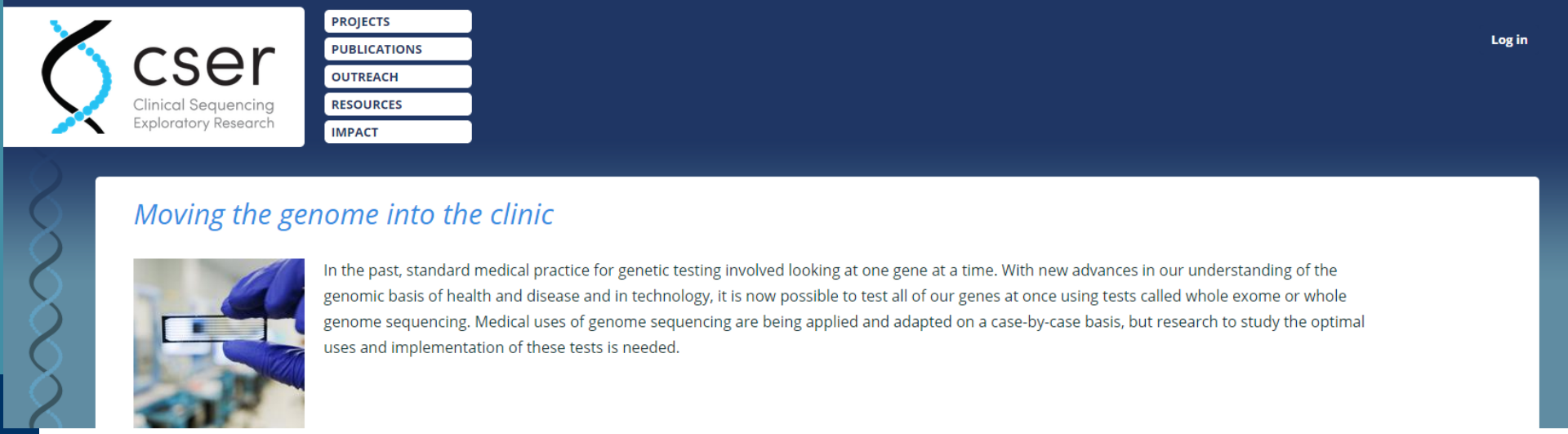

Clinical Sequencing Exploratory Research Consortium

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Funded by NIH, NHGRI & NCI (U01HG006507, U01HG007307)

Clinical Sequencing Exploratory Research

Goal: **Responsibly integrate genomic sequencing into routine medical care**

- Explore the clinical application of genomic sequence data
  - Generate and interpret data
  - Communicate these to the physician and patient
- Provide best practices
- Provide an evidence base
- Overcome obstacles

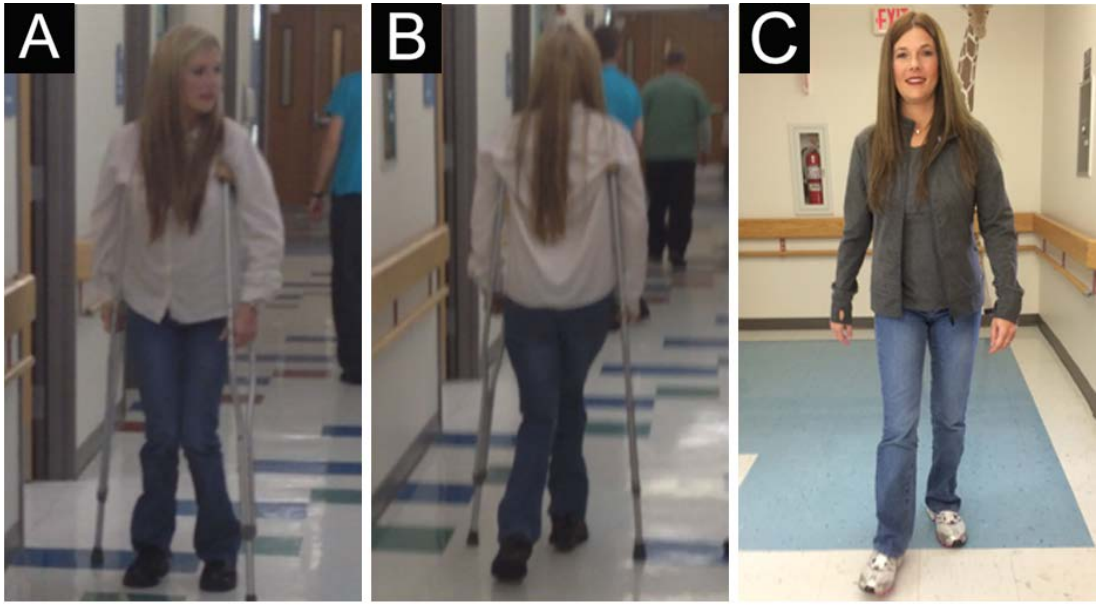
(ANOTHER) NEW MEDICAL TECHNOLOGY

- Requires systematic study, evidence base, and best practices to safely succeed

A case: CSER goes Cosmo

- 36 yo diagnosed at 6 with “hereditary spastic paraplegia”
  - Confined to crutches and wheelchair for decades
  - Daily painful episodes of spasticity, 5 surgeries
- CSER UNC WES: GCH1 [p.Arg216*], diagnosis of dopa-responsive dystonia
- Dramatic dopa response
  - Walking without crutches, free of pain

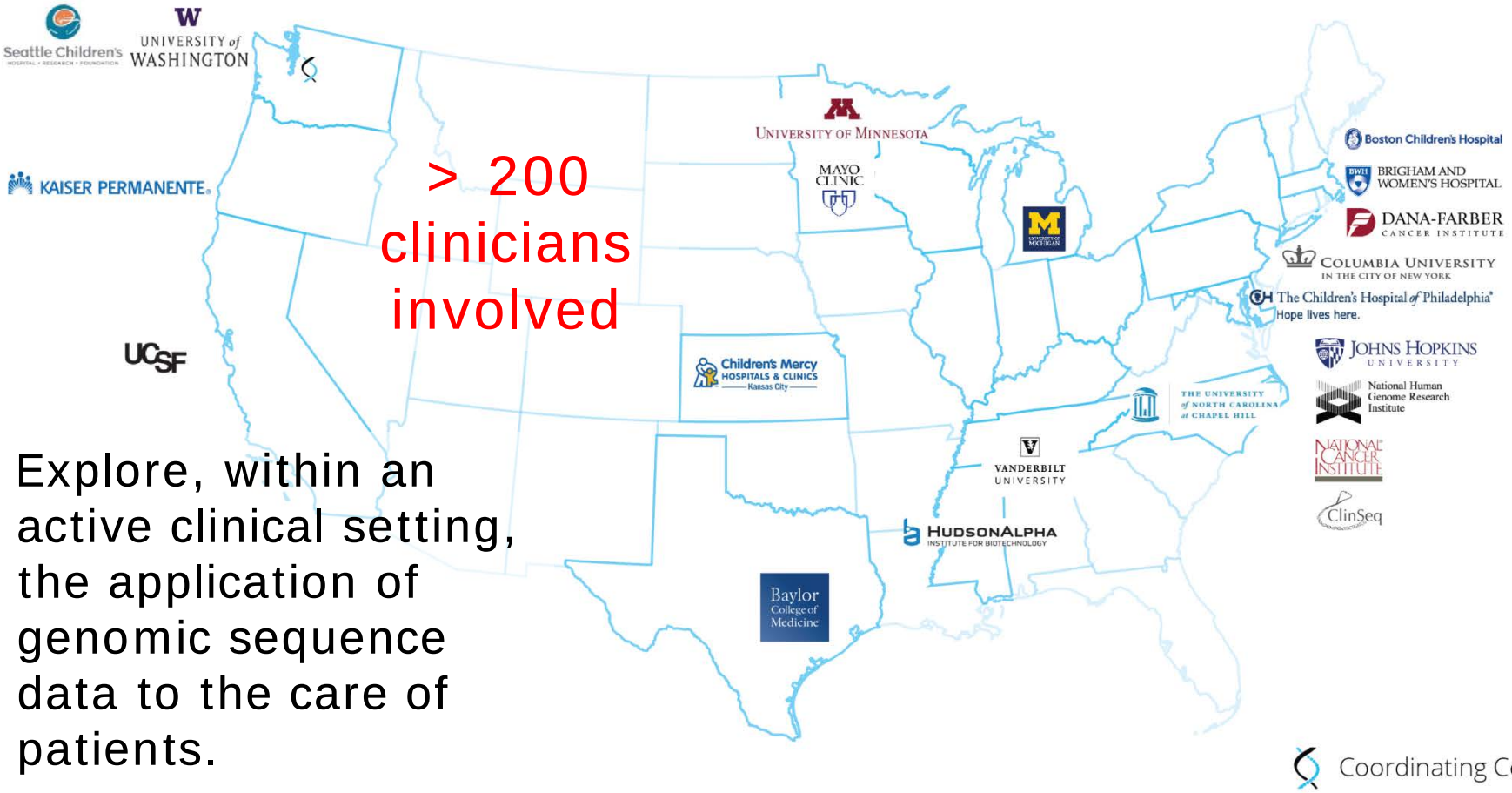
http://www.cosmopolitan.com/_mobile/advice/health/mystery-diagnosis-paralyzed?src=email



