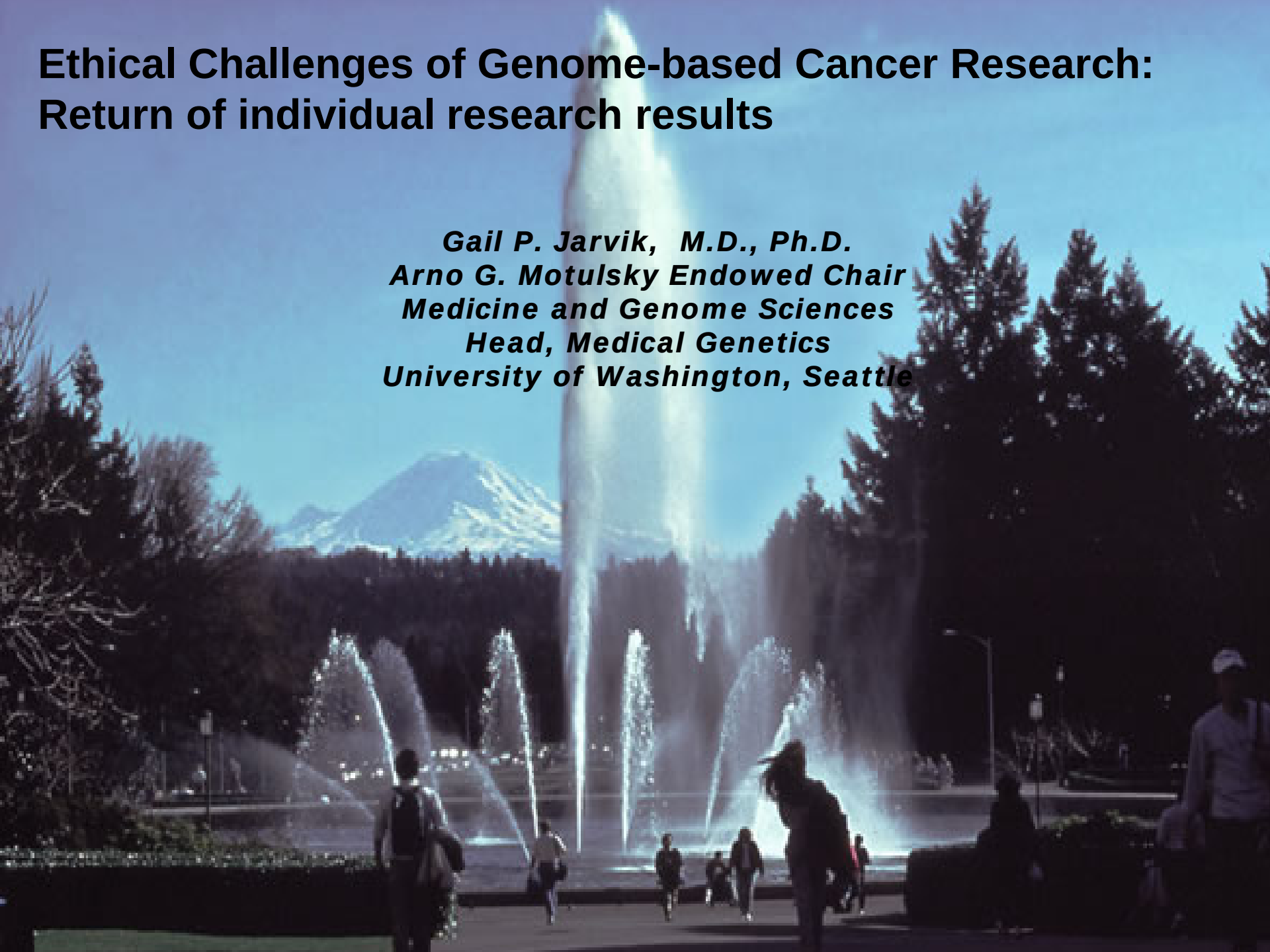
Ethical Challenges of Genome-based Cancer Research: Return of individual research results



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Overview: Return of Research Results

- Areas of Agreement: Return of germline genomic results CSER/eMERGE consensus
- What are actionable genes?
- Estimated returnable results from EVS 6503
- VUS's
- Areas requiring consensus

