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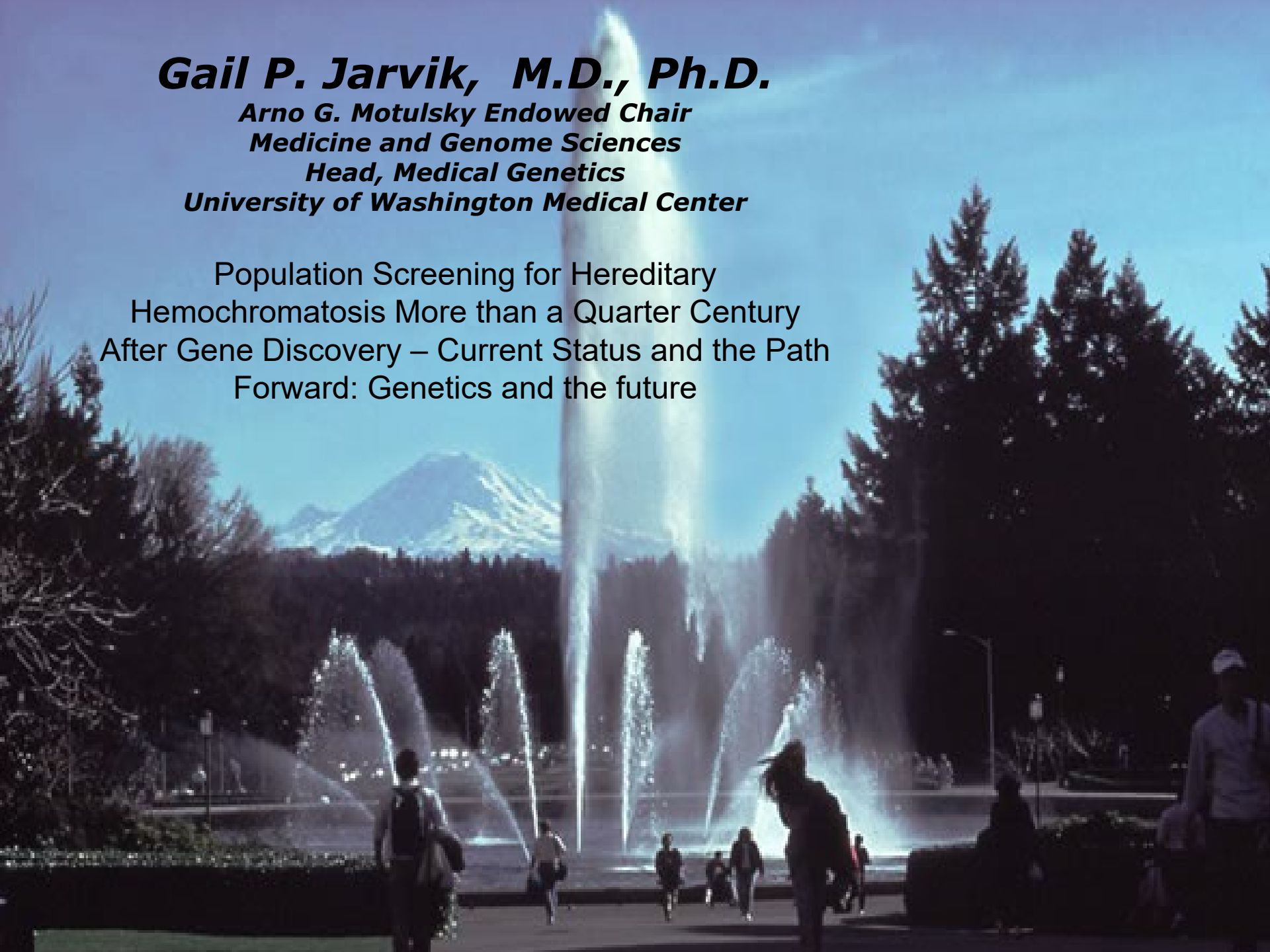
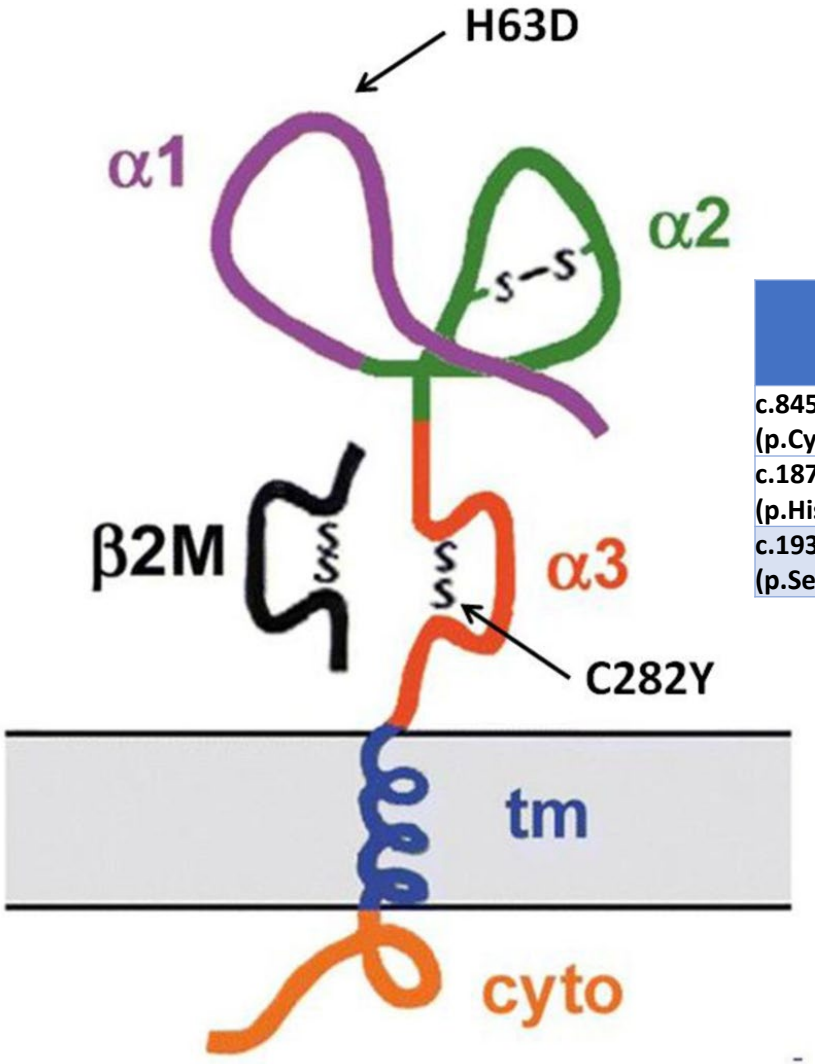
Population Screening for Hereditary Hemochromatosis More than a Quarter Century After Gene Discovery – Current Status and the Path Forward: Genetics and the future