Photos courtesy of Jim Evans and permission of patient

CSER Consortium

377 Researchers
21 Institutions
1 Consortium



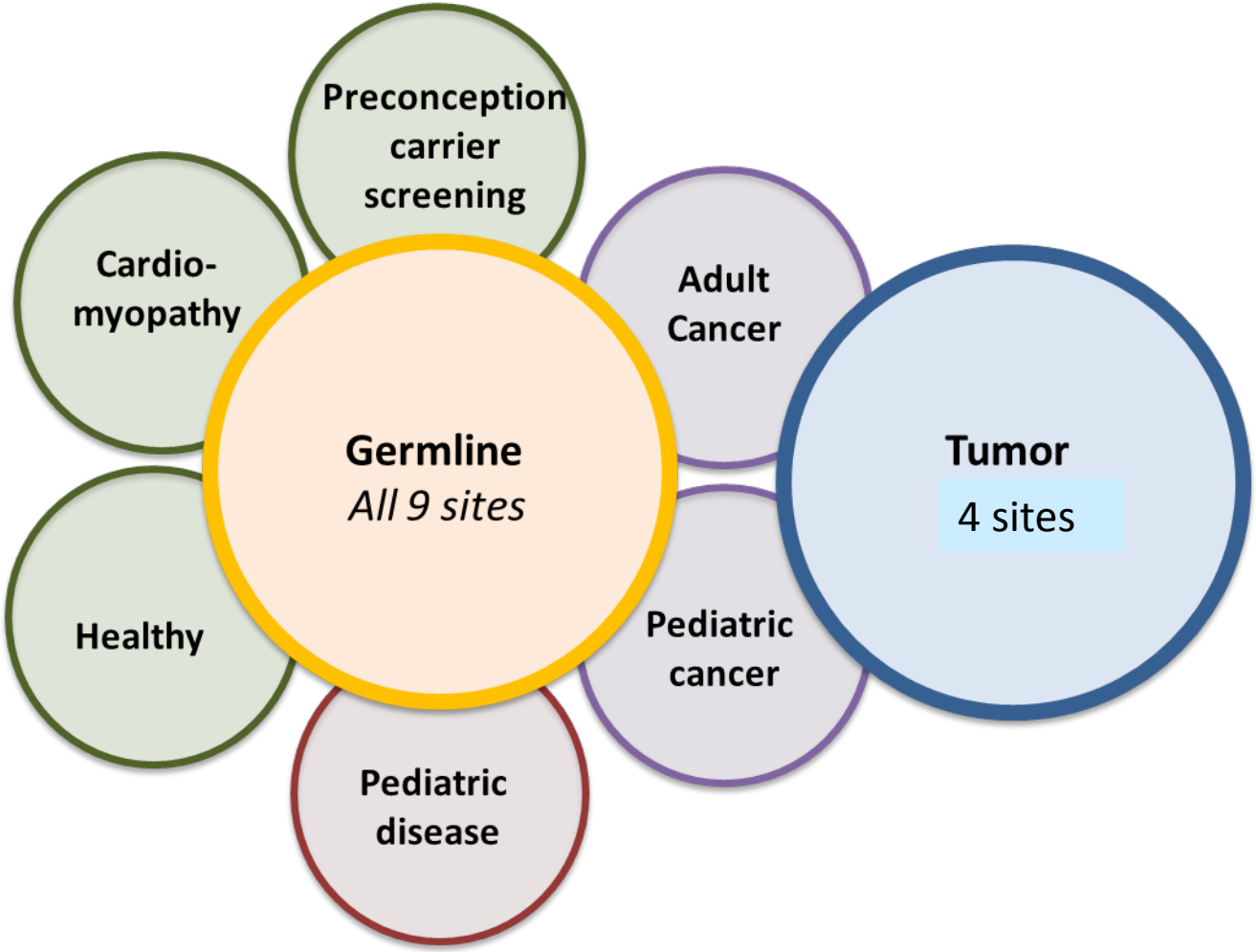
Explore, within an active clinical setting, the application of genomic sequence data to the care of patients.

Connect with CSER for news & networking:

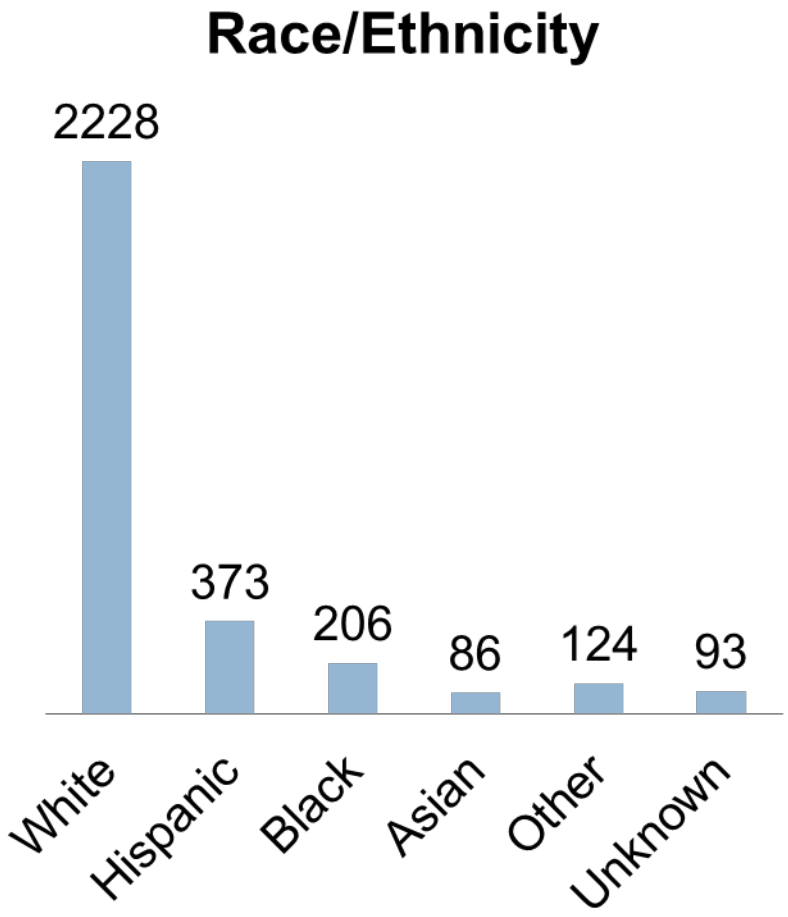
Twitter *@hail_CSER* LinkedIn via *www.tiny.cc/CSER_on_LinkedIn*

