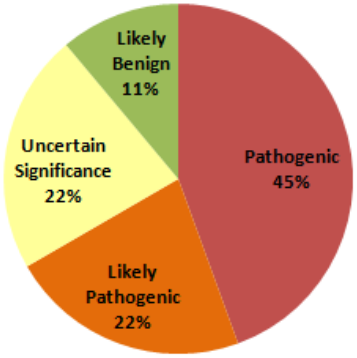
2015 CSER Variant "bake-off"

Variant with major disagreement: Why?

ACMG Classification



Laboratory Classification



***SPG7*:c.1529C>T (p.Ala510Val)**

- Present in 0.4% (267/66688) of European chromosomes (ExAC)
- Associated with late-onset +/- reduced penetrance spastic paraplegia

Laboratory	ACMG Rules	PP3	PS3	PM3	PP1	PS1	PS4	PP5	PM2	BS1	PP2	PP4
Pathogenic	Pathogenic	X	X	X			X	X				
Pathogenic	Pathogenic	X	X	X	X	X		X				
Pathogenic	Pathogenic	X	X	X	X	X	X					
Pathogenic	Pathogenic			X	X							
Likely Path.	Likely Path.	X	X	X	X		X		X			
Likely Path.	Likely Path.	X				X		X				
VUS	Pathogenic	X	X						X		X	
Likely Benign			X			X	X			X		
VUS	VUS	X			X					X		

Jarvik et al. ASHG 2015 Poster #1896F

Actionability & Return of Results WG

Cross-platform comparison

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Genes in poorly covered regions: 4-of-6 WES + Site G (WGS)

ABCC6	C1QTNF5	CSF2RA	EVC	GALNS	IKBKG	LFNG	NTRK1	RAX	SIX5	STAT5B	TUBB2B
ADAMTS13	CACNA1H	CYB5R3	FGF8	GATA6	INF2	LRP5	OPN1MW2	RB1	SLC29A3	STRC	VWF
ADAMTS17	CCM2	CYP21A2	FLG	GCSH	INSR	MATN3	OTOA	RECQL4	SLC37A4	SYN1	WNT4
ADAMTSL2	CDKN1C	DOK7	FOXC1	GPR143	IRX5	MESP2	PCBD1	RPS17L	SLC46A1	SYNGAP1	ZIC2
ADAR	CDT1	DUOX2	FOXC2	GRM6	KCNC3	MNX1	PDE4D	RYR1	SLC6A8	TBX1	
AGRN	CEL	EHMT1	FOXE3	HOXA13	KCNQ1	MYO15A	PITPNM3	SCN1B	SMN1	TMLHE	
ALG9	CFC1	EIF2AK3	FOXG1	HSPG2	KCNQ4	NCF1	PKD1	SEPN1	SMS	TNXB	
ANKRD11	CHEK2	ENPP1	FTCD	HTRA1	KL	NIPA1	PMS2	SETBP1	SNTA1	TPRN	
ARX	COL18A1	EPM2A	FXN	IDUA	KRT10	NOTCH3	PTF1A	SGCB	SOX18	TRIOBP	
ASXL1	CRLF1	ESPN	GABRD	IFNGR2	KRT81	NR2E3	RANBP2	SHOX	ST3GAL5	TTN	

- Poorly covered regions encompass **114 genes** totaling **18.3Kbp**
- **34 of the 114 genes** have poorly covered regions that intersect known variants in HGMD or ClinVar
- **49 Genes** (Blue) contain regions commonly missed in ALL centers

Sequencing Standards WG

Yield (Germline)

Clinical Characteristics	Sample Size	% of subjects with ≥ 1 finding (median # of variants reported)			
		P or LP	VUS	Single* Recessive	Other
Cancer (all)	1111	6.1%(1)	35% (1)	2.3% (1)	0.5% (1)
DD/ID					
Syndromic ID/Autism	392	18% (1)	12% (1)	0.5% (1.5)	1.3% (2)
Other	45	16% (1)	18% (1)	6.7% (2)	0%
Cardiovascular					
Cardiomyopathy	103	26% (1)	27% (1)	0%	1.0% (1)
Other	55	18% (1)	53% (2)	0%	1.8% (1)
Ophthalmology	73	42% (1)	18% (1)	8.2% (1)	0%
All Other Characteristics	254	16% (1)	23% (1)	11% (1)	2.8% (1)

*__Single recessive__ means the individual has one copy of a recessive mutation in a gene related to the phenotype

Cancer Yield (Germline)

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		% of subjects with ≥ 1 finding (median # of variants reported)			
Cancer Ascertainment	**Sample Size**	**P or LP**	**VUS**	**Single Recessive**	**Other**
Cancer (all)	1111	6.1%(1)	35% (1)	2.3% (1)	0.5% (1)
Pediatric					
CNS Solid Tumor	106	6.6% (1)	71% (3)	9.4% (1)	0%
Non-CNS Solid Tumor	201	11%(1)	72% (3)	5.0% (1)	0%
Leukemia	29	3.4% (1)	41% (1)	0%	0%
Cancer					
Lung	122	1.6% (1)	3.3% (1)	0%	0%
Breast	69	8.7% (1)	45% (1)	1.4% (1)	0%
Colorectal	97	1.0% (1)	9.3% (1)	0%	0%
Other	229	6.6% (1)	35% (1)	1.3% (1)	0%
Hereditary Cancer					
CRCP-Related Risk	133	4.5% (1)	16% (2)	0.8% (1)	0%
Breast/Ovarian	82	2.4% (1)	1% (1)	0%	6.1% (1)
Other	43	12% (1)	9.3% (1)	0%	0%

Other Findings (Germline)

