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ACMG STATEMENT

ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

The American College of Medical Genetics and Genomics (ACMG) previously published guidance for reporting secondary findings (SFs) in the context of clinical exome and genome sequencing.[1-5] The ACMG Secondary Findings Working Group (SFWG) and Board of Directors (BODs) have agreed that the list of recommended genes should now be updated annually, but with an ongoing goal of maintaining this as a minimum list. Reporting of SFs should be considered neither a replacement for indication-based diagnostic clinical genetic testing nor a form of population screening.

Per nomenclature guidance put forth by the ACMG SFWG and approved by the BODs,[2] versioning of the SF list was designed to differentiate major vs minor revisions. Major

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revisions include conceptual changes to the categories or genes/variants in the SF list or the removal/addition of a large number of genes in a single update; these changes are denoted by updating the version number to the next integer (eg, v4.0, v5.0). Minor revisions reflect the addition or removal of 1 or a few genes or variants without any policy change, and they are denoted by an incremental change to the number after the decimal point (eg, v3.1, v3.2).

The current SFWG includes clinical geneticists, molecular and/or cytogenetics clinical laboratory directors, genetic counselors, cardiologists, a bioinformatician, and a bioethicist. The SFWG has met at least monthly via web conferencing to review nomination forms and vote on the inclusion or exclusion of gene-phenotype pairs for the ACMG SF v3.2 list. Details on the nomination and review process have been published.[3]

Internal nominations from SFWG committee members and external nominations were considered for the SF v3.2 list. Internal nominations from committee members included the *CALM1*, *CALM2*, and *CALM3* genes as gene-phenotype pairs with long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia. An external nomination was reviewed for the *ATP7A* gene that is associated with Menkes disease. No nominations were requested by other professional organizations. The final proposed ACMG SF v3.2 list from the SFWG was sent to the ACMG BODs for review and approval in October 2022. Member comments were received in January 2023, and the working group submitted a revision to the Board in February 2023.

Recommendations for the ACMG SF v3.2 List

The overall responsibility of the SFWG is to provide recommendations for a minimum list of gene-phenotype pairs for opportunistic screening to facilitate the identification and/or management of risks for selected genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality.[2] The complete ACMG SF v3.2 list is presented in Table 1 (and is also presented as a spreadsheet in Supplemental Table 1). As shown in Table 2, 3 new genes, *CALM1*, *CALM2*, and *CALM3*, were added to the v3.2 list, with a brief description of the factors considered in adding each of these genes. Only 1 gene, *ATP7A*, was considered for inclusion, but it was ultimately excluded from the v3.2 list (Table 3); *ATP7A* could be reviewed again in the future if new data emerge that are related to either Menkes disease or other phenotypes associated with this gene.

Considerations for Specific Phenotypic Categories

Genes related to cancer phenotypes

Recommended for addition to, or removal from, the SF v3.2 list: None

Genes related to cardiovascular phenotypes

Recommended for addition to the SF v3.2 list: *CALM1*, *CALM2*, and *CALM3*

Cardiovascular genes have been represented on the SF list since its inception because of the morbidity and mortality of heart failure and sudden cardiac death, which can both be treated or prevented with well-established interventions.[9,10]

For version 3.2, 3 additional genes (*CALM1*, *CALM2*, and *CALM3*) were reviewed. These genes cause predisposition to LQTS, and the available evidence supports a similar or greater risk of morbidity and mortality compared with other sudden cardiac death genes that are already included in the previous versions of the SF list. The 3 calmodulin genes (*CALM1*, *CALM2*, and *CALM3*) are located on different chromosomes, but they encode identical 149 amino acid proteins. All 3 were previously classified by ClinGen as having definitive evidence for LQTS with atypical features such as presentation in infancy or early childhood and with functional heart block and severe QT prolongation.[11]

A member comment suggested updating the nomenclature that is used for reportable variants in the *TTN* gene, as outlined in the Table 1 footnote. Because the exact disease mechanisms are still being elucidated, it was suggested to refer to *TTN* truncating variants as *TTN*tv, instead of loss-of-function variants. This update has been included as part of the ACMG SF v3.2 list. A member comment also requested additional guidance regarding which truncating variants in the Titin gene (*TTN*tv) should be reported as SFs. Specifically, a suggestion was made to "add specific details to include consideration of the cardiac isoforms/transcripts, highly expressed exons, and established regions with enrichment for *TTN*tv and dilated cardiomyopathy (DCM)."