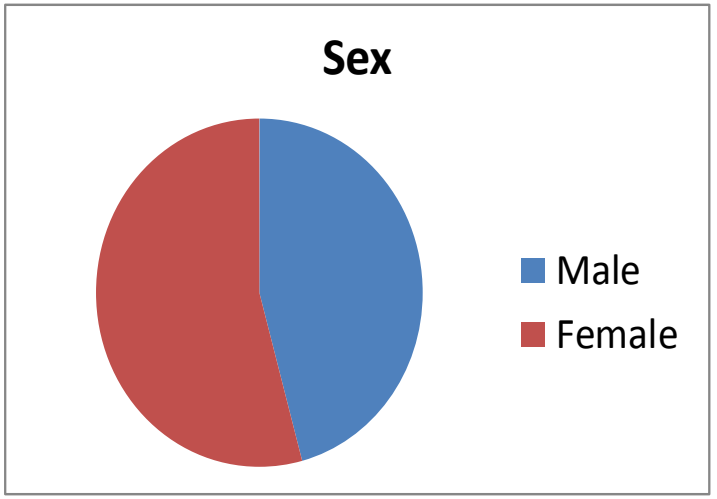

Meeting
g 2015

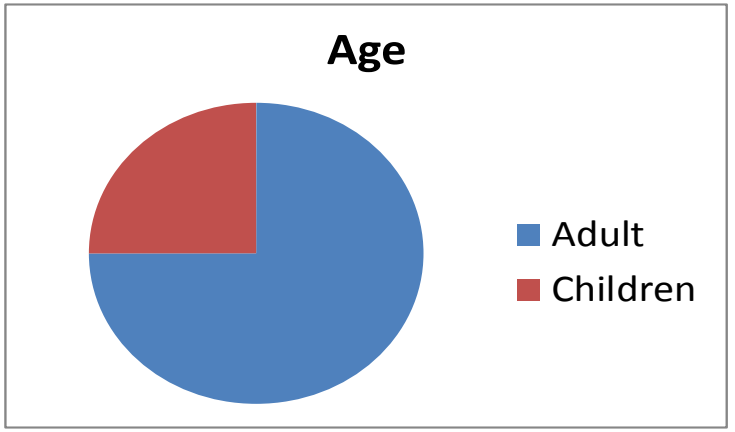
CSER Study Populations



Enrollment Summary







Current enrollment = 3152/4745 expected

Diagnostic Yield

		% of subjects with ≥ 1 finding (median # of variants reported)			
Clinical Characteristics	**Sample Size**	**P or LP**	**VUS**	**Single Recessive**	**Other**
Cancer (adult)	226	2.7% (1)	8% (1)	0%	1.8% (1)
Cancer (pediatric)	11	9% (1)	64% (3)	9% (1)	0%
DD/ID	122	21% (1)	21% (1)	1.6% (4.5)	0%
Heart disease	104	23% (1)	26% (1)	1.0% (3)	1.0% (1)
Hematology	13	8% (1)	8% (1)	0%	0%
Hearing Loss	5	40% (2.5)	60% (1)	60% (1)	-
Mitochondrial	1	0%	100% (1)	100% (1)	-
Neurological	130	9% (1)	13% (1)	3% (1)	4% (1)
Ophthalmology	67	28% (1)	13% (1)	9% (1)	0%
Syndromic	143	14% (1)	9% (1)	1.4% (1.5)	4% (1)

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Cancer Germline Diagnostic Yield Varies by Diagnosis

	Cases	(+)	Possible	(-)	Yield
Cancer (Adult)	346	33	176	273	10%
Colorectal	78	5	9	48	6%
Other GI	31	5	18	24	16%
Lung	75	6	13	61	8%
Breast & Ovarian	54	7	32	43	13%
Skin	21	1	11	17	5%
Leukemia/Lymphoma	27	1	17	22	4%
Ovarian	7	1	5	6	14%
Sarcoma	25	1	17	18	4%
Other	106	11	63	82	10%

Often change management

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Exomes can save money without changing management: a case

- Patient in teens
- Movement disorder early in life
- Saw 12 experts in centers from Vancouver to Texas without a diagnosis, numerous tests
- PE: choreoathetosis and dystonia of limbs, most prominent at rest; progressed to include facial twitches and mild dysarthria
- ***Exome:*** *de novo* R418W (c.1252C>T) in ADCY5
  - **Familial Dyskinesia with Facial Myokymia**
- **Ended diagnostic odyssey**

Chen et al, Annals of Neurology.

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Rate of Actionable Incidental Findings (IFs)

- Establish list of adult “actionable” gene-disease pairs
- Classify all Exome Variant Server (EVS) SNVs called “Disease Causing” by HGMD (615) and novel expected pathogenic (12)
    - 4300 European Ancestry
    - 2203 African Ancestry
- Contribute to national databases of variants (ClinVar)
- We will likely come across these again

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Genes with Actionable Variants relevant to Adults

Highlighted genes are recommended for return by the American College of Medical Genetics and Genomics guidelines.

Amendola et al. Genome Res 2015. PMID: 25637381

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

=112 Total Genes

cser Clinical Sequencing Exploratory Research

Mendelian Disease Variant Classification Terminology

ACMG Recommendation:

- Pathogenic (≠ mutation)
- Likely pathogenic (90%)
- Uncertain significance (VUS)
- Likely benign
- Benign (≠ polymorphism)

Classification criteria (strict for IFs)

Pathogenic	Segregation* in >= 2 unrelated families OR 2 of 3: 1. Segregation * in 1 family 2. Identified in >= 3 unrelated individual 3. De novo event in trio OR Protein truncation known to cause disease AND Below allele frequency cut off
Likely pathogenic	Identified in >= 3 unrelated individuals OR Segregation* in 1 family OR De novo event in trio AND Below allele frequency cut off

*1/16 probability cut-off to define segregation

Expected Rate of Actionable Variants:

Exome Variants Server (EVS) Results by Ancestry Group

Participants with classification	European ancestry* N=4300	African ancestry N=2203
Pathogenic variants (known)	30 (0.7%)	6 (0.3%)
Likely pathogenic variants (known)	52 (1.2%)	13 (0.6%)
Novel expected disruptive	6 (0.1%)	6 (0.3%)
Total pts with IFs	36 (0.8%)	12 (0.5%)

626 variant classifications deposited to ClinVar

**Caveats: No CNV included, HIGHER in Ashkenazi*

Amendola et al., *Genome Res. 2015. PMID: 25637381*

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EVS 6503, Pathogenic Cancer Variants

Table 4. Pathogenic and likely pathogenic variants

	Associated phenotype	Pathogenic variants (participants)	Likely pathogenic variants (participants)	Expected disruptive variants (participants)
ACMG genes				
BRCA1 or *BRCA2*	Breast/ovarian cancer	7 (7)	0 (0)	3 (3)
MSH6, PMS2, CHD1	GI cancer	4 (4)	1 (2)	2 (3)
LDLR	Hypercholesterolemia	4 (6)	7 (12)	0 (0)
LMNA1, MYBPC3, DSG2, MYH7, MYL2, MYL3, PKP2, TNNI3, TNNT2	Cardiomyopathy	4 (4)	14 (24)	2 (2)
RYR1	Malignant hyperthermia	4 (5)	1 (2)	0 (0)
KCNQ1, SCN5A	Arrhythmia	1 (1)	3 (7)	0 (0)
RET	Multiple endocrine neoplasia	1 (1)	0 (0)	0 (0)
TP53	Li-Fraumeni syndrome	1 (1)	2 (6)	0 (0)
DSC2, DSP	Arrhythmogenic right ventricular dysplasia	0 (0)	0 (0)	2 (2)
ACMG gene total		26 (29)	28 (53)	9 (10)
Non-ACMG genes				
SERPINA1	Alpha-1 antitrypsin def.	2 (4[a])	2 (3[b])	0 (0)
PROC	Protein C deficiency	1 (1)	2 (2)	0 (0)
PROS	Protein S deficiency	0 (0)	0 (0)	1 (1)
ATP7B	Wilson disease	1 (3[c])	0 (0)	0 (0)
ENG, ACVRL1	Hereditary hemorrhagic telangiectasia	1 (1)	1 (1)	0 (0)
FLCN	Birt-Hogg-Dube	1 (1)	0 (0)	0 (0)
DMD	Cardiomyopathy	0 (0)	1 (1)	0 (0)
KCNE1, KCNE2	Arrhythmia	0 (0)	2 (4)	0 (0)
SLC7A9	Cystinuria	0 (0)	1 (1[c])	0 (0)
HMBS	Porphyria	0	1 (1)	0 (0)
PTCH1	Basal cell nevus syndrome	0 (0)	0 (0)	1 (1)
Non-ACMG gene total		6 (7)	10 (12)	2 (2)
Grand total		32 (36)	38 (65)	11 (12)

[a]Participant was compound heterozygote for two pathogenic variants.
[b]Participant was compound heterozygote for one pathogenic variant and one likely pathogenic variant.
[c]Participant was heterozygous for a pathogenic variant or a likely pathogenic variant and does not count toward the total number of participants.