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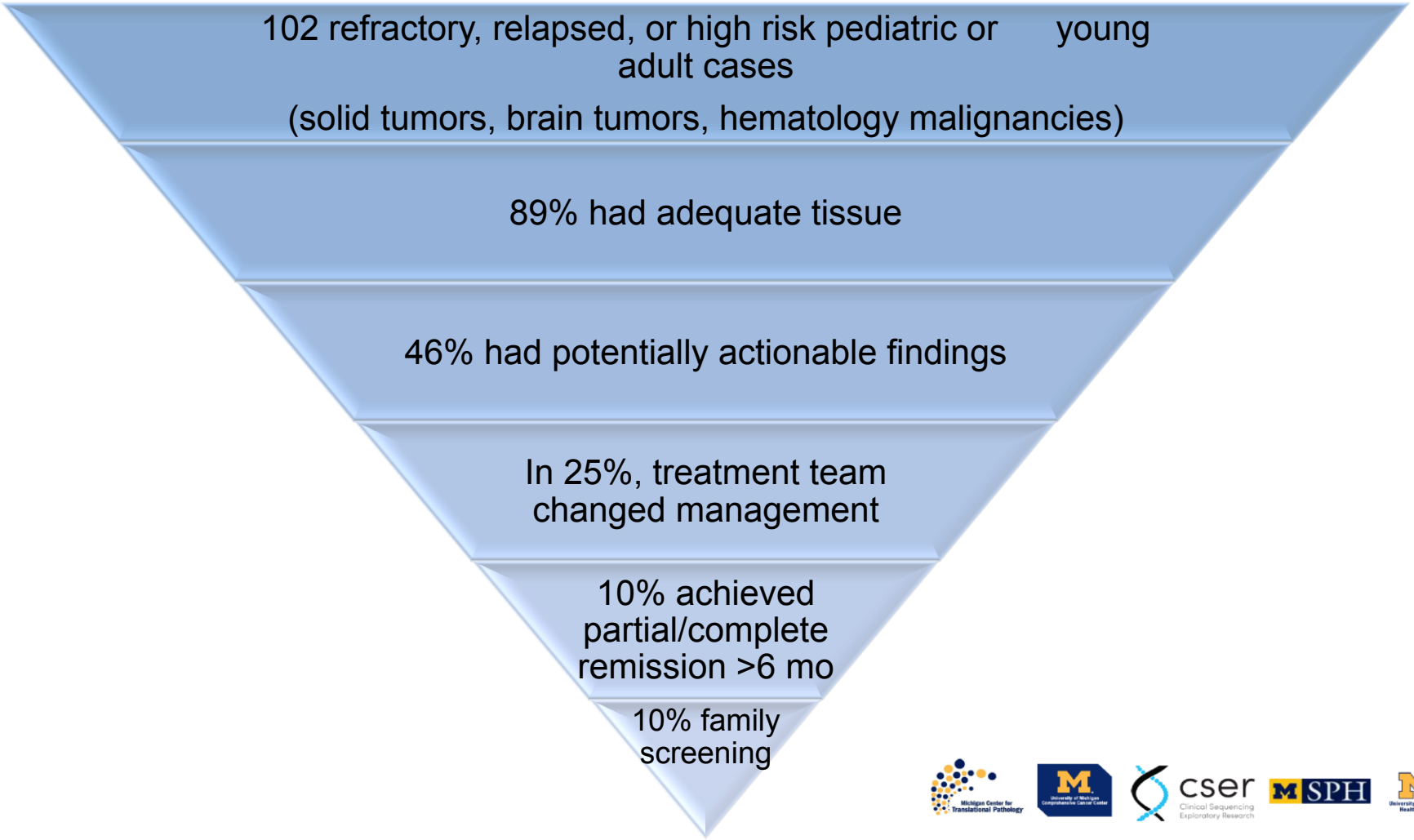
Category	Sample Size	Number (%) of subjects with ≥1 Finding	Range (sites)
ACMG Incidental Findings: Pathogenic	3383	58 (1.7%)	0%-4%
ACMG Incidental Findings: Likely Pathogenic	3052	17 (0.6%)	0%-4%
Non-ACMG: Pathogenic	3384	51 (1.5%)	0%-3%
Non-ACMG: Likely Pathogenic	3052	21 (0.7%)	0%-5%
PGx Genes: FDA Indication	2747	330 (12%)	0%-95%
PGx Genes: Other	2547	56 (2.2%)	0%-2%
Carrier Genes: Pathogenic	2799	607 (22%)	0%-87%
Carrier Genes: Likely Pathogenic	2615	222 (8.5%)	0%-41%
Tumor: Potentially Clinically Relevant	687	400 (58%)	26%-89%

Data as of August 15, 2015

Benefits of Sequencing in Childhood Cancer (Tumor + Germline)



Mody et al. JAMA 2015;314(9):913-925

Approaches to ROR

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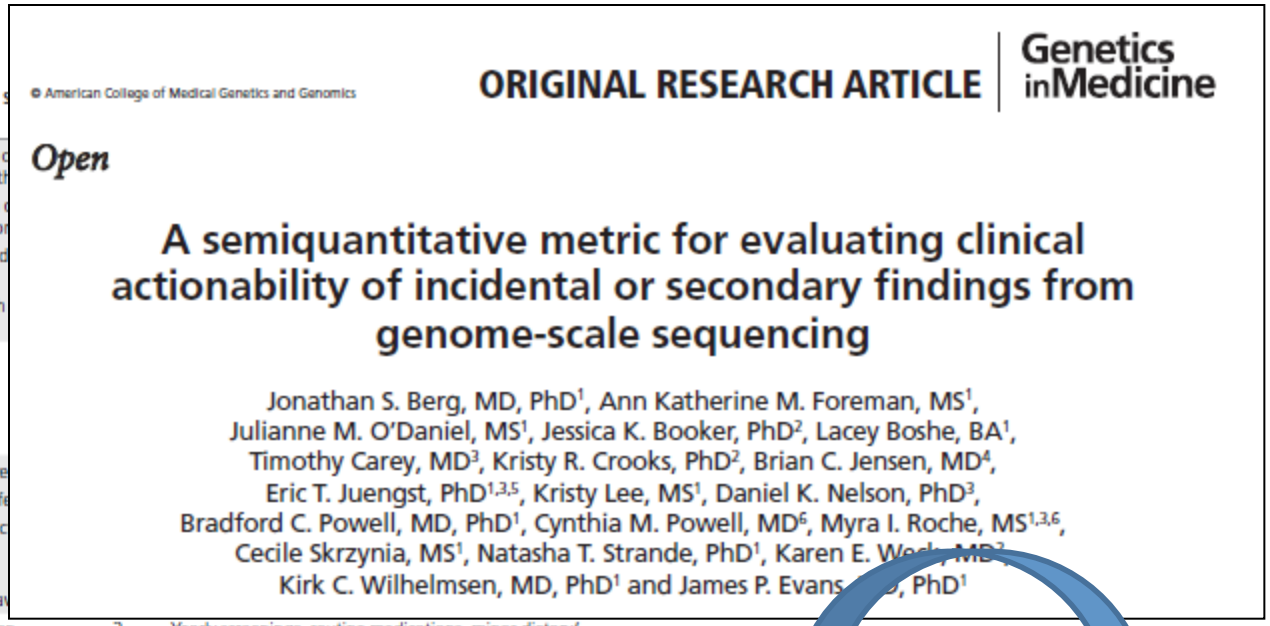


ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

A semiquantitative metric for evaluating clinical actionability of incidental or secondary findings from genome-scale sequencing

Jonathan S. Berg, MD, PhD[1], Ann Katherine M. Foreman, MS[1], Julianne M. O'Daniel, MS[1], Jessica K. Booker, PhD[2], Lacey Boshe, BA[1], Timothy Carey, MD[3], Kristy R. Crooks, PhD[2], Brian C. Jensen, MD[4], Eric T. Juengst, PhD[1,3,5], Kristy Lee, MS[1], Daniel K. Nelson, PhD[3], Bradford C. Powell, MD, PhD[1], Cynthia M. Powell, MD[6], Myra I. Roche, MS[1,3,6], Cecile Skrzynia, MS[1], Natasha T. Strande, PhD[1], Karen E. We[illegible], Kirk C. Wilhelmsen, MD, PhD[1] and James P. Evans[illegible], PhD[1]

Table 1 Semiquantitative metric framework, questions, s

Category	Level		
Severity of disease: "What is the nature of the threat to health for an individual carrying a deleterious allele in this gene?"	Sudden death c inevitable death		
	Possible death c illness or comor		
	Modest morbid		
	Minimal health		
Likelihood of disease: "What is the chance that a serious threat will materialize?" (somewhat akin to penetrance)	>50%		
	6–49%		
	1–5%		
	<1%		
Efficacy of intervention: "How effective are the interventions for preventing harm in a presymptomatic individual?"	Highly effective		
	Moderately effe		
	Minimally effec		
	Ineffective/no interventions av		
Burden of intervention: "What are the burdens or potential harms of initiating interventions in a presymptomatic individual?"	Very low burden	3	Yearly screenings, routine medications, minor dietary/ lifestyle modification
	Somewhat burdensome	2	Invasive screening, significant lifestyle alteration, medications with a substantial chance of side effects or more intensive delivery regimens, transplantation with rare complications
	Moderately burdensome	1	Removal of a nonvital organ, transplantation with frequent complications
	Highly burdensome	0	Removal of a vital organ
Knowledge base: "What is the evidence base for decisions about the natural history of the disease and interventions used for preventing serious outcomes?"	Substantial evidence	3	All categories scored confidently, high-quality review or practice guideline
	Moderate evidence	2	Strong primary literature, some details scored by analogy to another well-known disorder
	Minimal evidence	1	Unable to confidently score one or more categories, sparse primary literature or few reported patients
	Controversial or poor evidence	0	Uncertain natural history of disease, primary literature lacking or controversial