Focus on *HFE*

p.H63D and **p.S65C** affect the α1 binding groove but do not prevent HFE presentation on cell surfaces.

p.C282Y disrupts a critical disulfide bond in the α3 domain of HFE, abrogating its binding to β_2M and limiting its localization mostly to the cytoplasm



	FAF% in GnomAD V4	Major ancestry group	MAF % in AllofUs
c.845G>A (p.Cys282tYr)	7.00	European	4.00
c.187C>G (p.His63Asp)	15.00	European	11.00
c.193A>T (p.Ser65Cys)	1.60	European	1.00

PMID: 26456104

C282Y MAF by ancestry

gnomAD | HGDP | 1KG | Local Ancestry

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (non-Finnish)	83807	1180000	3173	0.07102
Remaining	3507	62506	155	0.05611
Amish	41	912	3	0.04496
European (Finnish)	2357	64038	44	0.03681
Admixed American	904	60020	11	0.01506
Ashkenazi Jewish	356	29606	6	0.01202
African/African American	790	75038	6	0.01053
South Asian	196	91088	1	0.002152
Middle Eastern	10	6048	0	0.001653
East Asian	9	44878	0	0.0002005
XX	48154	812460	1818	0.05927
XY	43823	801674	1581	0.05466
Total	**91977**	**1614134**	**3399**	**0.05698**

HFE c.845G>A (p.Cys282Tyr)

Data From

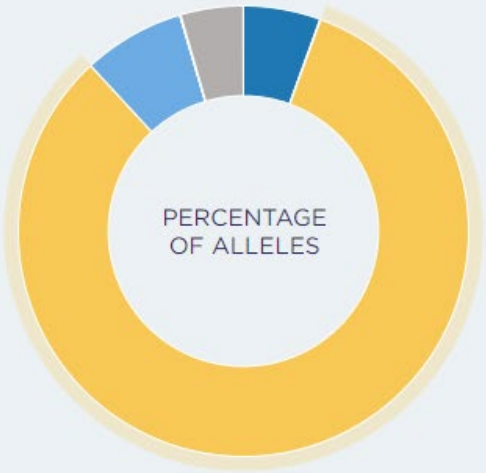
gnomAD

genome aggregation database

Mixed ancestry leads to C282Y alleles in each All of Us ancestry groups

Genetic Ancestry Populations

	Allele Count	Allele Number	Allele Frequency	Homozygote Count
African	1,083	107,896	0.010037	8
East Asian	10	10,752	0.000930	0
European	16,151	256,812	0.062890	596
Latin American	1,431	79,968	0.017895	23
Middle Eastern	2	786	0.002545	0
South Asian	9	4,652	0.001935	0
Remaining	880	29,914	0.029418	13
Total	**19,566**	**490,780**	**0.039867**	**640**