Amendola et al., *Genome Res* 2015. PMID: 25637381

cser Clinical Sequencing Exploratory Research

Data from CSER studies

Category	Sample Size	Number (%) of subjects with ≥1 Finding	Range (sites)
ACMG Incidental Findings: Pathogenic	2429	41 (1.7%)	0%-8% (10)
ACMG Incidental Findings: Likely Pathogenic	2372	15 (0.6%)	0%-8% (8)
Non-ACMG: Pathogenic	2429	39 (1.6%)	0%-8% (10)
Non-ACMG: Likely Pathogenic	2372	15 (0.6%)	0%-5% (8)
PGx Genes: FDA Indication	1820	28 (1.5%)	0.16%-88% (3)
PGx Genes: Other	206	4 (1.9%)	1.9% (1)
Carrier Genes: Pathogenic	1976	324 (16%)	0%-79% (9)
Carrier Genes: Likely Pathogenic	1968	138 (7%)	0%-40% (8)
Tumor: Potentially Clinically Relevant	120	106 (88%)	28%-100% (3)

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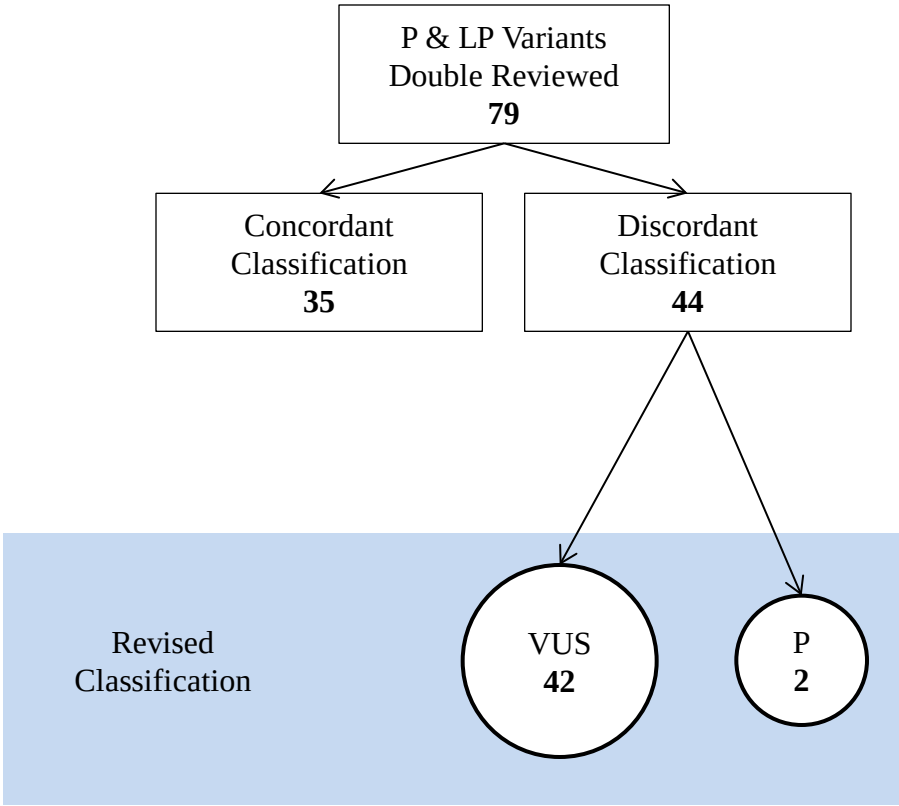
Variant Classification QC: Overcalling

- Recall random 25% of 615:
  - 83/156 (53%) discrepant
  - 52 reviewers, a few made systematic errors: all recalled
- Recall all pathogenic & likely pathogenic variants:
  - 44/79 (56%) discordant;
  - 42/44 (95%) overcalled (final call VUS)
- NOTE: Overcalling is a clinical problem



Amendola et al. *Genome Res* 2015. *PMID: 25637381*

Final CSER calls match other experts

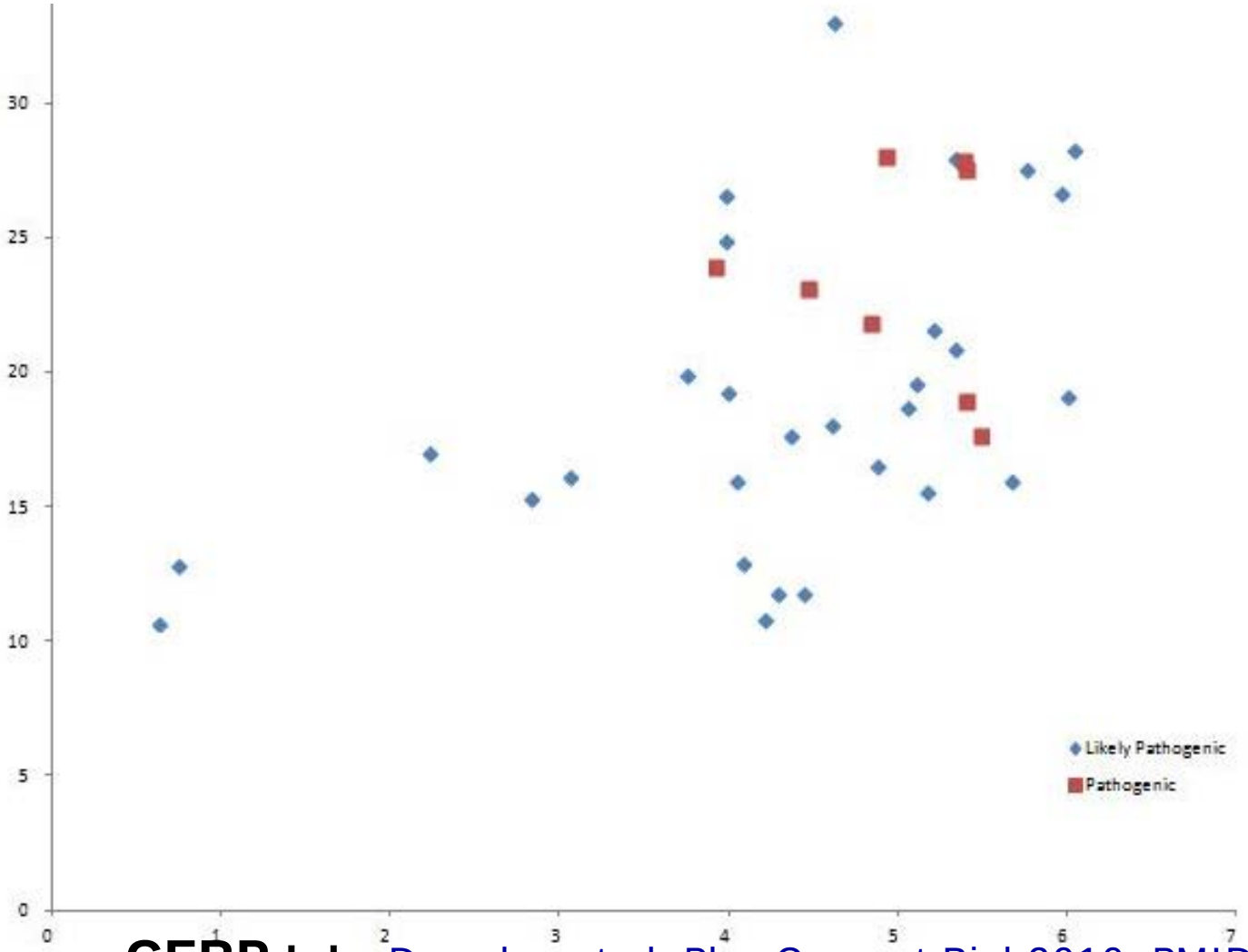
- 45/45 (100%) match with Sharing Clinical Reports Project (SCRP)
- 97/99 (98%) match with Partners Laboratory for Molecular Medicine (LMM)

Amendola et al. *Genome Res* 2015. *PMID: 25637381*

GERP vs. CAAD scores of pathogenic & likely pathogenic dominant variants

(excluding disruptive variants)

CADD
Kircher et al. Nat Genet 2014, PMID 24487276



GERP++ Davydov et al. Plos Comput Biol 2010, PMID 21152010

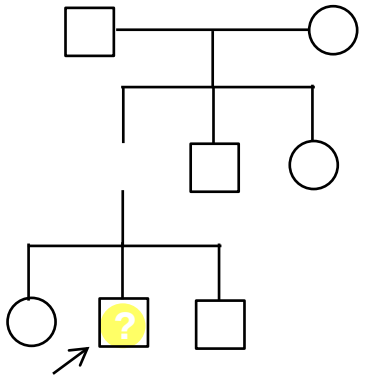
The Stakes are High in the Clinical Application of Genomics

Patients (& families) make serious decisions.