Research ROR of genomic findings

- What findings should be returned in research
- Motivated by increased genomics in research and by ACMG clinical recommendations
- Joint project of eMERGE and CSER
- Writing committee: Gail Jarvik, Laura Amendola, Jonathan Berg, Ellen Clayton, Barbara Evans, James Evans, Stephanie Fullerton, Carlos Gallego, Nanibaa' Garrison, Stacy Gray, Ingrid Holm, Iftikhar Kullo, Lisa Lehmann, Cathy McCarty, Cynthia Prows, Heidi Rehm, Richard Sharp, Joseph Salama, Sara Van Driest, Marc Williams, Susan Wolf, Wylie Burke, eMERGE ROR Committee, eMERGE CERC Committee, CSER Act-ROR Committee

cser
Clinical Sequencing Exploratory Research

Research ROR Principles

1. Research, even in a clinical setting, differs from clinical care in both its goals and its procedures; as a result, the minimal and maximal information returned… may differ...
2. Resources for research should be primarily directed at scientific discovery; thus, researchers do not have a duty to look for actionable genomic findings beyond those uncovered in the normal process of their investigations.
3. Research assessing the outcomes of a wide range of potential practices for returning genomic results is required for the ultimate formulation of best practices in both the research and clinical settings.
4. Analytically and clinically valid information of an important and actionable medical nature that is identified as part of the research process should be offered to a research subject.
5. Participants should have the right to refuse any results that may be offered…*

Research ROR Recommendations

1. At a minimum, researchers should offer individual genomic research results that are valid, medically important, and actionable, if discovered purposefully or by chance during the course of data analysis. Investigators are not obligated to search for actionable genomic variants to be returned beyond those identified in the course of their research, that is, there is no duty to hunt.
    a) Given that there is no definitive “list” of medically actionable findings … those involved in genomics research should give thought to the types of findings that would represent the “floor” for return in their study, in consultation with local IRBs and funding agencies.
    b) The responsibility to offer disclosure of results and incidental findings is limited to…identifiable participants and…the term of funding

Research ROR Recommendations

2. Participants should have the option to refuse research genomic test results, both those related to the study purpose and incidental findings, unless the study aims are related to the return of these data. Plans for return and participants' option to refuse offered results should be addressed at the time of consenting.
    a) When studies do not allow participants to opt out of potentially receiving results, this…should be clearly addressed in the consent...
    b) The consent …should clarify…when a participant may be contacted in the future…
    c) Participation in research studies should be…non-coercive….
    d) Parents of minors…have the same right to refuse, unless… significance to the minor in childhood. Investigators may offer the parents of minors…the option of accepting or refusing results for adult-onset conditions… In…trio testing, parents should be offered only their own adult onset results, rather than their child's, unless the child has a relevant *de novo* mutation.

Research ROR Recommendations

3. Researchers may be ethically and scientifically justified in returning all genomic information, in some format, and any level of information between the floor of actionable results and the ceiling of all genomic information.

a) Special care should be taken when the benefits and harms…are uncertain.

b) …assure adequate analytic and clinical validity for return… Further work is needed on the role of CLIA compliance in return of research results.