NCGenes
North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing

ClinGen
Clinical Genome Resource

Genet Med (2015)
PMID: 26270767

Case studies

Review

Personalized Medicine

Illustrative case studies in the return of exome and genome sequencing results

Amendola et al. *Per. Med. (2015) 12(3):283-295*

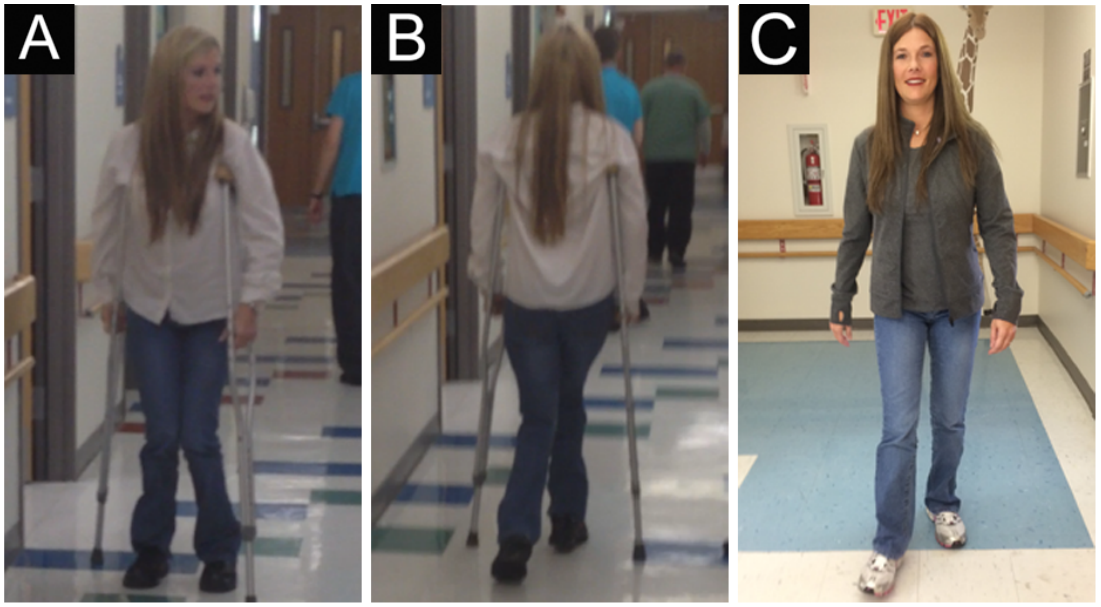
Genetic Counseling WG

Table 1. Summary of themes, lessons learned and challenges specific to the return of exome and genome sequencing results.

Theme	Lesson(s) learned	Challenges specific to exome and genome sequencing
Managing expectations in pretest and post-test counseling, negative findings do not mean the condition is not genetic	Elicit perceived goals and expectations both during informed consent and after return of results to identify and address misconceptions	Belief that all pathogenic genetic variation can be identified and the clinical significance will be clear
Context matters: follow-up for recommendations from IFs in healthy and ill patient-participants	Both healthy and ill patient-participants who receive IFs may face challenges with adherence to screening/testing recommendations. Ill patient-participants may focus on the diagnostic results and over-interpret a negative result as 'good news'	Limited pretest discussion of the unanticipated condition(s) and implications of results. (Ill) Emphasizing importance of follow-up for medically actionable IFs in the context of more acute concerns. (Healthy) Lack of personal/family history may affect motivation and access to care

Case Study Example

- 36 yo diagnosed at 6 with “hereditary spastic paraplegia”
  - Confined to crutches and wheelchair for decades
  - Painful episodes of spasticity on daily basis, 5 surgeries
- GCH1 [p.Arg216*], diagnosis of dopa-responsive dystonia
- Dramatic response
  - Walking without crutches, free of painful daily symptoms



Photos courtesy of Jim Evans and permission of patient

Cost analyses, utilization studies

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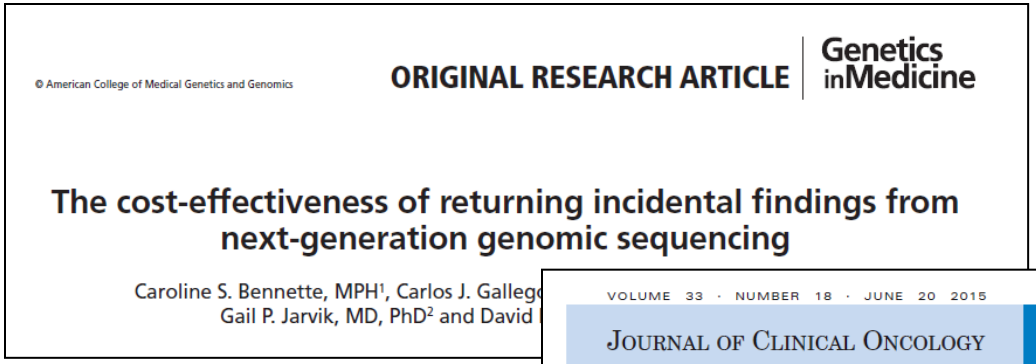
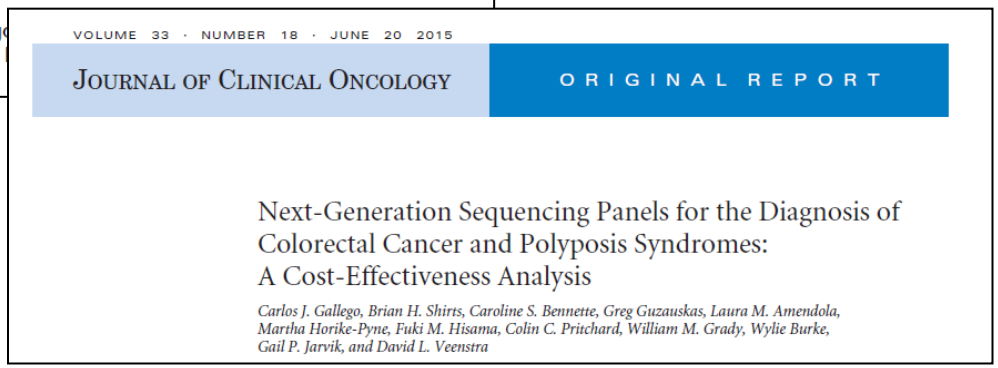