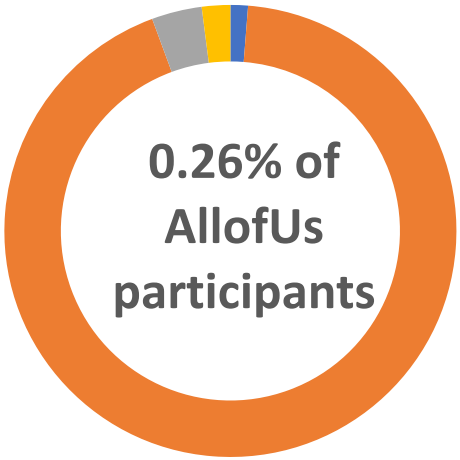


HFE c.845G>A (p.Cys282Tyr) in AllofUS database

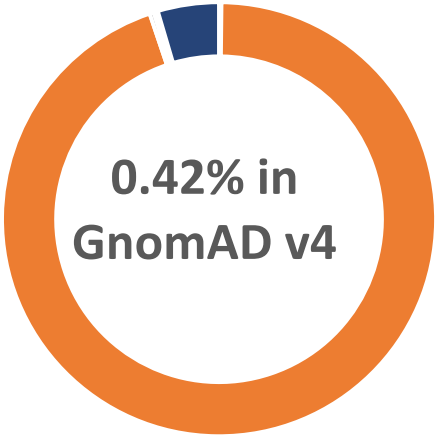
Data From

All of Us RESEARCH PROGRAM

C282Y/C282Y genotype ancestry diversity



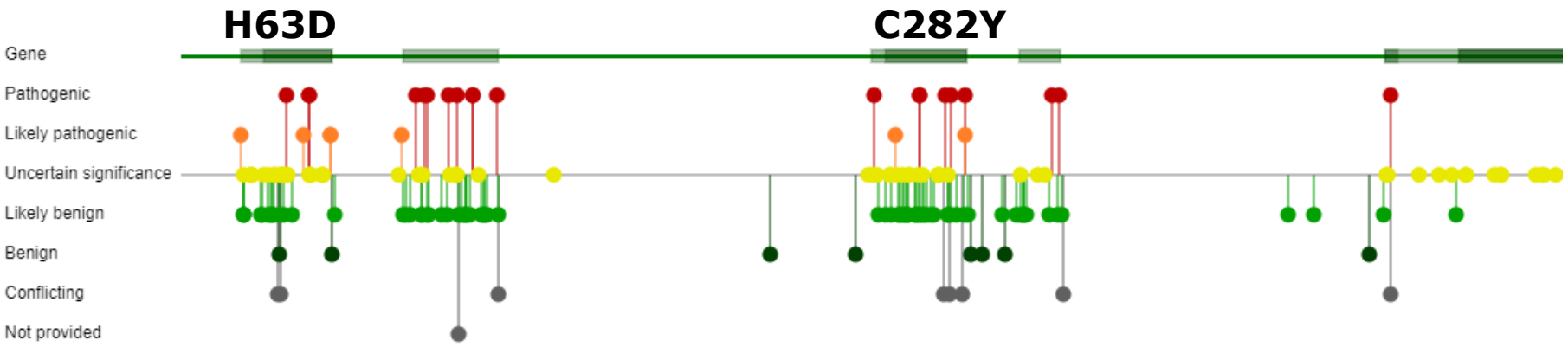
- African 1.3%
- European 93%
- Latin American 4%
- Remaining 2%



- African/African American 0.18%
- European 95%
- Admixed American 0.3%
- South Asian 0.03%
- Amish 0.09%
- Ashkenazi Jewish 0.18%
- Remaining 4.6%

Expect HFE C282Y/C282Y in 1/300 persons of European ancestry

Rare pathogenic *HFE* variants



Other rare *HFE* mutations have been reported in compound heterozygosity with p.C282Y in single families and delimited geographical clusters, and rare *HFE* deletions have been described only in Sardinia (Italy)

Data From

ClinVar
Clinically relevant variation

Rare pathogenic *HFE* variants

Potentially pathogenic variants in HFE	FAF% in GnomAD V4	Major ancestry group	MAF % in AllofUs
c.187C>G (p.His63Asp)	**15.00**	European	11.00
c.845G>A (p.C282Y)	**7.00**	European	4.00
c.193A>T (p.Ser65Cys)	**1.60**	European	1.00
c.1015_1016insG (p.M339fs)	0.0420	African American	0.0163
c.1006+1G>A	0.0253	East Asian	0.0045
c.546_547del (p.L183fs)	0.0058	Admixed American	0.0006
c.1022_1034del (p.H341fs)	0.0030	European	0.0008
c.480del (p.R161fs)	0.0030	European	0.0008
c.277G>C (p.G93R)	0.0027	European	0.0012
c.279del (p.Trp94fs)	0.0025	European	0.0006
c.616+1G>T	0.0015	European	0.0002
c.548T>C (p.L183P)	0.0014	European	0.0020
c.211C>T (p.R71*)	0.0009	East Asian	0.0004
c.892G>T (p.Glu298*)	0.0005	European	0.0006
c.414C>G (p.Y138*)	0.0004	Admixed American	-
c.697C>T (p.Q233*)	0.0002	European	-
c.832C>T (p.Gln278*)	0.0002	south asian	-
c.502G>T (p.E168*)	0.0001	European	0.0002
c.340+1G>A	0.0001		-
c.989G>T (p.R330M)	0.0001	European	-
c.506G>A (p.W169*)	0.0001	European	-
c.848A>C (p.Q283P)	0.0001	European	0.0002
c.892+1G>T	0.0001	European	-
c.968del (p.Gly323fs)	0.0001	African American	0.0002
c.626del (p.L209fs)	0.0001	European	-

Data From

ClinVar
Clinically relevant variation

Actionable Gene Consensus List *for eMERGE III*

Genes for which Pathogenic or Likely Pathogenic Variants will be Returned as Incidental Findings