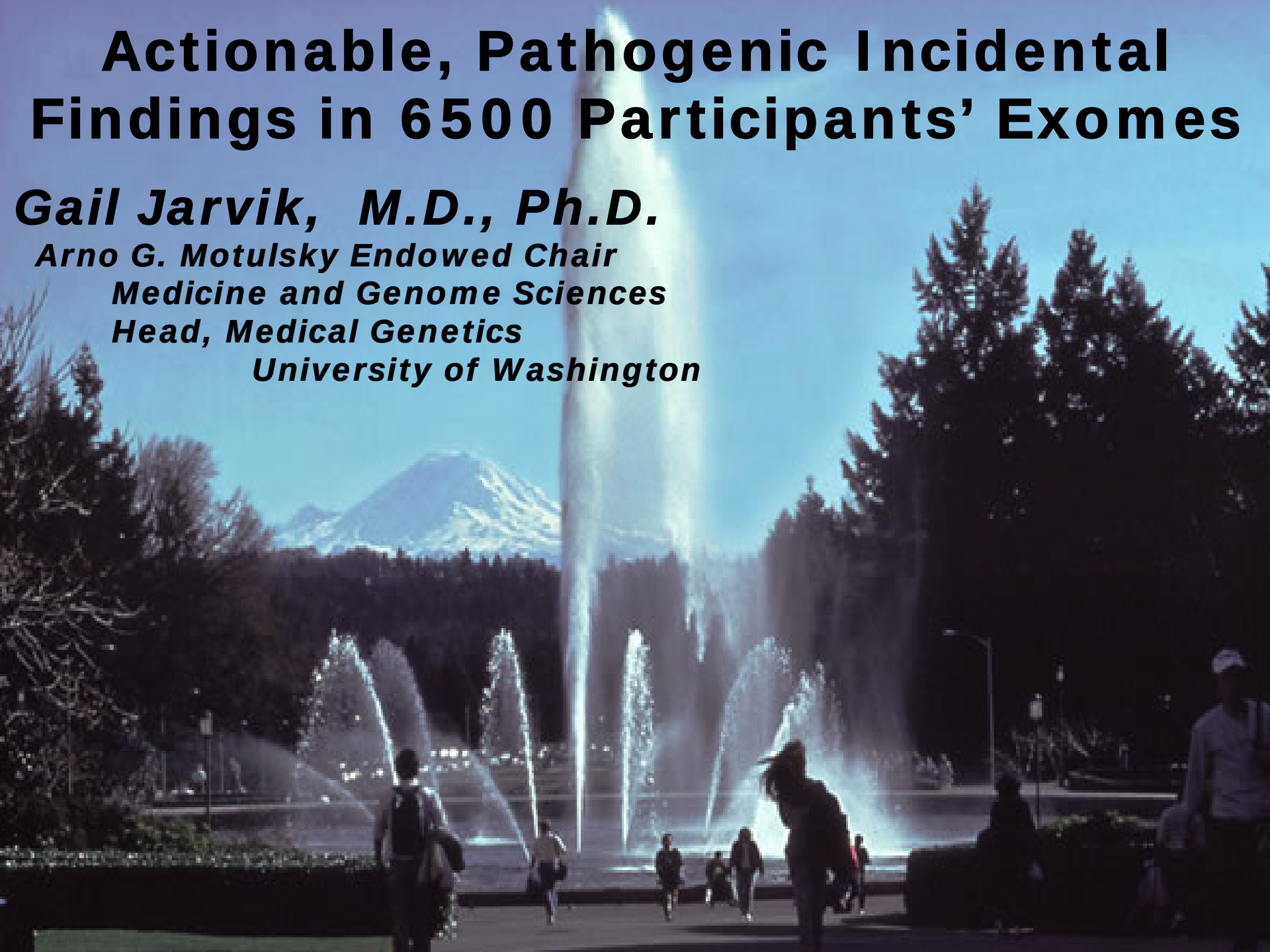
c) Research studies intended to examine…the return of genomic information should include measurements of benefits and harms…

Research ROR

Recommendation 4:

4. Additional research projects that examine the potential benefits and harms of receiving genomic results and evaluate practices for returning genomic information are required to inform the increasing use of genomic sequencing in clinical research.

Actionable, Pathogenic Incidental Findings in 6500 Participants' Exomes



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Step 1: Actionable genes in adults

- **Our definition of “actionable”:**
  - **clearly deleterious mutation**
  - **specific, evidence-based medical recommendations**
  - **Action expected to improve health outcomes**
  - **Sufficient benefit**
  - **Not consider carrier status**
  - **Committee *unanimously* agreed**

Return of Results Committee

MEMBER	EXPERTISE(s)
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Benjamin Wilfond, MD	Pediatrics, bioethics
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Carlos Gallego, MD	Medical genetics
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William Grady, MD	Gastroenterology, Cancer, genetics
Wylie Burke, MD PhD	Medical genetics, internal medicine, bioethics


NEXT Medicine Return of Results Committee, September 2012
TOSHIBA

Would a pathogenic mutation be reported as a medically actionable incidental finding by Clinical Sequencing Exploratory Research (CSER) sites

	Sites				Comments
	BCM	CHOP	UNC	UW	
CYP2C19 genotype (metabolism of Plavix and other drugs	Yes	No	No	No	
Malignant hyperthermia (*RYR1*)	Yes	Yes[2]	Yes	Yes	
Neurofibromatosis 1 (*NF1*)	Yes	Yes[2]	No	No	Management guidelines for children, but uncertain evidence for benefits when diagnosed incidentally, esp. in adults
Familial Mediterranean Fever (*MEFV*)	Yes	Yes[2]	Yes	No	Long diagnostic odyssey, effective treatment
Factor V Leiden (*F5*) - Homozygous	Yes	Yes[2]	No	Yes	For CHOP, whether or not categorized as "medically actionable" or "immediately medically actionable" depends on age and gender
Factor V Leiden (*F5*) - Heterozygous	No	No	No	No	Unclear clinical implications
Hemochromatosis (*HFE*) - Homozygous C282Y	Yes	Yes	Yes	Yes	Potentially severe long-term complications, completely preventable

UW Genes with Actionable Variants relevant to Adults

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	

(a)YELLOW: Recommended for return by the ACMG guidelines[1]
(b)Return only homozygotes for common mutation