MEDSEQ

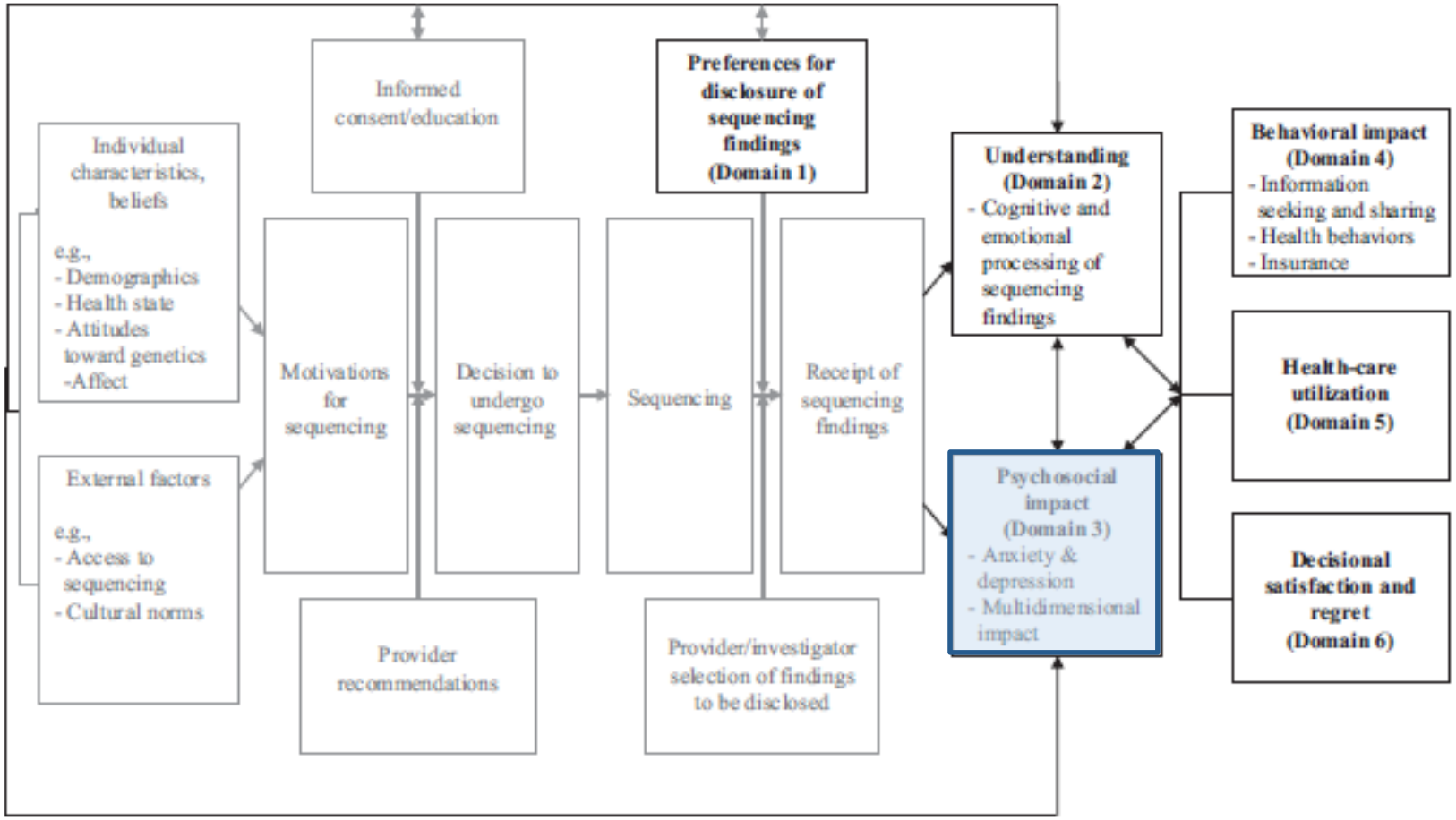
NextGen
Understanding the impact of genome sequencing for reproductive decisions

Vassy et al. Impact of genome sequencing on the medical care of healthy adults. ASHG 2015 Platform #256F

Dukhovny et al. Short-term costs of integrating genome sequencing into clinical care. ASHG 2015 Platform #257F

Himes et al. Economic impact of genome sequencing for preconception carrier screening. ASHG 2015 Platform #130Th

Psychosocial & Behavioral Outcomes



Outcomes & Measures WG

Gray et al. *Genet Med* 2014 16(10):727- 735

Normative & Legal Analyses

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Perspective

Can I be sued for that? Liability risk and the disclosure of clinically significant genetic research findings

Amy L. McGuire,[1,4] Bartha Maria Knoppers,[2] Ma'n H. Zawati,[2] and Ellen Wright Clayton[3]

[1]Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, Texas 77030, USA; [2]Centre of Genomics and Policy, McGill University, Montreal, Quebec H3A 0G1, Canada; [3]Center for Biomedical Ethics and Society, Vanderbilt University, Nashville, Tennessee 37203, USA

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

The FDA and Genomic Tests — Getting Regulation Right

Barbara J. Evans, Ph.D., J.D., Wylie Burke, M.D., Ph.D., and Gail P. Jarvik, M.D., Ph.D.

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 166C:105–111 (2014)

ARTICLE

Return of Results: Ethical and Legal Distinctions Between Research and Clinical Care

WYLIE BURKE,* BARBARA J. EVANS, AND GAIL P. JARVIK

Professionally Responsible Disclosure of Genomic Sequencing Results in Pediatric Practice

Laurence B. McCullough, PhD[a], Kyle B. Brothers, MD[b], Wendy K. Chung, MD, PhD[c], Steven Joffe, MD, MPH[d], Barbara A. Koenig, PhD[e], Benjamin Wilfond, MD[f], Joon-Ho Yu, MPH, PhD[f], on behalf of the Clinical Sequencing Exploratory Research (CSER) Consortium Pediatrics Working Group

Perspective

JANUARY 29, 2015

GINA, Genetic Discrimination, and Genomic Medicine

Robert C. Green, M.D., M.P.H., Denise Lautenbach, M.S., C.G.C., and Amy L. McGuire, J.D., Ph.D.

Am J Bioeth. 2014 March ; 14(3): 3–9. doi:10.1080/15265161.2013.879945.

ADDRESSING THE ETHICAL CHALLENGES IN GENETIC TESTING AND SEQUENCING OF CHILDREN

Ellen Wright Clayton, M.D. J.D.
Center for Biomedical Ethics and Society, Department of Pediatrics, and School of Law, Vanderbilt University, Nashville, TN

Pediatrics WG & U & R Award sites

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Professional Guidelines

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ACMG POLICY STATEMENT | Genetics inMedicine

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4–6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy L. McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[3], Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, PhD, FACMG[2,12], Michael S. Watson, PhD, FACMG[13], Marc S. Williams, MD, FACMG[14] and Leslie G. Biesecker, MD[15]

Genet Med 2013 15(7):565-574

Acknowledgements: Margaret Adam, Jeffrey Botkin, Wendy Chung, David Dimmock, Christine Eng, Madhuri Hegde, Gail Jarvik, Stephen Kingsmore, Michael Murray, Katherine Nathanson, Sharon Plon, Reed Pyeritz, Cheryl Reid, V. Reid Sutton, and Benjamin Wilfond.

NES | Genetics inMedicine

Genet Med 2015 17(5):405-424

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

NES | Genetics inMedicine

ACMG clinical laboratory standards for next-generation sequencing

Heidi L. Rehm, PhD[1,2], Sherri J. Bale, PhD[3], Pinar Bayrak-Toydemir, MD, PhD[4], Jonathan S. Berg, MD[5], Kerry K. Brown, PhD[6], Joshua L. Deignan, PhD[7], Michael J. Friez, PhD[8], Birgit H. Funke, PhD[1,2], Madhuri R. Hegde, PhD[9] and Elaine Lyon, PhD[4]; for the Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee

Genet Med 2013 15(9):733-747

Responses to the ACMG guidelines

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COMMENTARY | Genetics inMedicine

Open

Genetic incidental findings: autonomy regained?

Effy Vayena, PhD[1] and John Tasioulas, DPhil[2]

Recommendations for returning genomic incidental findings? We need to talk!

Genet Med 2013

Wylie Burke, MD, PhD[1], Armand H. Matheny Antommaria, MD, PhD[2], Robin Bennett, MS, CGC[3], Jeffrey Botkin, MD, MPH[4], Ellen Wright Clayton, MD, JD[5], Gail E. Henderson, PhD[6], Ingrid A. Holm, MD, MPH[7,8,9], Gail P. Jarvik, MD, PhD[3], Muin J. Khoury, MD, PhD[10], Bartha Maria Knoppers, JD, PhD[11], Nancy A. Press, PhD[12], Lainie Friedman Ross, MD, PhD[13], Mark A. Rothstein, JD[14], Howard Saal, MD[15], Wendy R. Uhlmann, MS, CGC[16], Benjamin Wilfond, MD[17], Susan M. Wolf, JD[18], and Ron Zimmern, FRCP, FFPHM[19]

JAMA
The Journal of the American Medical Association

Reporting Genomic Sequencing Results to Ordering Clinicians
Incidental, but Not Exceptional

Robert C. Green, MD, MPH
Division of Genetics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

James R. Lupski, MD, PhD, DSc
Departments of Molecular and Human

Should incidental findings discovered with whole-genome sequencing or testing be sought and reported to ordering clinicians and to patients (or their surrogates)?—**Yes**.