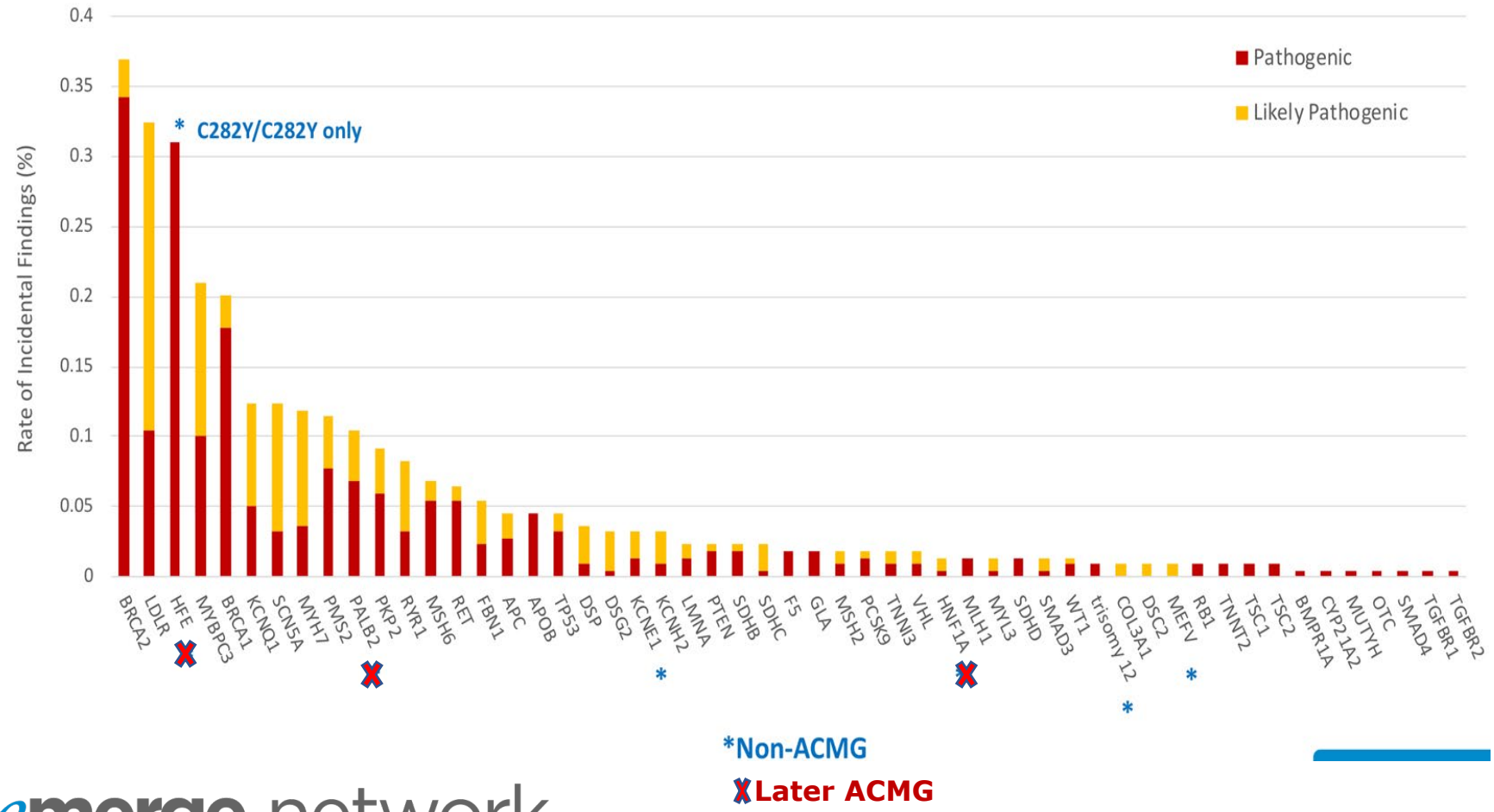
Phenotype	Gene‡
Cancer susceptibility and tumor diseases	APC, BMPR1A, BRCA1, BRCA2, MEN1, MLH1, MSH2, MSH6, MUTYH[#], NF2, PALB2, PMS2, POLD1, POLE, PTEN, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11, TSC1, TSC2, TP53, VHL, WT1
Cardiac Diseases	ACTA2, ACTC1, COL3A1, COL5A1, DSC2, DSG2, DSP, FBN1, GLA[+], HFE, KCNE1[§], KCNH2, KCNJ2, KCNQ1, LMNA, MYBPC3, MYH7, MYH11, MYL2, MYL3, MYLK, PKP2, PRKAG2, RYR2, SCN5A, SMAD3, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TPM1
Hypercholesterolemia	APOB, LDLR, PCSK9
Diabetes & Kidney Disease	HNF1A, HNF1B, HFE (C282Y/C282Y only)
Ehlers-Danlos Syndrome	COL3A1, COL5A1
Neuromuscular Diseases	CACNA1S, RYR1
Ornithine Transcarbamylase (OTC) Deficiency	OTC[+]

emerge network

[+]x-linked, [#]recessive, [§] dominant or recessive

‡ non-ACMG genes are indicated in blue

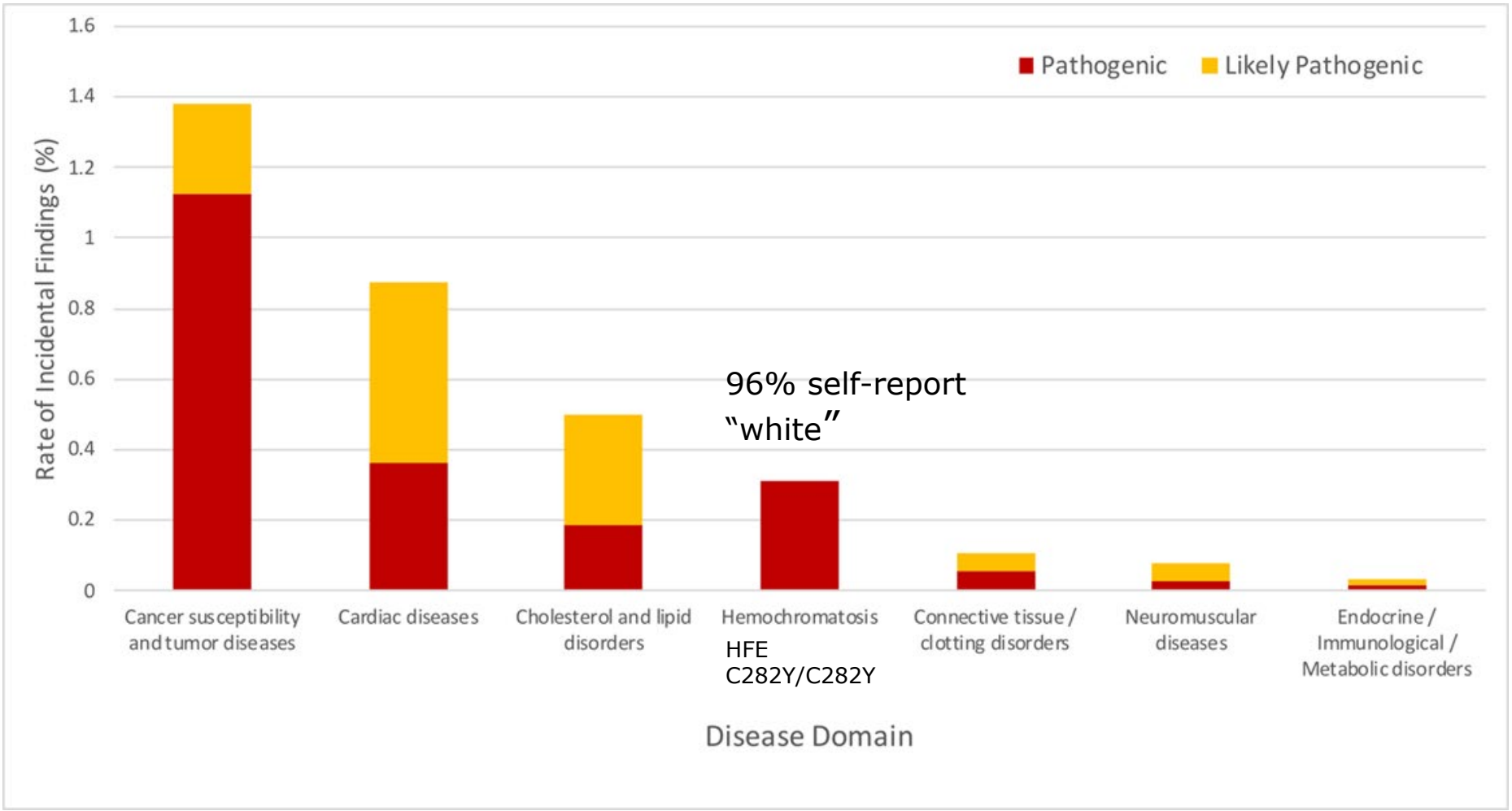
eMERGE3 Actionable Incidental Findings by Gene (N=21,915 , 66% self-identified as “white”)