False positives lead to:

- Unnecessary surgery; years of unnecessary screening
- Premature end to diagnostic pursuit, forgoing the true answer

- False negatives lead to:
  - Forgoing necessary preventive/therapeutic modalities
- Amplified by misclassification of family members as at-risk or not
- Family planning & abortion
- The psychological damage of misinformation



2014 Cross-Consortium Classification of 6 Variants (early ACMG rules)

Site	MSH6 c.2731C>T; p.Arg911*	RYR1 c.1840C>T; p.Arg614Cys	FBN1 c.4270C>G; p.Pro1424Ala	TSC2 c.736A>G; p.Thr246Ala	TNNT2 c.732G>T; p.Glu244Asp	LDLR c.967G>A; p.Gly323Ser
1	Pathogenic	Likely pathogenic/	VUS	VUS	VUS	VUS
2	Pathogenic	Pathogenic	Likely pathogenic/ VUS	VUS	VUS	VUS
3	Pathogenic	Pathogenic	VUS	VUS	VUS	VUS
4	Pathogenic	Pathogenic	VUS	VUS	Likely pathogenic	VUS
5	Pathogenic	Likely pathogenic/	Likely pathogenic/ VUS	Likely pathogenic	VUS	VUS
6	Pathogenic	Likely pathogenic	Pathogenic/ Likely pathogenic/	Likely pathogenic	VUS	Likely pathogenic/ VUS

Amendola et al., *Genome Res* 2015. PMID: 25637381

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

ACMG Standard Recs
Richards et al GIM 2015
PMID:25741868

ACMG Variant Classification Rules, continued

Pathogenic	(i) 1 Very strong (PVS1) *AND* (a) ≥1 Strong (PS1–PS4) *OR* (b) ≥2 Moderate (PM1–PM6) *OR* (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR* (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) *OR* (iii) 1 Strong (PS1–PS4) *AND* (a)≥3 Moderate (PM1–PM6) *OR* (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR* (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

2015 CSER "bakeoff"

99 germline variants
-9 classified by 9 sites
-90 classified by 2-3 sites

by ACMG and own rules

Intra-laboratory Usual vs. ACMG Classification Comparison: 98 variants, 90 average 2.85 calls, 9 have 9 calls

		ACMG class					
		P	LP	VUS	LB	B	Total
Lab class	P	59	12	2	0	0	73
	LP	5	58	5	0	0	68
	VUS	6	4	91	3	0	104
	LB	0	0	17	32	4	53
	B	0	0	4	5	28	37
Total		70	74	119	40	32	**335**

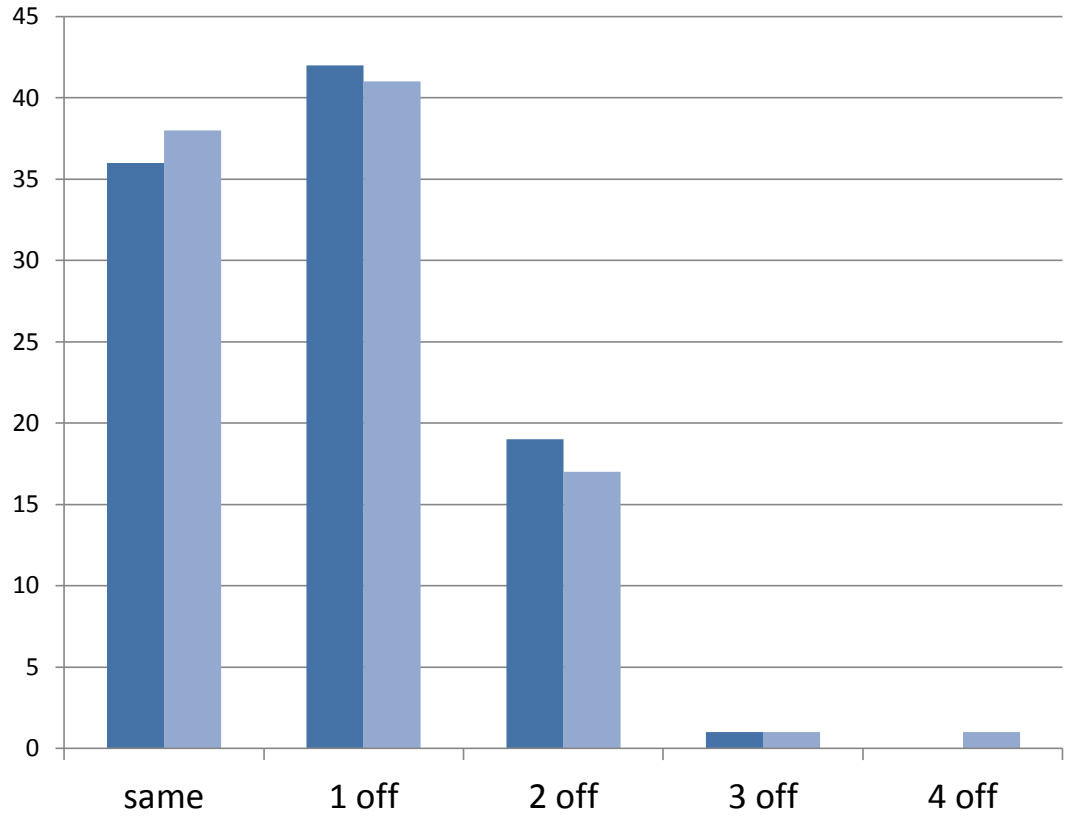
Benign	(i) 1 Stand-alone (BA1) *OR*
	(ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR*
	(ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR
	(ii) the criteria for benign and pathogenic are contradictory

MAF > 5%

MAF > disease frequency

Inter-laboratory Concordance of 98 variants

Count



P=0.9

ACMG criteria

Lab criteria

All labs agree

Benign to pathogenic

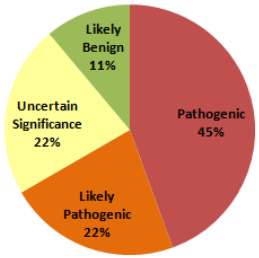
Range of classifications across labs

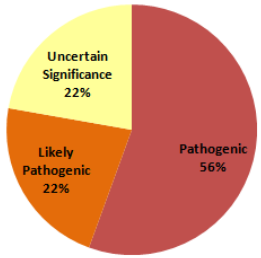
Variant with Major Disagreement: Why?

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

- 0.4% EU chromosomes (267/66688; 0.8% people; ExAC); 3/50 people in CSER
- AR, late-onset, +/- reduced penetrance, spastic paraplegia Sanger confirmed

Laboratory classification





ACMG Classification

Time: 25 (LB/VUS) to >200 (VUS/P) minutes

Cosegregation

Functional evidence

Computational

MAF > disease frequency

Laboratory class	ACMG Rules	PP3	PS3	PM3	PP1	PS1	PS4	PP5	PM2	BS1	PP2	PP4	ACMG lines of evidence
Pathogenic	Pathogenic	X	X	X			X	X					PS3,PS4,PM3,PP3,PP5
Pathogenic	Pathogenic	X	X	X	X	X		X					PS1, PS3, PM3, PP1, PP3, PP5
Pathogenic	Pathogenic	X	X	X	X	X	X						PS1, PS3(moderate) ,PS4, PM3, PP1, PP3
Pathogenic	Pathogenic			X	X								PM3 (strong), PP1 (strong)
Likely Pathogenic	Likely Pathogenic	X	X	X	X		X		X				PP1, PP3, PM2, PM3, PS3(weak), PS4
Likely Pathogenic	Likely Pathogenic	X				X		X					PS1, PP3, PP5
Uncertain Significance	Pathogenic	X	X						X		X	X	PS3, PM2, PP2, PP3, PP4
Likely Benign	Uncertain Significance		X			X	X			X			PS1, PS3, PS4, BS1
Uncertain Significance	Uncertain Significance	X			X					X			PP1, PP3, BS1
		7	6	5	5	4	4	3	2	2	1	1	

CSER Ongoing Outcomes Efforts:

Steps to access to genomic medicine

Research → Evidence base → Practice Guidelines → Insurance Coverage

Next generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: a cost-effectiveness analysis.
Gallego, Shirts, Bennette, et al.