We currently recommend that only frameshift and nonsense variants, and variants known to affect the splicing of *TTN* exons with high proportion spliced-in, be evaluated for pathogenicity and returned as SFs if classified as pathogenic and likely pathogenic.[6-8] This update has been included as part of the ACMG SF v3.2 list and provided as a footnote in Table 1. We anticipate that additional guidance may be provided from experts in the field over time and defer to further guidance that may be published in the future (Note "variants known to impact splicing" refers to variants affecting the invariable +/− 1, 2 positions and other coding or noncoding variants with demonstrated impact.).

Genes related to inborn errors of metabolism phenotypes

Nominated for addition to the SF list: *ATP7A*

The working group carefully considered the nomination of *ATP7A* as a gene-disease pair for Menkes disease. Menkes disease is infantile onset, has a high morbidity rate, the causative gene (*ATP7A*) can be assessed by standard exome sequencing, and there is a potential treatment. To further evaluate this gene-phenotype pair, we consulted an

Table 1 ACMG SF v3.2 gene and associated phenotypes recommended for return as secondary findings from clinical exome and genome sequencing

Phenotype	ACMG SF List Version	MIM Disorder	Gene	Inheritance	Variants to Report[a]
Genes related to cancer phenotypes					
Familial adenomatous polyposis	1.0	175100	*APC*	AD	All P and LP
Familial medullary thyroid cancer/multiple endocrine neoplasia 2	1.0	155240	*RET*	AD	All P and LP
		171400			
		162300			
Hereditary breast and/or ovarian cancer	1.0	604370	*BRCA1*	AD	All P and LP
	1.0	612555	*BRCA2*		
	3.0	114480	*PALB2*		
Hereditary paraganglioma-pheochromocytoma syndrome	1.0	168000	*SDHD*	AD	All P and LP
	1.0	601650	*SDHAF2*		
	1.0	605373	*SDHC*		
	1.0	115310	*SDHB*		
	3.0	171300	*MAX*		
	3.0	171300	*TMEM127*		
Juvenile polyposis syndrome	2.0	174900	*BMPR1A*	AD	All P and LP
Juvenile polyposis syndrome/hereditary hemorrhagic telangiectasia syndrome	2.0	175050	*SMAD4*	AD	All P and LP
Li-Fraumeni syndrome	1.0	151623	*TP53*	AD	All P and LP
Lynch syndrome (hereditary nonpolyposis colorectal cancer)	1.0	609310	*MLH1*	AD	All P and LP
		120435	*MSH2*		
		614350	*MSH6*		
		614337	*PMS2*		
Multiple endocrine neoplasia type 1	1.0	131100	*MEN1*	AD	All P and LP
MUTYH-associated polyposis	1.0	608456	*MUTYH*	AR	P and LP (2 variants)
NF2-related schwannomatosis	1.0	101000	*NF2*	AD	All P and LP
Peutz-Jeghers syndrome	1.0	175200	*STK11*	AD	All P and LP
PTEN hamartoma tumor syndrome	1.0	158350	*PTEN*	AD	All P and LP
Retinoblastoma	1.0	180200	*RB1*	AD	All P and LP
Tuberous sclerosis complex	1.0	191100	*TSC1*	AD	All P and LP
	1.0	613254	*TSC2*		
von Hippel-Lindau syndrome	1.0	193300	*VHL*	AD	All P and LP
WT1-related Wilms tumor	1.0	194070	*WT1*	AD	All P and LP
Genes related to cardiovascular phenotypes					
Aortopathies	1.0	154700	*FBN1*	AD	All P and LP
	1.0	609192	*TGFBR1*		
	1.0	610168	*TGFBR2*		
	1.0	613795	*SMAD3*		
	1.0	611788	*ACTA2*		
	1.0	132900	*MYH11*		
Arrhythmogenic right ventricular cardiomyopathy (a subcategory of arrhythmogenic cardiomyopathy)	1.0	609040	*PKP2*	AD	All P and LP
	1.0	607450	*DSP*[b]		
	1.0	610476	*DSC2*		
	1.0	604400	*TMEM43*		
	1.0	610193	*DSG2*		
Catecholaminergic polymorphic ventricular tachycardia	1.0	604772	*RYR2*	AD	All P and LP
	3.0	611938	*CASQ2*	AR	P and LP (2 variants)
	3.0	615441	*TRDN*[c]	AR	
DCM	1.0	601494	*TNNT2*[d]	AD	All P and LP (See text)
	1.0	115200	*LMNA*[e]		
	3.0	617047	*FLNC*[d]		
	3.0	604145	*TTN*[f]		
	3.1	613881	*BAG3*		
	3.1	604765	*DES*		
	3.1	613172	*RBM20*		
	3.1	611879	*TNNC1*		
Ehlers-Danlos syndrome, vascular type	1.0	130050	*COL3A1*	AD	All P and LP