The use of genomic sequencing in medicine is increasing substantially as this technology becomes less expensive and of demonstrated diagnostic utility.[1,2] Potentially clinically relevant incidental findings from clinical exome or genome sequencing (hereafter referred to as genomic sequencing) will arise whenever an individual undergoes genomic sequencing. There is a great deal of controversy regarding how such findings should be addressed by clini-

chest x-ray for the evaluation of a possible rib fractu
he or she has been trained to perform a systematic
view of the film, reporting any abnormalities that ris
an established professional standard, regardless of
indication for the study.[7] Importantly, radiologists
specifically trained neither to report every conceiva
finding, nor to stop after "satisfaction of search"[8]
veals an indicated finding. Rather radiologists use p
fessional standards to assess and report a subse
unexpected findings that are likely to be medically
portant. Even though such findings are not always c
cally useful, depriving clinicians and patients of these

VOLUME 32 · NUMBER 21 · JULY 20 2014

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Clinical Tumor Sequencing: An Incidental Casualty of the American College of Medical Genetics and Genomics Recommendations for Reporting of Incidental Findings

D. Williams Parsons, Angshumoy Roy, and Sharon E. Plon, *Baylor College of Medicine and Texas Children's Cancer Center, Houston, TX*
Sameek Roychowdhury, *Ohio State University Comprehensive Cancer Center, Columbus, OH*
Arul M. Chinnaiyan, *Michigan Center for Translational Pathology and University of Michigan, Ann Arbor, MI*

POINT-COUNTERPOINT

Science 2013 340(6136):1047-48.

Ethics and Genomic Incidental Findings

Amy L. McGuire, [1*†] Steven Joffe, [2*] Barbara A. Koenig, [3] Barbara B. Biesecker, [4] Laurence B. McCullough, [1] Jennifer S. Blumenthal-Barby, [1] Timothy Caulfield, [5] Sharon F. Terry, [6] Robert C. Green[7†]

"The recommendations represent an initial attempt to set a professional standard for best laboratory practices…"

POINT-COUNTERPOINT

Science *2013 340(6136):1049-50.*

Patient Autonomy and Incidental Findings in Clinical Genomics

Susan M. Wolf, [1*] George J. Annas, [2] Sherman Elias[3]

"Autonomy protects the patient's right to make a decision different from what the clinician might choose."

Major Accomplishments

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- ✓Contributions to the Evidence Base:
  - Analytic validity
  - Clinical validity
  - Clinical utility
  - Ethical, legal, regulatory & social issues
- ✓Contributions to Professional Guidelines
- ✓Development of infrastructure, methods, resources & tools

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cser
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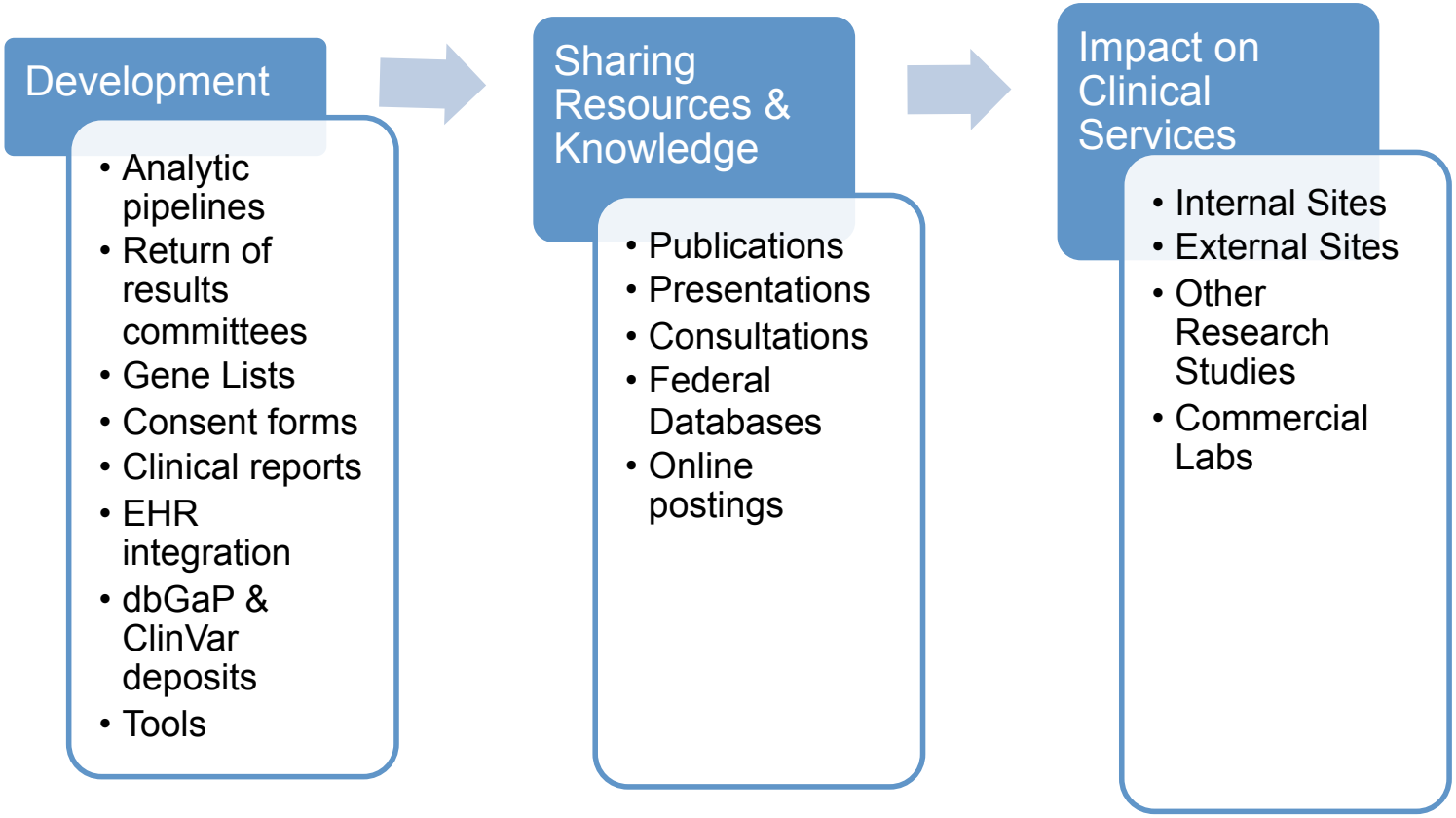

Examples

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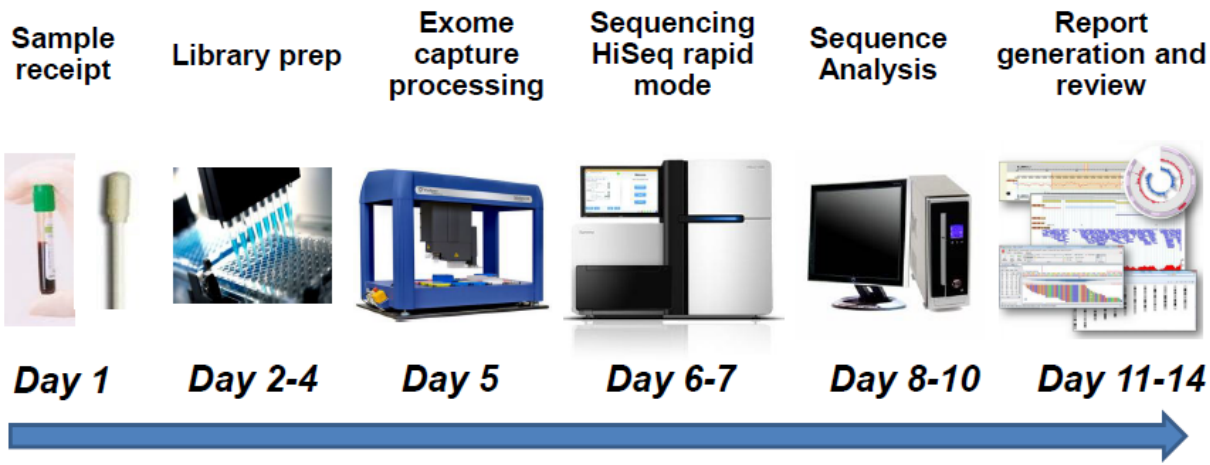
Development

- Analytic pipelines
- Return of results committees
- Gene Lists
- Consent forms
- Clinical reports
- EHR integration
- dbGaP & ClinVar deposits
- Tools

Slide courtesy of Dan Robinson

Timeline of Sequencing Analysis

Tissue Biopsy to Sequencing Results using v4 chemistry and rapid mode.