J Clin Onc. 2015. PMID 25940718

The cost-effectiveness of returning incidental findings from next-generation genomic sequencing

Caroline S. Bennette, MPH[1], Carlos J. Gallego, MD, MS[1,2], Wylie Burke, MD, PhD[3], Gail P. Jarvik, MD, PhD[2] and David L. Veenstra, PharmD, PhD[1,4]

Genet Med. 2014. PMID: 25394171

Comparative effectiveness of next generation genomic sequencing for disease diagnosis: Design of a randomized controlled trial in patients with colorectal cancer/polyposis syndromes☆

Carlos J. Gallego [a,b], Caroline S. Bennette [b], Patrick Heagerty [c], Bryan Comstock [c], Martha Horike-Pyne [a], Fuki Hisama [a], Laura M. Amendola [a], Robin L. Bennett [a], Michael O. Dorschner [d], Peter Tarczy-Hornoch [e], William M. Grady [f], S. Malia Fullerton [g], Susan B. Trinidad [g], Dean A. Regier [h], Deborah A. Nickerson [i], Wylie Burke [g], Donald L. Patrick [j], Gail P. Jarvik [a], David L. Veenstra [b,*]

Contemp Clin Trials. 2014. PMID: 24997220

Goal: Compare colorectal cancer panel cost-effectiveness

Categories of Associated Conditions	Genes	Panel 1	Panel 2	Panel 3	Panel 4
Lynch	*MLH1, MSH2, PMS2, MSH6, EPCAM*	✔	✔	✔	✔
Autosomal Dominant ↑Penetrance	*APC, BMPR1A, SMAD4, CDH1, STK11*		✔	✔	✔
Autosomal Recessive ↑Penetrance	*MUTYH*			✔	✔
Autosomal Dominant ↓Penetrance	*PTEN, TP53, GALNT12, POLE, POLD1, GREM1, AKT1, PIK3CA*				✔

Gallego et al, *J Clin Oncol* 2015, PMID 25940718

Results: Incremental Cost-Effectiveness Ratios

Compared to Standard of Care or Next Best Strategy	5 Lynch genes	10 genes =5+AD ↑ Penet	11 genes= 10+AR ↑ Penet	19 genes 11+AD ↓ Penet
Δ Costs	$2,800	$4,500	$4,700	$670
Δ Quality Adjusted Life Years (QALY)	0.019	0.121	0.128	0.009
Cost per QALY gained	$144,200	$37,500	$36,500	$77,300

Gallego et al, *J Clin Oncol* 2015, PMID 25940718

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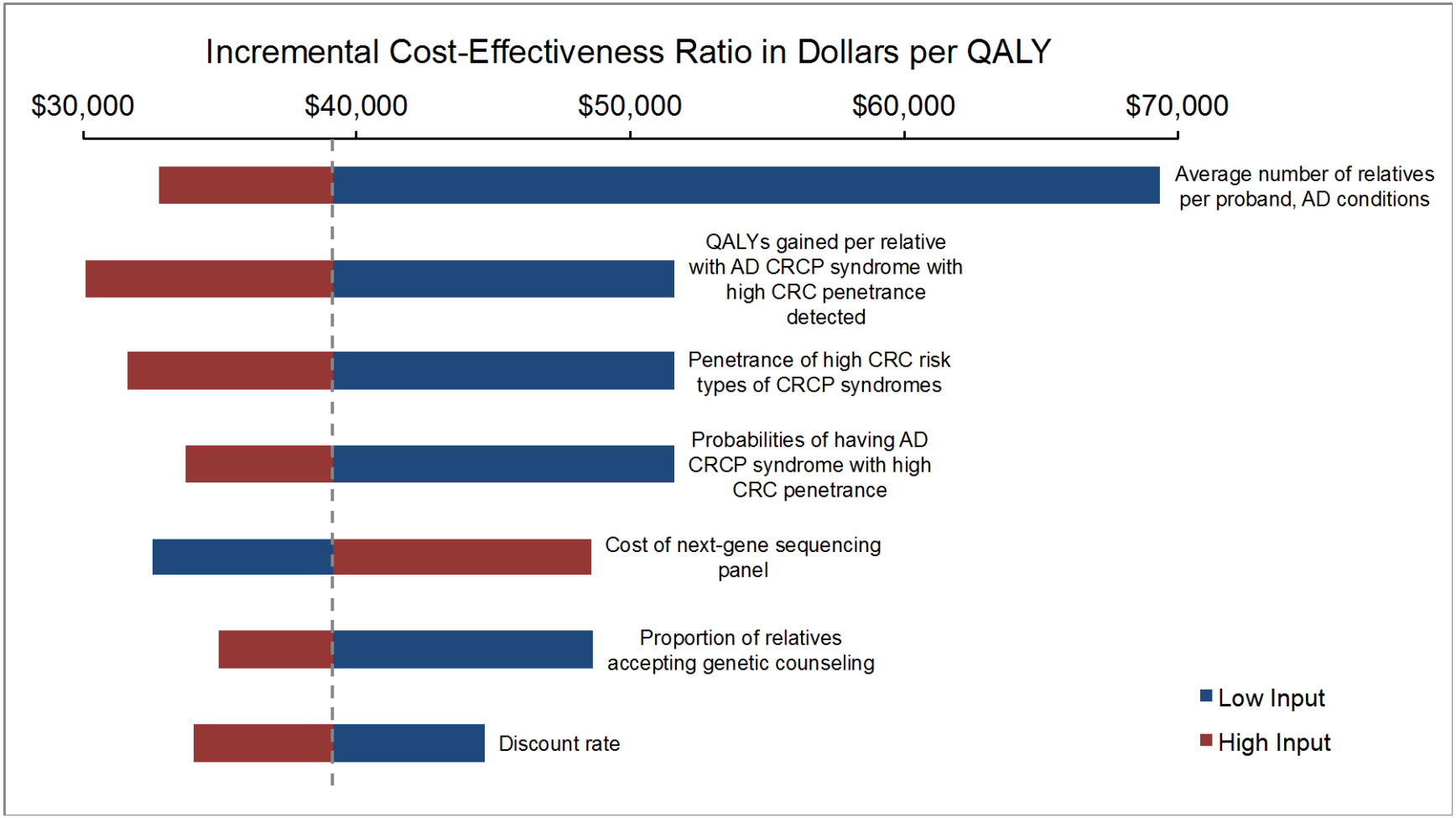
Sensitivity Analysis: Relatives improve outcomes



Gallego et al, *J Clin Oncol* 2015, PMID 25940718

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FDA Regulation of Genomic Tests

Regulatory changes raise troubling questions for genomic testing

Barbara J. Evans, PhD, JD[1], Michael O. Dorschner, PhD[2,3], Wylie Burke, MD, PhD[4] and Gail P. Jarvik, MD, PhD[5,6]

By 6 October 2014, many laboratories in the United States must begin honoring new individual data access rights created by recent changes to federal privacy and laboratory regulations. These access rights are more expansive than has been widely understood and pose complex challenges for genomic testing laboratories. This article analyzes regulatory texts and guidances to explore which laboratories are affected. It offers the first published analysis of which parts of the vast trove of data generated during next-generation sequencing will be accessible to patients and research subjects. Persons tested at affected laboratories seemingly will have access, upon request, to uninterpreted gene variant information contained in their stored variant call format, binary alignment/map, and FASTQ files. A defect in the regulations will subject some non-CLIA-regulated research laboratories to these new access requirements unless the Department of Health and Human Services takes swift action to avert this apparently unintended consequence. More broadly, all affected laboratories face a long list of daunting operational, business, compliance, and bioethical issues as they adapt to this change and to the Food and Drug Administration's recently announced plan to publish draft guidance outlining a new oversight framework for lab-developed tests.