= **120** Total Genes

See Dorschner et al AJHG 2013; 3 new genes

Estimate Pathogenic Incidental Findings in the actionable genes

- 6,503 (1000+5503) individuals from Exome Variant Server (EVS) http://evs.gs.washington.edu/EVS/
- Considered 643 SNVs in the 120 actionable genes
- Juried actionable pathogenic single nucleotide variants
  - Flagged HGMD 'Disease Causing Mutation'
  - Excluded if allele frequency >0.005 for AD
  - Literature from HGMD; also PubMed, ClinVar, OMIM, LSDBs
  - Classifications from Myriad via BIC database
  - Reviewers: **~45** medical geneticists, genetic counselors, genomics experts~
  - ~1/3 double reviewed, discrepancies resolved

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 cases (low N) 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 returnable mutations:

6503 Exome Variant Server (EVS) Results by Ancestry Group

Participants with classification	European ancestry N=4300	African ancestry N=2203
Pathogenic variants from HGMD	34 (0.8%)	5 (0.2%)
Likely pathogenic variants from HGMD	68 (1.6%)	20 (0.9%)
Novel disruptive variants	12 (0.3%)	17 (0.7%)
Total	**114 (2.7%)**	**42 (1.9%)**

VUS are a significant problem

- Case: colon cancer at ~35 years old
  - Normal IHC
  - Parent with ≥5 adenomatous colon polyps

- Normal clinical test – Coloseq
  - 11 gene panel (*MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDH1, PETN, STK11, TP53*)

Exome finds VUS

- ***SDHB* c.299C>G, p.Ser100Cys**

***SDHB* Tumor Sites (high malignancy rate)**	**Penetrance**
Skull base and neck paragangliomas	**15%**
Extra-adrenal abdominal or thoracic tumors	**69%**
Renal clear cell carcinoma and papillary thyroid carcinoma	**?**

  - *SDHB* known to be not associated with colon cancer
  - Novel VUS: ESP: 0%; Not in OMIM, NCBI, ClinGen, HGMD, LOVD
  - BAD: Grantham: 112, GERP: 6.17, polyPhen: 0.995
  - Pathogenic: Ser100**Phe**, Ser100**Pro,** Ser100**Glu** & p.Ser100**LeufsX4**
  - **What do we tell this patient/participant?**

Needing consensus

- What is actionable
  - ACMG list?
- Adult onset findings found in children
  - CSER/eMERGE agreement here
- non-CLIA labs
  - Barbara Evans article
- Clinical – Research boundaries
  - Refer

Thank you UW Team!

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Pathogenic actionable variants in HGMD N=6503

- 39 unique variants in 20 genes
  - **ACMG:** *BRCA1/2 (N=3), FLCN (1), LDLR (5), LMNA (1), MSH2 (1), MSH6 (1), MYBPC3 (6), PKP2 (1), PMS2 (4), RET (1), RYR1 (1), TNN13 (1), TNNT2 (1), TP53 (2), TSC2 (1)*
  - **Not ACMG:** *PRKAR1A (1), PROC (1), RBM20 (1), SERPINA1(4),*
- 39/6503 total individuals (34 ACMG)
  - 4 individuals compound heterozygous for pathogenic AR variants
  - 34/39 (87%) European vs. 5/39 (13%) African vs. 0 in Ashkenazi Jewish ancestry

Likely pathogenic actionable variants in HGMD; N=6503

- 88 unique variants in 25 genes
  - **ACMG:** *BRCA1 (1), CACNA1S (1), CDH1 (1), DSG2 (1), HMBS (1), KCNE1 (2), KCNE2 (1), KCNQ1 (3), LDLR (10), MSH2 (1), MYBPC3 (9), MYH7 (2), MYL3 (1), PKP2 (3), RET (2), RYR1 (5), SCN5A (1), TNN13 (1), TNNT2 (2), TP53 (1)*
  - **Not ACMG**: *CACNB2 (1), MYH7 (2), PROC (4), RBM20 (1), SERPINA1 (2)*
- 88/6503 total individuals (79 ACMG)
  - 3 individuals compound heterozygous for 1 pathogenic and 1 likely pathogenic AR variants
  - 59/88 (67%) European vs. 20/88 (23%) African vs. 9/88 (10%) in Ashkenazi Jewish ancestry

Disruptive variants* *NOT* in HGMD, BIC, or ClinGen

- 20 unique variants in 16 genes
  - **ACMG:** *BRCA1/2 (3), CACNA1S (1), DSC2 (1), MSH6 (1), PKP2 (1), PMS2 (1), TGFBR2 (2), RYR1 (1), TMEM43 (1)*
  - **Not ACMG:** *DMD (1), DSP (2), MAX (1), MYH7 (1), PROS1 (1), PTCH1 (2),*
- 29 total individuals (21 ACMG)
  - 12/29 (41%) European vs. 17/29 (59%) African vs. 0 in Ashkenazi ancestry

***Stop or splice in first 90% of transcript; genes with truncation mutations**