emerge network

Gordon et al. 2020, PMID 32546831

eMERGE3 Actionable Incidental Findings by type of gene (N=21,915, 66% self-identified as “white”)



emerge network

Gordon et al. 2020, PMID 32546831

Hemochromatosis penetrance in eMERGE3

	MALE (N=222)			FEMALE (N=273)		
	C282Y/C282Y (N=47)	C282Y/H63D (N=175)	p-value	C282Y/C282Y (N=51)	C282Y/H63D (N=222)	p-value
CLINICAL						
Diagnosis rate HH	24.4% (11/45)	3.4% (6/174)	<0.001	14.0% (7/50)	2.3% (5/218)	<0.001
Liver disease	34.3% (12/35)	24.4% (29/119)	0.279	29.0% (9/31)	29.0% (42/145)	1
Liver biopsy (not incidental to gastric bypass)	10.9% (5/46)	1.8% (3/166)	0.013	9.1% (4/44)	2.0% (4/205)	0.035
Liver cirrhosis [a]	4.5% (2/44)	4.8% (8/166)	1	2.5% (1/40)	4.9% (10/203)	0.697
Other chronic liver disease [b]	7.0% (3/43)	6.7% (11/164)	1	0% (0/41)	7.8% (16/205)	0.081
Hepatocellular carcinoma	0% (0/46)	0% (0/169)	NA	0% (0/50)	0% (0/218)	NA
Congestive heart failure	21.7% (10/46)	16.8% (29/173)	0.515	18.4% (9/49)	8.7% (19/219)	0.067
Cardiomyopathy	6.7% (3/45)	7.5% (13/174)	1	4.1% (2/49)	1.8% (4/218)	0.304
Diabetes	44.7% (21/47)	28.0% (49/175)	0.034	12.0% (6/50)	19.5% (43/220)	0.308
Arthritis	29.5% (13/44)	35.3% (61/173)	0.594	26.0% (13/50)	30.3% (66/218)	0.609
Hypogonadism	2.2% (1/45)	1.8% (3/167)	1	NA	NA	NA
FAMILY HISTORY						
Family history of HH	8.1% (3/37)	0% (0/157)	0.006	6.7% (3/45)	1.5% (3/199)	0.078

emerge network

Gallego et al. PMID: 26365338, 2015

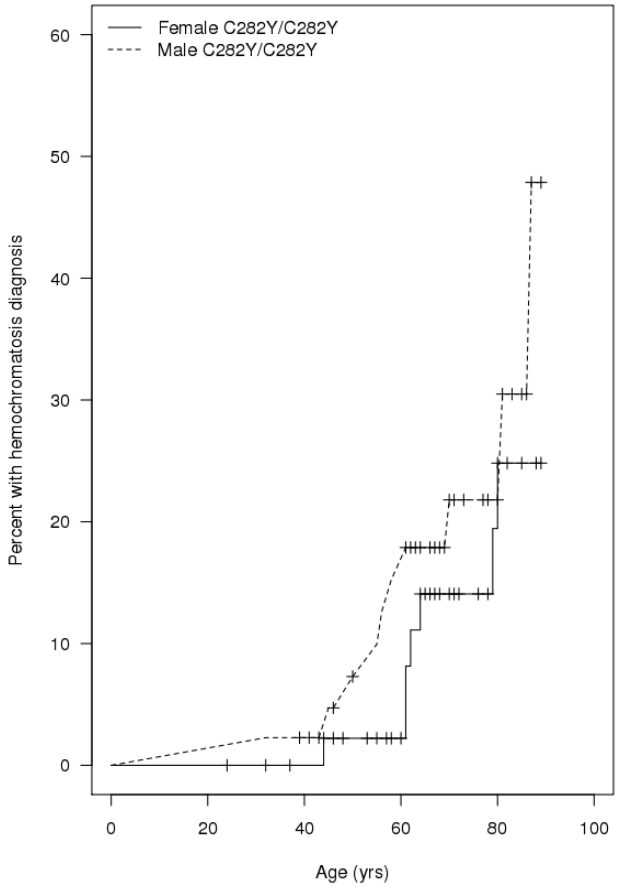
Hemochromatosis penetrance in eMERGE3, continued