Genet Med advance online publication 25 September 2014

Key Words: access rights; CLIA; FDA; HIPAA; return of results

Genet Med. 2014
PMID: 25255365

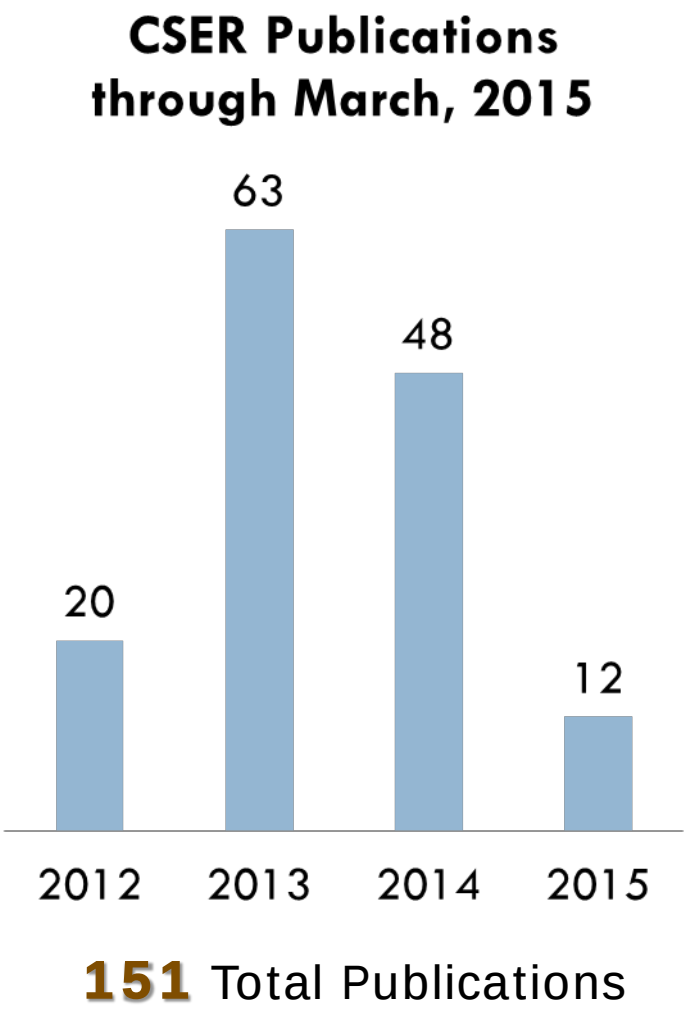
Evans BJ et al., Statutory change for FDA to require submission of data.

Major Medical Journal
In press, 2015
embargoed

Comments of Barbara J. Evans, Ph.D., J.D., LL.M. and Gail P. Jarvik, M.D., Ph.D. in Dockets FDA-2011-D-0360: Framework for Regulatory Oversight of Laboratory Tests; Draft Guidance.

20 Signatures

Highly Cited CSER *Publications*



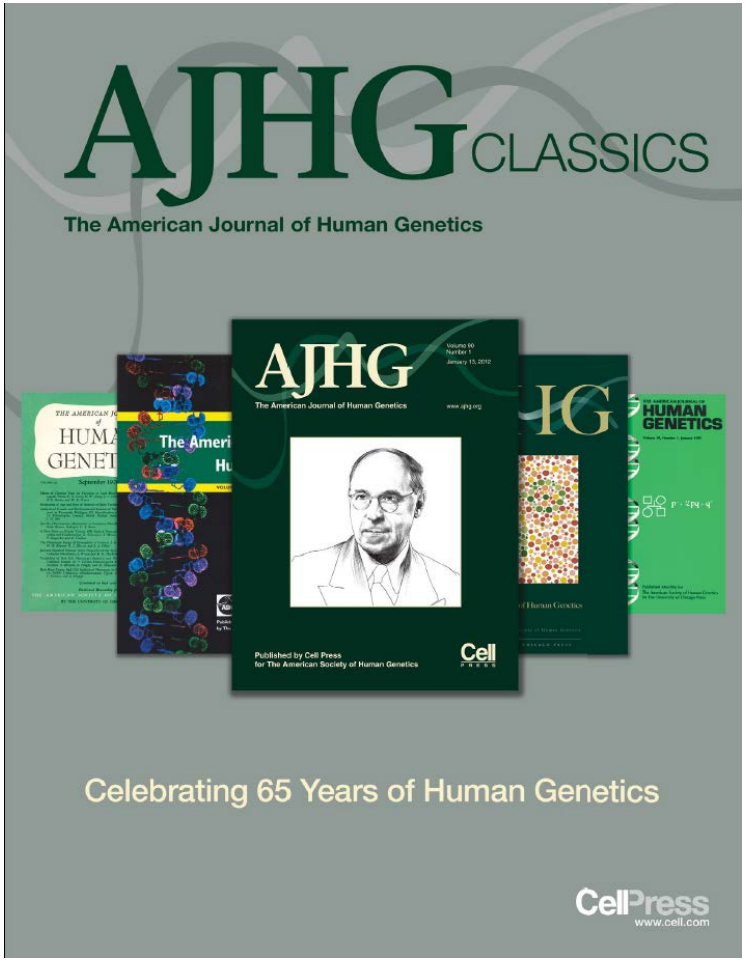
1. Green RC, et al., ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med.* 2013 Jul;15(7):565-74.
2. Zaidi S, et al., De novo mutations in histone-modifying genes in congenital heart disease. *Nature.* 2013 Jun 13;498(7453):220-3.
3. Rehm HL, et al., ACMG clinical laboratory standards for next-generation sequencing. *Genet Med.* 2013 Sep;15(9):733-47.
4. Green RC, et al., Exploring concordance and discordance for return of incidental findings from clinical sequencing. *Genet Med.* 2012 Apr;14(4):405-10.
5. Foster MW, et al., Evaluating the utility of personal genomic information. *Genet Med.* 2009 Aug;11(8):570-4.
6. Johnston JJ, et al., Secondary variants in individuals undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. *Am J Hum Genet.* 2012 Jul 13;91(1):97-108.
7. Burke W, et al., Recommendations for returning genomic incidental findings? We need to talk! *Genet Med.* 2013 Nov;15(11):854-9.
8. Biesecker LG., Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. *Genet Med.* 2012 Apr;14(4):393-8.
9. Wolf SM, et al., Point-counterpoint. Patient autonomy and incidental findings in clinical genomics. *Science*. 2013 May 31;340(6136):1049-50.
10. Dorschner MO, et al., Actionable, pathogenic incidental findings in 1,000 participants' exomes. *Am J Hum Genet.* 2013 Oct 3;93(4):631-40.

Top 17 Most Influential CSER Publications: per PIs

1. Amendola et al., Actionable exomic incidental findings in 6503 participants: challenges of variant classification. *Genome Res*, 2015.
2. Appelbaum et al., Informed consent for return of incidental findings in genomic research. *Genet Med* 2014.
3. Berg et al., Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequencing data in the CSER Consortium. *Genet Med.* 2013.
4. Bernhardt, Genetic counselors and the future of clinical genomics. *Genome Medicine*, 2014.
5. Biesecker & Green, Diagnostic clinical genome and exome sequencing. *NEJM*. 2014.
6. Burke et al., The translational potential of research on the ethical, legal, and social implications of genomics. *Genet Med.* 2014.
7. Dorschner et al., Actionable, pathogenic incidental findings in 1,000 participants' exomes. *AJHG* 2013.
8. Evans et al., Regulatory changes raise troubling issues for genomic testing. *Genet Med*. 2014.
9. Facio et al., A Genetic Counselor's Guide to Using Next-Generation Sequencing in Clinical Practice *J Genet Couns.* 2013.
10. Fan et al., GCH1 heterozygous mutation identified by whole-exome sequencing as a treatable condition in a patient presenting with progressive spastic paraplegia. *J Neurol.* 2014.
11. Green et al., GINA, genetic discrimination and genomic medicine. *NEJM* 2015.
12. Henderson et al., The challenge of informed consent and return of results in translational genomics: empirical analysis and recommendations. *J Law Med Ethics*
13. Jarvik et al., Return of genomic results to research participants: The floor, the ceiling, and the choices in be-tween. *AJHG* 2014.
14. Kircher et al., A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet.* 2014.
15. McLaughlin et al., A systematic approach to the reporting of medically relevant findings from whole genome sequencing. *BMC Med Genet* 2014.
16. Parsons et al., Clinical tumor sequencing: an incidental casualty of the American College of Medical Genetics and Genomics recommendations for reporting of incidental findings. *JCO* 2014.
17. Yang et al., Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *NEJM* 2013.