MI-ONCOSEQ

Michigan Center for Translational Pathology
University of Michigan Comprehensive Cancer Center
cser Clinical Sequencing Exploratory Research
M SPH
University of Michigan Health System

Examples

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Development

- Analytic pipelines
- Return of results committees
- Gene Lists
- Consent forms
- Clinical reports
- EHR integration
- dbGaP & ClinVar deposits
- Tools

Genetics inMedicine | SPECIAL ARTICLE

Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium

Jonathan S. Berg, MD, PhD[1-4], Laura M. Amendola, MS[5], Christine Eng, MD[6], Eliezer Van Allen, MD[7-9], Stacy W. Gray, MD, AM[8,10,11], Nikhil Wagle, MD[8,11,12], Heidi L. Rehm, PhD[10,13,14], Elizabeth T. DeChene, MS[15,16], Matthew C. Dulik, PhD[15,16], Fuki M. Hisama, MD[5], Wylie Burke, MD, PhD[5,17], Nancy B. Spinner, PhD[15], Levi Garraway, MD, PhD[7,12,18], Robert C. Green, MD, MPH[12,19], Sharon Plon, MD, PhD[6,20], James P. Evans, MD, PhD[1-4] and Gail P. Jarvik, MD, PhD[5,21] and the members of the CSER Actionability and Return of Results Working Group

Genet Med 2013 15(11): 860-867

Table 1 Process for determining incidental findings by CSER site

	BCM BASIC3	BWH/HMS MedSeq	CHOP PediSeq	DFCI/Broad CanSeq	UNC NCGENES	UW NEXT Medicine
Return of results committee	No[a]	Yes	Yes	Yes	Yes[b]	Yes
Participants						
Medical geneticists	Yes	Yes	Yes	Yes	Yes	Yes
Genetic counselors	Yes	Yes	Yes	Yes	Yes	Yes
Physicians (nongeneticists)	Yes	Yes	Yes	Yes	Yes	Yes
Bioethicists	Yes	Yes	Yes	Yes	Yes	Yes
CLIA-certified laboratory representatives	Yes	Yes	Yes	Yes	Yes	Yes
PhD-holding molecular geneticists	Yes	Yes	Yes	Yes	Yes	Yes
Others	Bioinformatics specialists, other specialties on consultation	Bioinformatics specialists, other scientists	Bioinformatics specialists, other scientists	Bioinformatics specialists, other scientists	Pharmacists, institutional review board chair	Other scientists
A priori list	No	No	Yes	Yes[c]	Yes	Yes

Actionability & Return of Results WG

Examples

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Dominant			X-Linked
ACTA2[a]	*KCNE3*	*PTEN*	
ACTC1	*KCNH2*	*RBM20*	*DMD*
ACVRL1	*KCNJ2*	*RET*	*EMD*
APC	*KCNQ1*	*RYR1*	*GLA*
BMPR1A	*KIT*	*RYR2*	*OTC*
BRCA1	*LDLR*	*SCN1B*	
BRCA2	*LMNA*	*SCN3B*	Recessive
CACNA1C	*MAX*	*SCN5A*	*ATP7B*
CACNA1S	*MEN1*	*SDHAF2*	*BCHE*
CACNB2	*MET*	*SDHB*	*BLM*
CDC73	*MLH1*	*SDHC*	*CASQ2*
CDH1	*MLH3*	*SDHD*	*COQ2*
CNBP	*MSH2*	*SERPINC1*	*COQ9*
COL3A1	*MSH6*	*SGCD*	*CPT2*
DMPK	*MUTYH*	*SMAD3*	*F5*[b]
DSC2	*MYBPC3*	*SMAD4*	*GAA*
DSG2	*MYH11*	*SMARCB1*	*HAMP*
DSP	*MYH7*	*STK11*	*HFE*[b]
ENG	*MYL2*	*TGFB2*	*HFE2*
EPCAM	*MYL3*	*TGFB3*	*IDUA*
FBN1	*MYLK*	*TGFBR1*	*LDLRAP1*
FH	*NF2*	*TGFBR2*	*PAH*
FLCN	*PDGFRA*	*TMEM127*	*PCBD1*
GCH1	*PKP2*	*TMEM43*	*PTS*
GPD1L	*PLN*	*TNNI3*	*QDPR*
HCN4	*PMS2*	*TNNT2*	*SERPINA1*
HMBS	*PRKAG2*	*TP53*	*SLC25A13*
KCNE1	*PRKAR1A*	*TPM1*	*SLC37A4*
KCNE2	*PROC*	*TSC1*	*SLC7A9*
	PROS1	*TSC2*	
	PTCH1	*VHL*	

www.genome.gov/27560596

=112 Total Genes

Amendola et al. 2015
Genome Res 25(3):305-15

Examples

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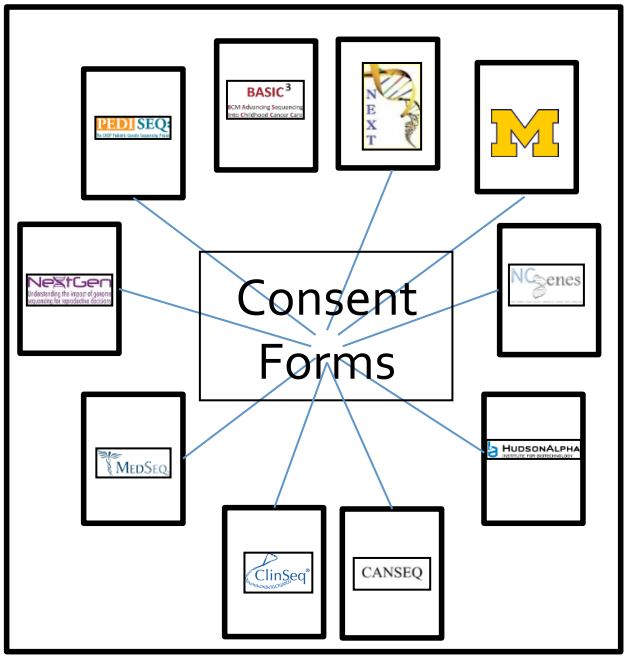
- Tools

The Challenge of Informed Consent and Return of Results in Translational Genomics: Empirical Analysis and Recommendations

Gail E. Henderson, Susan M. Wolf, Kristine J. Kuczynski, Steven Joffe, Richard R. Sharp, D. Williams Parsons, Bartha M. Knoppers, Joon-Ho Yu, and Paul S. Appelbaum

The nine studies are among the first NIH-funded studies to consider the many practical issues associated with clinical applications of WES/WGS. Each made relatively independent decisions about how to explain sequencing, its limitations, and potential findings. Our analysis addresses four key questions: (1) What results do these studies plan to return to participants? (2) How are participant preferences taken into account in determining whether to return results? (3) What potential benefits and risks are identified? and (4) How are privacy, placement of results into the medical record, risk of re-identification, and data-sharing addressed?