	MALE (N=222)			FEMALE (N=273)		
	C282Y/C282Y (N=47)	C282Y/H63D (N=175)	p-value	C282Y/C282Y (N=51)	C282Y/H63D (N=222)	p-value
CLINICAL						
Diagnosis rate HH	24.4% (11/45)	3.4% (6/174)	<0.001	14.0% (7/50)	2.3% (5/218)	<0.001
LABORATORIES						
AST > 80 u/L	2.5% (1/40)	12.4% (19/153)	0.082	8.5% (4/47)	8.9% (17/191)	1
ALT > 110 u/L	0% (0/35)	7.5% (10/133)	0.124	5.1% (2/39)	8.2% (13/158)	0.740
Transferrin Saturation > 50%	100% (9/9)	37.5% (6/16)	0.003	50.0% (4/8)	37.5% (15/40)	0.695
Ferritin >200 ng/mL(females); >300 ng/mL(males)	77.8% (14/18)	33.3% (8/24)	0.006	30.8% (4/13)	30.2% (16/53)	1

emerge network

Gallego et al. PMID: 26365338, 2015

Age dependent penetrance can underestimate impact in cross-sectional data



Kaplan-Meier curves of HH diagnosis. Frequency of HH diagnosis with age by sex, for HFE p.C282Y homozygotes. Each crosshair represents a new HH diagnosis

UK Biobank data in next talk by Dr. Melzer

emerge network

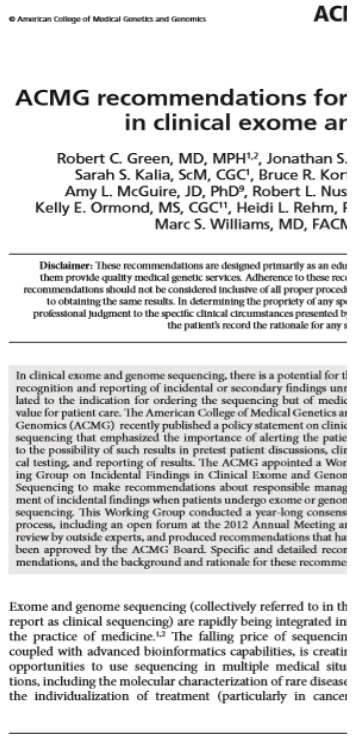
Gallego et al. PMID: 26365338, 2015

ACMG recommends return of incidental (secondary) findings

2013: 56 gene-disease pairs

2016: 59 (+4, -1)

2021: 73



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ACI

ACMG recommendations for
in clinical exome ar

Robert C. Green, MD, MPH[1,2], Jonathan S.
Sarah S. Kalia, ScM, CGC[1], Bruce R. Kor
Amy L. McGuire, JD, PhD[9], Robert L. Nus
Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, F
Marc S. Williams, MD, FACM

Disclaimer: These recommendations are designed primarily as an edu
them provide quality medical genetic services. Adherence to these rec
recommendations should not be considered inclusive of all proper proced
to obtaining the same results. In determining the propriety of any sp
professional judgment to the specific clinical circumstances presented b
the patient's record the rationale for any s

In clinical exome and genome sequencing, there is a potential for t
recognition and reporting of incidental or secondary findings unr
lated to the indication for ordering the sequencing but of medic
value for patient care. The American College of Medical Genetics a
Genomics (ACMG) recently published a policy statement on clini
sequencing that emphasized the importance of alerting the patie
to the possibility of such results in pretest patient discussions, clir
cal testing, and reporting of results. The ACMG appointed a Wor
ing Group on Incidental Findings in Clinical Exome and Genon
Sequencing to make recommendations about responsible manag
ment of incidental findings when patients undergo exome or genon
sequencing. This Working Group conducted a year-long consens
process, including an open forum at the 2012 Annual Meeting a
review by outside experts, and produced recommendations that ha
been approved by the ACMG Board. Specific and detailed recor
mendations, and the background and rationale for these recomme

Exome and genome sequencing (collectively referred to in th
report as clinical sequencing) are rapidly being integrated in
the practice of medicine.[1,2] The falling price of sequencin
coupled with advanced bioinformatics capabilities, is creatir
opportunities to use sequencing in multiple medical situ
tions, including the molecular characterization of rare disease
the individualization of treatment (particularly in cance

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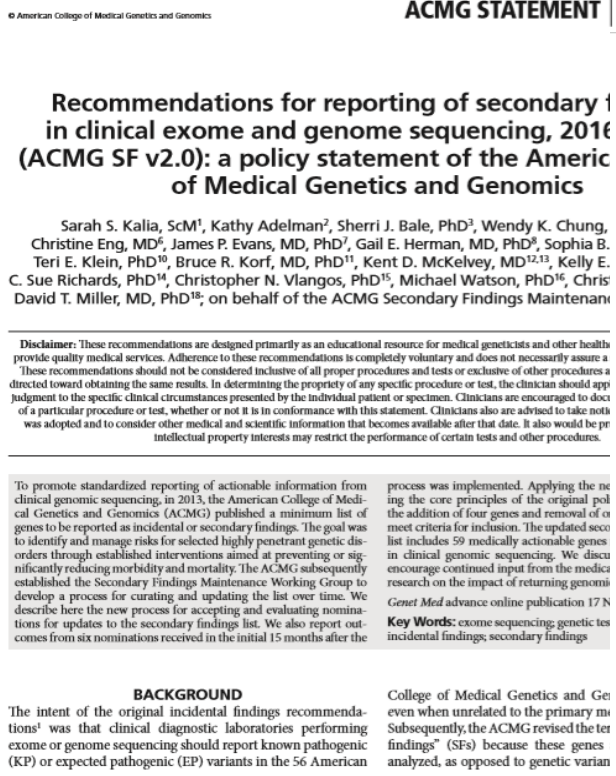