(Ordered by 1st author)

Recent Impact



Recent Highlights
Volumes 93 & 94

Review

Beyond GWASs: Illuminating the Dark Road from Association to Function	*Stacey L. Edwards, Jonathan Beesley, Juliet D. French, and Alison M. Dunning*

Articles & Reports

Actionable, Pathogenic Incidental Findings in 1,000 Participants' Exomes	*Michael O. Dorschner, Laura M. Amendola, Emily H. Turner, Peggy D. Robertson, Brian H. Shirts, Carlos J. Gallego, Robin L. Bennett, Kelly L. Jones, et al.*
Reliable Identification of Genomic Variants from RNA-Seq Data	*Robert Piskol, Gokul Ramaswami, and Jin Billy Li*
Pulling out the 1%: Whole-Genome Capture for the Targeted Enrichment of Ancient DNA Sequencing Libraries	*Meredith L. Carpenter, Jason D. Buenrostro, Cristina Valdiosera, Hannes Schroeder, Morten E. Allentoft, Martin Sikora, Morten Rasmussen, Simon Gravel, et al.*
Gain-of-Function Mutations in *SCN11A* Cause Familial Episodic Pain	*Xiang Yang Zhang, Jingmin Wen, Wei Yang, Cheng Wang, Luna Gao, Liang Hong Zheng, Tao Wang, Kaikai Ran, et al.*
Whole-Exome Sequencing Identifies Rare and Low-Frequency Coding Variants Associated with LDL Cholesterol	*Leslie A. Lange, Youna Hu, He Zhang, Chenyi Xue, Ellen M. Schmidt, Zheng-Zheng Tang, Chris Bizon, Ethan M. Lange, et al.*
A Higher Mutational Burden in Females Supports a "Female Protective Model" in Neurodevelopmental Disorders	*Sébastien Jacquemont, Bradley P. Coe, Micha Hersch, Michael H. Duyzend, Niklas Krumm, Sven Bergmann, Jacques S. Beckmann, Jill A. Rosenfeld, et al.*
GeMes, Clusters of DNA Methylation under Genetic Control, Can Inform Genetic and Epigenetic Analysis of Disease	*Yun Liu, Xin Li, Martin J. Aryee, Tomas J. Ekström, Leonid Padyukov, Lars Klareskog, Amy Vandiver, Ann Zenobia Moore, et al.*
Joint Analysis of Functional Genomic Data and Genome-wide Association Studies of 18 Human Traits	*Joseph K. Pickrell*
Convergence of Genes and Cellular Pathways Dysregulated in Autism Spectrum Disorders	*Dalila Pinto, Elsa Delaby, Daniele Merico, Mafalda Barbosa, Alison Merikangas, Lambertus Klei, Bhooma Thiruvahindrapuram, Xiao Xu, et al.*
Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between	*Gail P. Jarvik, Laura M. Amendola, Jonathan S. Berg, Kylo Brothers, Ellen W. Clayton, Wendy Chung, Barbara J. Evans, James P. Evans, et al.*
Transcriptional Consequences of 16p11.2 Deletion and Duplication in Mouse Cortex and Multiplex Autism Families	*Ian Blumenthal, Ashok Ragavendran, Serkan Erdin, Lambertus Klei, Aarathi Sugathan, Jolene R. Guide, Poornima Manavalan, Julian Q. Zhou, et al.*

2014 AJHG Anniversary issue listed 11 notable papers of last 3 years: 2/11 from CSER

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CSER @ ACMG 2015

Presentations/Community Dissemination

20 presentations, 14 posters, 9 sites

1. Amendola. How to educate/counsel patients about WES and secondary findings.
2. Rehm. ACMG Short Course: Clinical Exome Sequencing: Comparison of Practices across Labs.
3. Chung. Case studies from the clinician's perspective and comparison of WES vs. WGS.
4. Spinner. The Yield of exomes for various clinical indications: CSER experience.
5. Plon. Use of exomes/RNA-Seq in oncology. ACMG Short Course: Clinical exome.
6. MacRae. An approach to cardiomyopathy phenotypes: The devil is in the details.
7. Biesecker. Genotype-phenotype correlations in the ClinSeq project.
8. Berg. Technical challenges in the application of genomic tools for healthy populations.
9. Veenstra. Economic considerations in the realm of public health genomics.
10. Henderson. Gene-Screen: A report on a pilot study implementing targeted genomic analyses in a healthy population.
11. Plon et al. Display of genetic information in the electronic health record: From varied chaos to everything in its place.
12. Li et al. Phenotype capture and utilization of a common electronic health record system to evaluate pediatric individuals with intellectual disability undergoing exome sequencing.
13. Bedoukian et al. The individualized medical genetics center: Facilitating systematic integration of genetic testing into patient care.
14. Akkari et al. Carrier screening using whole genome sequencing in a healthy population: Is the future now?
15. Scollon. Genetic counselor luncheon and forum: Frontline experiences in obtaining informed consent for genomic sequencing.
16. Rehm. Big data meets big sequencing – A vision for the future: "Deciphering the genome: Community-driven Approaches".
17. Yang et al. Key elements for clinical exome sequencing.
18. Jarvik et al. The CSER Consortium: Clinical Sequencing Exploratory Research: Integrating genomic sequencing into the clinic.
19. Slack et al. From PediSeq to PediSeekers: A crowd-sourcing approach to variant interpretation.
20. Gornick et al. The public's preferences for the return of secondary findings identified through genome sequencing: Information and deliberation make a difference.

CSER Working Group Papers

Published/in press/submitted

Actionability & Return of Results (ROR)

Berg et al., "Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequencing data in the CSER Consortium." *Genet Med.* 2013; 15(11):860-7. PMID: 24195999

Jarvik et al., "Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices in Between. *Am J Hum Genet.* 2014; 94(6):818-26. PMID: 24814192

Amendola et al., "Challenges of variant classification: Pathogenicity classification from 6503 participant's exomes." *Genome Research* 2015. PMID: 25637381

Electronic Health Records

Tarczy-Hornoch et al., "A survey of informatics approaches to whole-exome and whole-genome clinical reporting in the electronic health record." *Genet Med.* 2013; 15(10):824-32. PMID: 24071794

Brian Shirts, et al. "Optimal management of different types of genetic information in the Electronic Medical Record." *JAMIA, in press*

Genetic Counselors

Amendola LM, et al., "Illustrative Case Studies in the Return of Exome and Genome Sequencing Results." *Personalized Medicine,* in-press.

Informed Consent & Governance

Henderson GE, et al., "The challenge of informed consent and return of results in translational genomics: empirical analysis and recommendations." *J Law Med Ethics.* 2014 Sep;42(3). PMID: 25264092

Appelbaum PS, et al., "Models of consent to return of incidental findings in genomic research." *Hastings Cent Rep.* 2014 Jul-Aug. PMID: 24919982

Outcomes & Measures

Gray SW, et al. "Social and behavioral research in genomic sequencing: approaches from the Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group." *Genet Med.* 2014 Mar 13. PMID: 24625446

Pediatrics

Clayton EW et al., "Addressing the ethical challenges in genetic testing and sequencing of children." *Am J Bioeth.* 2014 Mar;14(3):3-9. PMID: 24592828

Brothers KB, et al., "When Participants in Genomic Research Group Up: Contact and Consent at the Age of Majority." (submitted to *Pediatrics*)

McCullough LB, et al., "Professionally Responsible Disclosure of Genome Sequencing Results in Pediatrics Clinical Practice." (submitted to *Pediatrics*)

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Summary

- Hit rate differs by clinical indication
- Incidental finding rate is low
- CSER is working to resolve obstacles to genomic medicine
  - Classify variants
    - Improve ACMG criteria
  - Provide an evidence base
    - When
    - Best practices
- ELSI work, regulatory analyses

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University of North Carolina	Jim Evans
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Columbia University	Paul Appelbaum Wendy Chung
Children's Mercy Hospital	Jeremy Garrett
Johns Hopkins University	Michelle Lewis
Mayo Clinic	Rich Sharp
Seattle Children's Hospital	Holly Tabor
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Vanderbilt University & McGill University	Ellen Clayton & Bartha Knoppers

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