J Law Med Ethics. 2014 42(3):344-55



Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

© American College of Medical Genetics and Genomics

2015 17(8):644-50

Researchers' views on informed consent for return of secondary results in genomic research

Paul S. Appelbaum, MD[1], Abby Fyer, MD[1], Robert L. Klitzman, MD[1], Josue Martinez, BA[2], Erik Parens, PhD[3], Yuan Zhang, MS, MA[4] and Wendy K. Chung, MD, PhD[2,5]

cser-consortium.org/cser-research-materials

Informed Consent & Governance WG

Examples

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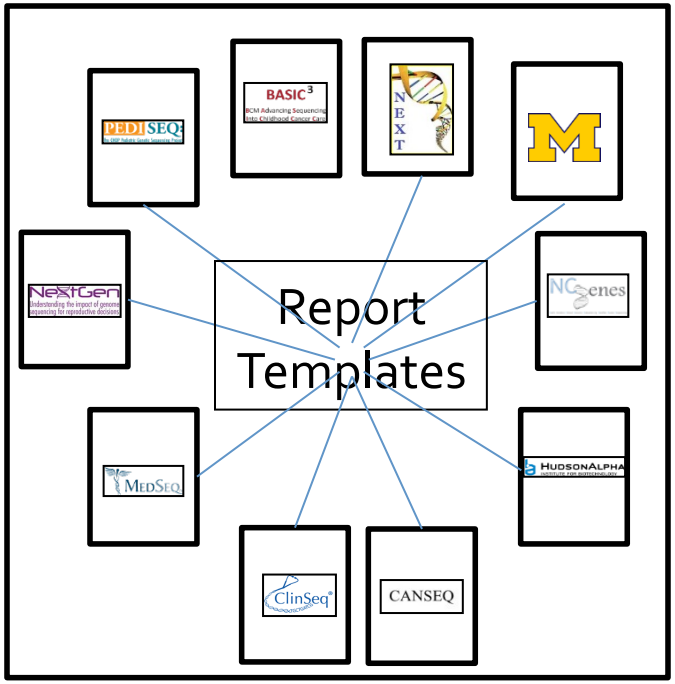
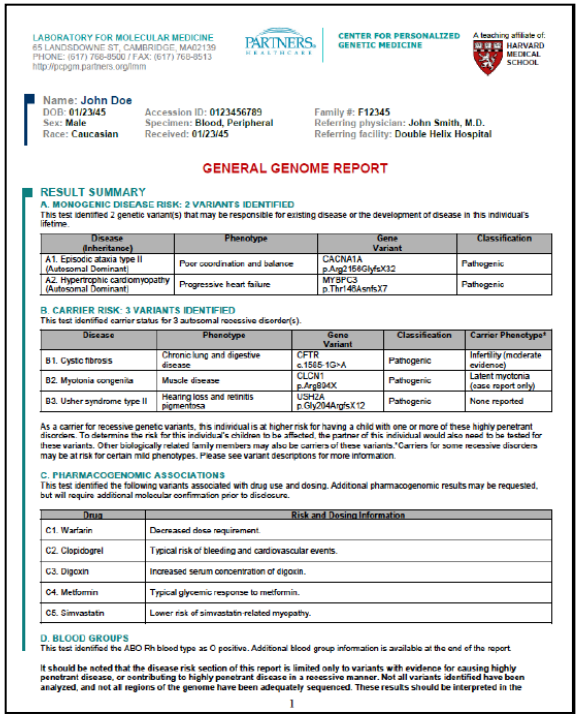
MEDSEQ

cser-consortium.org/
cser-research-materials





LABORATORY FOR MOLECULAR MEDICINE
65 LANSDOWNE ST, CAMBRIDGE, MA02139
PHONE: (617) 768-8500 / FAX: (617) 768-8513
http://pcpgm.partners.org/lmm

PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

Name: John Doe
DOB: 01/23/45
Sex: Male
Race: Caucasian
Accession ID: 0123456789
Specimen: Blood, Peripheral
Received: 01/23/45
Family #: F12345
Referring physician: John Smith, M.D.
Referring facility: Double Helix Hospital

GENERAL GENOME REPORT

RESULT SUMMARY

A. MONOGENIC DISEASE RISK: 2 VARIANTS IDENTIFIED

This test identified 2 genetic variant(s) that may be responsible for existing disease or the development of disease in this individual's lifetime.

Disease (Inheritance)	Phenotype	Gene Variant	Classification
A1. Episodic ataxia type II (Autosomal Dominant)	Poor coordination and balance	CACNA1A p.Arg2156GlyfsX32	Pathogenic
A2. Hypertrophic cardiomyopathy (Autosomal Dominant)	Progressive heart failure	MYBPC3 p.Thr146AsnfsX7	Pathogenic

B. CARRIER RISK: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorder(s).

Disease	Phenotype	Gene Variant	Classification	Carrier Phenotype*
B1. Cystic fibrosis	Chronic lung and digestive disease	CFTR c.1585-1G>A	Pathogenic	Infertility (moderate evidence)
B2. Myotonia congenita	Muscle disease	CLCN1 p.Arg894X	Pathogenic	Latent myotonia (case report only)
B3. Usher syndrome type II	Hearing loss and retinitis pigmentosa	USH2A p.Gly294ArgfsX12	Pathogenic	None reported

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's children to be affected, the partner of this individual would also need to be tested for these variants. Other biologically related family members may also be carriers of these variants.*Carriers for some recessive disorders may be at risk for certain mild phenotypes. Please see variant descriptions for more information.

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following variants associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
C1. Warfarin	Decreased dose requirement.
C2. Clopidogrel	Typical risk of bleeding and cardiovascular events.
C3. Digoxin	Increased serum concentration of digoxin.
C4. Metformin	Typical glycemic response to metformin.
C5. Simvastatin	Lower risk of simvastatin-related myopathy.

D. BLOOD GROUPS

This test identified the ABO Rh blood type as O positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the

1

Vassy et al. *Public Health Genomics* 2015 18(2):123-9.

McLaughlin et al. *BMC Med Genet* 2014 15:134

Examples

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Clinical Sequencing Exploratory Research

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- Tools

Genet Med 2013
15 (10):824- 832

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

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

Peter Tarczy-Hornoch, MD[1,2], Laura Amendola, MS[1,2], Samuel J. Aronson, MA, ALM[1,3], [1,5,7], bo, PhD[3,5,9], hite, PhD[1,5,7]

CSER and eMERGE: current and potential state of the display of genetic information in the electronic health record

RECEIVED 12 March 2015
REVISED 30 April 2015
ACCEPTED 12 May 2015

Brian H Shirts[1], Joseph S Salama,[2] Samuel J Aronson[3], Wendy K Chung[4], Stacy W Gray[5,6], Lucia A Hindorff[7], Gail
Peter Z Tarczy-Hornoch[11], Eliezer M Var
Robert R Freimuth[15], Robert W Grundm
Josh F Peterson[19], Luke V Rasmussen[2