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ACMG STATEMENT | Genetics inMedicine

Recommendations for reporting of secondary f
in clinical exome and genome sequencing, 201
(ACMG SF v2.0): a policy statement of the Americ
of Medical Genetics and Genomics

Sarah S. Kalia, ScM[1], Kathy Adelman[2], Sherri J. Bale, PhD[3], Wendy K. Chung,
Christine Eng, MD[6], James P. Evans, MD, PhD[7], Gail E. Herman, MD, PhD[8], Sophia B.
Teri E. Klein, PhD[10], Bruce R. Korf, MD, PhD[11], Kent D. McKelvey, MD[12,13], Kelly E.
C. Sue Richards, PhD[14], Christopher N. Vlangos, PhD[15], Michael Watson, PhD[16], Chris
David T. Miller, MD, PhD[18]; on behalf of the ACMG Secondary Findings Maintenan

Disclaimer: These recommendations are designed primarily as an educational resource for medical geneticists and other health
provide quality medical services. Adherence to these recommendations is completely voluntary and does not necessarily assure a
These recommendations should not be considered inclusive of all proper procedures and tests or exclusive of other procedures a
directed toward obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should app
judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to doc
of a particular procedure or test, whether or not it is in conformance with this statement. Clinicians also are advised to take noti
was adopted and to consider other medical and scientific information that becomes available after that date. It also would be pr
intellectual property interests may restrict the performance of certain tests and other procedures.

To promote standardized reporting of actionable information from clinical genomic sequencing, in 2013, the American College of Medical Genetics and Genomics (ACMG) published a minimum list of genes to be reported as incidental or secondary findings. The goal was to identify and manage risks for selected highly penetrant genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality. The ACMG subsequently established the Secondary Findings Maintenance Working Group to develop a process for curating and updating the list over time. We describe here the new process for accepting and evaluating nominations for updates to the secondary findings list. We also report outcomes from six nominations received in the initial 15 months after the process was implemented. Applying the ne
ing the core principles of the original pol
the addition of four genes and removal of o
meet criteria for inclusion. The updated seco
list includes 59 medically actionable genes
in clinical genomic sequencing. We discu
encourage continued input from the medica
research on the impact of returning genomi

Genet Med advance online publication 17 N

Key Words: exome sequencing; genetic tes
incidental findings; secondary findings

BACKGROUND

The intent of the original incidental findings recommendations[1] was that clinical diagnostic laboratories performing exome or genome sequencing should report known pathogenic (KP) or expected pathogenic (EP) variants in the 56 American College of Medical Genetics and Ge
even when unrelated to the primary m
Subsequently, the ACMG revised the ter
findings" (SFs) because these genes
analyzed, as opposed to genetic varian

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of Genetics and Genomics, Boston Children's Hospital, Boston, Massachusetts, USA. Correspondence: David T. Miller (david.miller2@childrens.har
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The Board of Directors of the American College of Medical Genetics and Genomics approved this statement on 26 September 2016.

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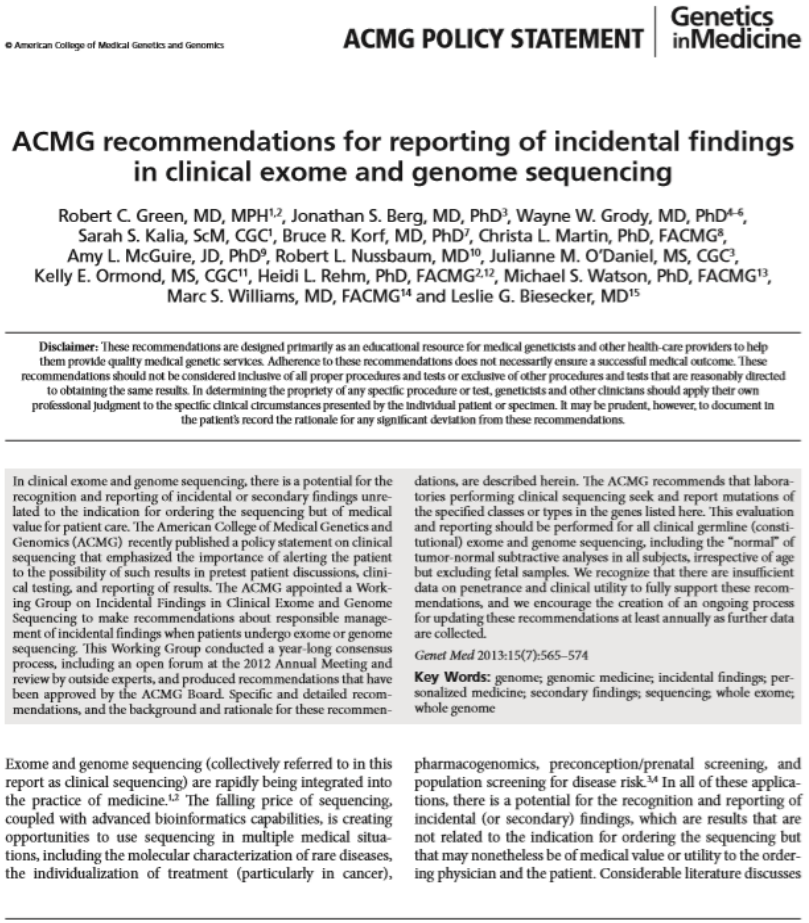

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ACMG POLICY STATEMENT | Genetics inMedicine

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

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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]

Disclaimer: These recommendations are designed primarily as an educational resource for medical geneticists and other health-care providers to help them provide quality medical genetic services. Adherence to these recommendations does not necessarily ensure a successful medical outcome. These recommendations should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, geneticists and other clinicians should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these recommendations.