(continued)

Table 1 Continued

Phenotype	ACMG SF List Version	MIM Disorder	Gene	Inheritance	Variants to Report[a]
Familial hypercholesterolemia	1.0	143890	*LDLR*	SD	All P and LP
	1.0	144010	*APOB*	AD	
	1.0	603776	*PCSK9*	AD	
HCM[g]	1.0	192600	*MYH7*[b]	AD	All P and LP
	1.0	115197	*MYBPC3*		
	1.0	613690	*TNNI3*		
	1.0	115196	*TPM1*		
	1.0	608751	*MYL3*		
	1.0	612098	*ACTC1*		
	1.0	600858	*PRKAG2*		
	1.0	608758	*MYL2*		
LQTS types 1 and 2	1.0	192500	*KCNQ1*	AD	All P and LP
	1.0	613688	*KCNH2*		
LQTS3; Brugada syndrome	1.0	603830, 601144	*SCN5A*[b]	AD	All P and LP
LQTS types 14-16	3.2	616247	*CALM1*[g]	AD	All P and LP
		616249	*CALM2*[g]	AD	
		618782	*CALM3*[g]	AD	
Genes related to inborn errors of metabolism phenotypes					
Biotinidase deficiency	3.0	253260	*BTD*	AR	P and LP (2 variants)
Fabry disease	1.0	301500	*GLA*[h]	XL	All hemi, het, homozygous P and LP
Ornithine transcarbamylase deficiency	2.0	311250	*OTC*	XL	All hemi, het, homozygous P and LP
Pompe disease	3.0	232300	*GAA*	AR	P and LP (2 variants)
Genes related to miscellaneous phenotypes					
Hereditary hemochromatosis	3.0	235200	*HFE*	AR	*HFE* p.C282Y[i] homozygotes only
Hereditary hemorrhagic telangiectasia	3.0	600376	*ACVRL1*	AD	All P and LP
	3.0	187300	*ENG*		
Malignant hyperthermia	1.0	145600	*RYR1*[j]	AD	All P and LP
	1.0	601887	*CACNA1S*		
Maturity-onset of diabetes of the young	3.0	600496	*HNF1A*	AD	All P and LP
RPE65-related retinopathy	3.0	204100, 613794	*RPE65*	AR	P and LP (2 variants)
Wilson disease	2.0	277900	*ATP7B*	AR	P and LP (2 variants)
Hereditary TTR amyloidosis	3.1	105210	*TTR*	AD	All P and LP

AD, autosomal dominant; *AR*, autosomal recessive; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *hemi*, hemizygous; *het*, heterozygous; *LP*, likely pathogenic; *LQTS*, long QT syndrome; *MIM*, Mendelian Inheritance of Man; *P*, pathogenic; *pLOF*, putative loss-of-function; *SD*, semidominant; *SF*, secondary finding; *TTR*, transthyretin; *XL*, X-linked.

[a]Variants within genes associated with autosomal dominant phenotypes should be classified as P or LP to be reportable. Genes associated with phenotypes inherited in an autosomal recessive fashion would need 2 LP and/or P variants to meet the threshold for reporting even when phase is undetermined, as follow-up family variant testing can often resolve phase. Finally, P and LP variants within genes associated with X-linked phenotypes that are apparently hemizygous, heterozygous, or homozygous should be reported, as often heterozygous females can have adverse medical events at a reasonable frequency and treatment or amelioration of disease is available. Variants of uncertain significance should not be reported in any gene.