JAMIA 2015
PMID: 26142422

Table 3: Location of genetic information

		Tab category						
Survey Question	*n*	Laboratory	Genetics	Pathology	Problem list	Pharmacogenetics/ drug interaction	Clinic notes	Outside medical records
Where is genetic information found in EHR?[a]								
Disease defining/diagnostic	17	88% (64–99)	29% (10–56)	18% (4–43)	59% (33–82)	0% (0–20)	59% (33–82)	24% (7–50)
Risk actionable	17	88% (64–99)	29% (10–56)	18% (4–43)	59% (33–82)	6% (0–29)	59% (33–82)	24% (7–50)
Low risk not actionable . . .	13	92% (64–99)	23% (5–54)	15% (2–45)	38% (14–68)	0% (0–25)	62% (32–86)	23% (5–54)
Large chromosomal changes . . .	16	81% (54–96)	25% (7–52)	25% (7–52)	50% (25–75)	0% (0–21)	56% (30–80)	31% (11–59)
Pharmacogenomics	17	82% (57–96)	24% (7–50)	18% (4–43)	41% (18–67)	18% (4–43)	59% (33–82)	24% (7–50)
Carrier recessive	17	88% (64–99)	29% (10–56)	18% (4–43)	35% (14–62)	0% (0–20)	65% (38–86)	35% (14–62)
Somatic/tumor genetics	15	87% (60–98)	27% (8–55)	33% (11–62)	40% (16–68)	0% (0–22)	60% (32–84)	33% (11–62)
Incidental	12	83% (52–98)	25% (5–58)	17% (2–48)	42% (15–72)	0% (0–26)	67% (35–90)	25% (5–58)
Variants of uncertain significance	13	85% (55–98)	38% (14–68)	15% (2–45)	38% (14–68)	0% (0–25)	62% (32–86)	38% (14–68)
Uninterpreted variants	7	57% (18–90)	14% (1–58)	0% (0–41)	43% (10–82)	0% (0–41)	29% (4–71)	0% (0–41)
Newborn Screening	16	81% (54–96)	25% (7–52)	19% (4–46)	38% (15–65)	0% (0–21)	69% (41–89)	31% (11–59)
Sensitive Genetic Information	15	87% (60–98)	33% (11–62)	13% (2–40)	40% (16–68)	0% (0–22)	60% (32–84)	27% (8–55)

[a]Genetic categories were designed to illustrate clinical or public health use cases and are not exclusive. Genetic results may fit multiple categories, e.g., sensitive – diagnostic results; actionable – incidental findings, etc., and some categories are clinical context dependent. Display locations are also not exclusive. Genetic information may be displayed in multiple locations simultaneously. Percentages are given with 95% binomial confidence intervals.

Electronic Health Records WG

Examples

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Development

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- Tools

CSER has 1149 dbGaP submissions
CSER is one of the top submitters to **ClinVar**

Submitter	Total Submissions with Assertions
OMIM	25994
GeneDx	19618
Emory Genetics Lab	15983
ISCA (all sites)	14438
Lab for Molecular Medicine	12207
Ambry Genetics	9995
Genetic Services Lab; U. Chicago	7147
Invitae	1949
GeneReviews	3928
CSER (all sites)	2617

Examples

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CANSEQ

BASIC^3
BCM Advancing Sequencing Into Childhood Cancer Care

PEDI SEQ:
The CHOP Pediatric Genetic Sequencing Project

MEDSEQ

ClinSeq®

- **MEG (MEdicine Gene Annotation),** the official CSER variant database. https://redcap.iths.org/
- **TARGET (Tumor Alterations Relevant for GEnomic-drive Therapy):** database of genes that, when somatically altered in cancer, are directly linked to a clinical action. http://www.broadinstitute.org/cancer/cga/target
- **PHIAL (Precisio Heuristics for Interpreting the Alteration Landscape):** heuristic algorithm for clinical interpretation of cancer genome sequencing data. http://www.broadinstitute.org/cancer/cga/phial
- **Cassandra** combines annovar output with other public data sources to output annotated .vcf files. https://www.hgsc.bcm.edu/software/cassandra
- **Atlas 2**: Suite of variant analysis tools. https://www.hgsc.bcm.edu/software/atlas-2
- **Proband**: app for taking family history pedigrees. http://probandapp.com/
- **Interactive Graphic Sequencin i Clinical Practice,** a NEJM interactive graphic on clinical genome and exome sequencing. http://www.nejm.org/action/showMediaPlayer?doi=10.1056/NEJMra1312543&aid...

Impact

These sites endorse the following statement:

"The knowledge shared from the CSER consortium has influenced and accelerated our plans and implementation of clinical sequencing"

- **Other Research Studies**
  - BabySeq (NSIGHT)
  - ClinGen
  - eMERGE sites (Brigham/MGH/Children's Hospital)
  - eMERGE site (CHOP)
  - NC NEXUS (NSIGHT)
  - Prostate Cancer Foundation/Stand Up 2 Cancer International Dream Team
  - NCI/Children's Oncology Group Trial
  - pedsNet (PCORI)
- **Internal Organizations**
  - OHSU Molecular Genetic Diagnostic Lab Services
  - Broad Institute CLIA Sequencing Lab
  - Laboratory for Molecular Medicine Clinical Services
  - Individualized Medical Genetics Center (CHOP)
  - Clinical Genetics Think Tank (International Collaboration)
- **External Organizations**
  - One-on-one consultations with major pediatric oncology institutions
  - Cerner, EPIC, IOM Roundtable
  - Vidant Cardiology

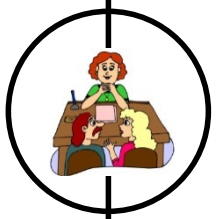
LOOKING AHEAD: ONGOING WORK IN THE CSER CONSORTIUM UNTIL JUNE 2017

CSER Consortium-wide Efforts

Topic	Lea Site(s)
Clinician bake-off	MedSeq, NCGenes
Combined outcomes	CANSEQ, NEXT
Compare approaches to carrier results reporting	NextGen: Understanding the impact of genome sequencing for reproductive decisions
Impact of changing the interpretation of findings	ClinSeq®
Secondary findings across the consortium	NCGenes

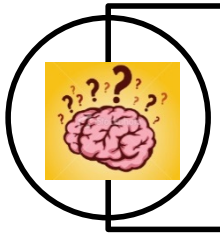
cser
Clinical Sequencing Exploratory Research

CSER Site-specific Questions

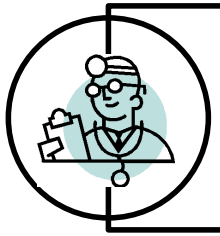


- How effective are the genomic educational programs?
- How should ROR visits be structured?
- What are patient preferences and expectations?
- How well were preferences and expectations met?

- What are the downstream healthcare costs?



- What are the long-term psychosocial impacts?
- Are patients satisfied with result delivery?
- Do patients understand results and genetic concepts?



- What is the impact of providing clinical decision support?
- What is the impact on care delivery?
- How are results used by patients/clinicians?

Summary

- Yield differs by clinical indication
- Incidental finding rate is low
- Need better ways to consistently classify variants
- Providing an evidence base & resolving obstacles t genomic medicine
    - When
    - Best practices
    - What do all those variants mean?
- Integration with ELSI work & regulatory analyses
    - How best to approach informed consent
    - Managing pediatric results
    - Impact of results disclosure

LOOKING TO THE FUTURE: WHAT QUESTIONS WILL REMAIN?

Future Directions

Today's Agenda Topic	CSER Consortium Recommended Priority Areas
Interpreting Variants/Actionability	• Clinical diagnosis of unsolved cases
Assessing Clinical Utility	• Determination of appropriate use of genome & exome sequencing
Patient-Centered Research	• Conduct biopsychosocial research • Continue ELSI investigations
Increasing Diversity	• Investigate the use of clinical sequencing in larger, more diverse populations
Healthcare utilization, economics & value	• Evaluation of downstream health and economic outcomes
Other	• Optimization of the delivery system • Iterative phenotyping

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HudsonAlpha Institute	Richard Myers
Kaiser Permanente	Katrina Goddard & Ben Wilfond
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University of North Carolina	Jim Evans
University of Washington	Gail Jarvik
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Columbia University	Paul Appelbaum Wendy Chung
Children's Mercy Hospita	Jeremy Garrett
Johns Hopkins University	Michelle Lewis
Mayo Clinic	Rich Sharp
Seattle Children's Hospital	Holly Tabor
UCSF, Mayo College of Medicine, & University of Minnesota	Barbara Koenig, Gloria Petersen, & Susan Wolf
Vanderbilt & McGill University	Ellen Clayton & Bartha Knoppers

NCI NHGRI cser Clinical Sequencing Exploratory Research