In clinical exome and genome sequencing, there is a potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing but of medical value for patient care. The American College of Medical Genetics and Genomics (ACMG) recently published a policy statement on clinical sequencing that emphasized the importance of alerting the patient to the possibility of such results in pretest patient discussions, clinical testing, and reporting of results. The ACMG appointed a Working Group on Incidental Findings in Clinical Exome and Genome Sequencing to make recommendations about responsible management of incidental findings when patients undergo exome or genome sequencing. This Working Group conducted a year-long consensus process, including an open forum at the 2012 Annual Meeting and review by outside experts, and produced recommendations that have been approved by the ACMG Board. Specific and detailed recommendations, and the background and rationale for these recommendations, are described herein. The ACMG recommends that laboratories performing clinical sequencing seek and report mutations of the specified classes or types in the genes listed here. This evaluation and reporting should be performed for all clinical germline (constitutional) exome and genome sequencing, including the "normal" of tumor-normal subtractive analyses in all subjects, irrespective of age but excluding fetal samples. We recognize that there are insufficient data on penetrance and clinical utility to fully support these recommendations, and we encourage the creation of an ongoing process for updating these recommendations at least annually as further data are collected.

Genet Med 2013:15(7):565–574

Key Words: genome; genomic medicine; incidental findings; personalized medicine; secondary findings; sequencing; whole exome; whole genome

Exome and genome sequencing (collectively referred to in this report as clinical sequencing) are rapidly being integrated into the practice of medicine.[1,2] The falling price of sequencing, coupled with advanced bioinformatics capabilities, is creating opportunities to use sequencing in multiple medical situations, including the molecular characterization of rare diseases, the individualization of treatment (particularly in cancer), pharmacogenomics, preconception/prenatal screening, and population screening for disease risk.[3,4] In all of these applications, there is a potential for the recognition and reporting of incidental (or secondary) findings, which are results that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility to the ordering physician and the patient. Considerable literature discusses

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Why did it take so long to add HH/HFE to the AMCG list?

- Autosomal recessive
- Lower penetrance (sex dependent) than earlier conditions
  - Evidence of higher penetrance and morbidity than previously reported likely impacted inclusion
  - Mitigated by low risk actionability
- ACMG ~ Opportunistic screening – what about population screening?
  - Prior underestimates of penetrance and morbidity

Wilson and Jungner population screening criteria, 1968

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a ‘once and for all’ project.

Genetic disorders, 2009: PMID: 19556749
50 year discussion, 2020: PMID: 32923689
DNA based screening, 2021: PMID: 33790422

HH Population Screening

- Likely just C282Y allele
- Likely as part of a tier 1 panel
  - See Jenssen et al NEJM 2023, re excess mortality across actionable genes (PMID: 37937776)
  - Benefit for more and diverse persons (~2% in US population)
  - Likely more cost effective (See PMID 37983801)
- What are the data needed to test the value of population screening?
  - Who (age), what, where, when, how?
  - Follow-up care?
  - See NHGRI Genomic Medicine XV, 2023

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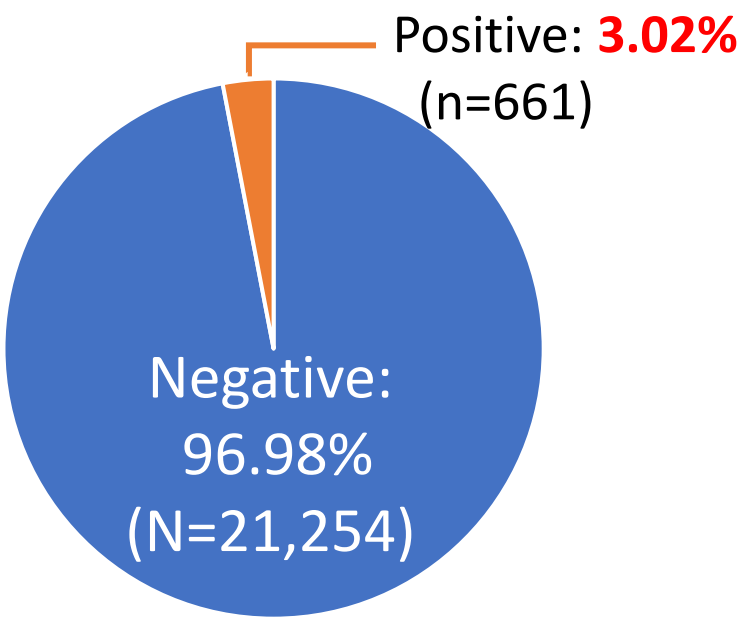
Actionable Incidental Findings in eMERGE3
(N=21,915; Gordon et al. 2020, PMID 32546831)

eMERGE CLINICAL ANNOTATION WORKGROUP



Self-reported Race/ethnicity	Number of participants	Number of Incidental Findings	Incidental Findings Rate % (95% CI)
American Indian, Alaska Native, or Pacific Islander	75	1	1.18 (0.26 – 7.87)
Hispanic or Latinx	1175	24	2.04 (1.28 – 3.34)
Black or African-American	3281	81	2.47 (2.25 – 3.55)
Asian	1497	41	2.74 (2.06 – 3.81)
White	14539	450	3.09 (3.01 – 3.57)
Unknown / Not reported	1348	64	4.75 (2.87 - 5.09)

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