[b]Also associated with DCM as a primary disease.

[c]Also associated with long QT syndrome.

[d]Also associated with HCM.

[e]P/LP *LMNA* variants that have any case level phenotype evidence of association with cardiac disease (eg, DCM, arrhythmogenic right ventricular cardiomyopathy, arrhythmogenic cardiomyopathy, and/or arrhythmia) should be reported, whereas previously reported P/LP missense variants never associated with cardiac disease should not be reported. Also, for novel pLOF variants that reach LP without case observations, these variants should be reported given the general association of pLOF *LMNA* variants with cardiac disease and the evidence summary should include mention of the spectrum of phenotypes that may be observed with LMNA pLOF variation.

[f]We currently recommend that only frameshift and nonsense variants, and variants known to impact the splicing of *TTN* exons with high PSI (see references[6-8]), be evaluated for pathogenicity and returned as secondary findings if classified as P/LP.

[g]Also associated with catecholaminergic polymorphic ventricular tachycardia.

[h]Gene also applies to the cardiovascular category.

[i]Transcript for the *HFE* gene is NM_000410.3.

[j]*RYR1* also causes a neuromuscular phenotype. Only P/LP variants associated with malignant hyperthermia should be reported as a secondary finding.

Table 2 New gene/phenotype pairs for SF v3.2 list

Gene/Phenotype	Additional Comments
Genes related to cardiovascular phenotypes	
CALM1/long QT syndrome	Similar prevalence/penetrance rates to other SCD genes previously on ACMG SF list
CALM2/long QT syndrome	Similar prevalence/penetrance rates to other SCD genes previously on ACMG SF list
CALM3/long QT syndrome	Similar prevalence/penetrance rates to other SCD genes previously on ACMG SF list

ACMG, American College of Medical Genetics and Genomics; *SCD*, sudden cardiac death; *SF*, secondary findings.

ad hoc expert for feedback about available treatment options. After careful consideration, we determined that there was insufficient evidence that the only available treatment, subcutaneous injections of copper histidinate, is efficacious. In addition, there was concern that this treatment is potentially toxic.[12] We also noted that pathogenic and likely pathogenic variants would likely be identified as a primary (diagnostic) result as opposed to an SF.

Pathogenic variants in *ATP7A* can also result in occipital horn syndrome (OHS) and *ATP7A*-related distal motor neuropathy (DMN). OHS and *ATP7A*-related DMN are childhood or adult onset and hence could be considered SFs, but this gene was only reviewed by the working group in relation to Menkes disease. Although the other conditions were not specifically reviewed, the concern about insufficient evidence for efficacy of copper histidinate would also apply to OHS and *ATP7A*-related DMN.

Conclusions

With the 2021 publication of the SF policy statements for reporting of SFs and the SF v3.0 gene list,[3,4] the SFWG created a mechanism for separating updates to the policy and principles for SF reporting from updates to the SF gene list. This dual publication approach facilitates more frequent updates to the actual SF gene list. Going forward, we foresee updates to the general policy only as needed, likely every few years. In contrast, updates to the gene list will be targeted to occur on an annual basis and to be published at approximately the same time each year so that all stakeholders can expect an update and be prepared to revise laboratory and reporting processes. We recognize that clinical laboratories must integrate updates into their workflow, and clinicians must familiarize themselves with the genes on the list for the purposes of genetic counseling and informed consent. Our intention is to publish an updated list each year in January.

Table 3 Genes not selected for SF v3.2 list

Gene/Phenotype	Category	Additional Comments
ATP7A/Menkes disease	Inborn errors of metabolism	Lack of demonstrated effectiveness and possible toxicity of the available treatment

SF, secondary findings.

The SFWG will continue to review this list of actionable genes, and new nominations, throughout the course of the year. We also wish to remind the community that ACMG members may nominate genes or variants to be added to, or removed from, the list based on an evolving evidence base and/or evolving standards in the practice of medicine. We will also consider nominations submitted through representatives of other professional organizations. Nomination forms can be found on the ACMG website (https://form.jotform.com/203275021199048). We hope that the detailed descriptions of our decision process during the preparation of this update will help the community better understand the types of genes and variants that we consider appropriate for this list to guide nominations going forward.

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Conflict of Interest

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Additional Information

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