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ACMG STATEMENT

ACMG SF v3.3 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.[1-7] The ACMG Secondary Findings Working Group (SFWG) and Board of Directors (BODs) have agreed that the list of recommended genes should be updated annually and with an ongoing goal of maintaining

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The Board of Directors of the American College of Medical Genetics and Genomics approved this statement on 24 February 2025.

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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.

The current SFWG includes clinical geneticists, molecular and/or cytogenetics clinical laboratory directors, genetic counselors, cardiologists, a bioethicist, and a pediatrician who also serves as a patient advocate. From March 2023 to July 2024, the SFWG met at least monthly via web conferencing and held an in-person meeting during the 2024 ACMG Annual Clinical Genetics Meeting in Toronto, Canada. Among other agenda items, the SFWG reviewed nomination forms and voted on inclusion or exclusion of gene-disease nominations to update the ACMG SF v3.2 list. Details on the nomination and review process have been published.[3,7]

Here, we report the new ACMG SF v3.3 list. Per previous nomenclature guidance put forth by the ACMG SFWG and approved by the BOD,[2] this update is considered a minor revision. Minor revisions reflect the addition or removal of 1 or a few genes or variants without any policy change and are denoted by an incremental change to the previous version.

Several external nominations from the community were considered for the SF v3.3 list, including the following gene-disease pairings: *ABCD1* (HGNC:61)/adrenal leukodystrophy (OMIM 300100); *ADA2* (HGNC:1839)/adenosine deaminase 2 deficiency (OMIM 615688); *CYP27A1* (HGNC:2605)/cerebrotendinous xanthomatosis (OMIM 213700); *GCK* (HGNC:4195)/glucokinase-related monogenic diabetes (OMIM 125851); *PLN* (HGNC:9080)/dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (OMIM 609909); *RUNX1* (HGNC:10483)/*RUNX1*-related thrombocytopenia (OMIM 601399), platelet defects and risk for hematologic malignancies; and *SLC4A1* (HGNC:11027)/hereditary spherocytosis type 4 (OMIM 612653), ovalocystosis, Southeast Asian (SA) type (OMIM 166900), and autosomal dominant distal renal tubular acidosis (OMIM 179800). No nominations were received from other professional organizations. The final proposed ACMG SF v3.3 list from the SFWG was sent to the ACMG BOD for review and approval in October 2024.

The Clinical Genome Resource (ClinGen) has recently added a webpage specific to the ACMG SF list of returnable findings. The goal of this page is to provide guidance for reporting of specific gene-disease pairs and variant types in SF genes. For example, the webpage will display that pathogenic and likely pathogenic (P/LP) variants are reportable in the *RYR1* gene for malignant hyperthermia but not for congenital myopathy. Additionally, the page will indicate which genes and diseases' hemizygous, heterozygous, and homozygous variants are appropriate to return for P/LP variants. The webpage will be continually updated as new list versions are made available (https://search.clinicalgenome.org/kb/genes/acmgsf).

Recommendations for the ACMG SF v3.3 List

The purpose of the SFWG is to provide recommendations for a minimum list of gene-disease 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 while balancing potential harms of reporting this information, such as additional testing and raising concerns for patients and family members through cascade testing.[2] The best interest of children should still be prioritized when considering disclosure of SF for adult-onset conditions.[3] Although considering nominations for the v3.3 list, we continue to be mindful that the penetrance in asymptomatic individuals with no family history is likely lower than published penetrance estimates; however, penetrance estimates based on unbiased ascertainment methods are currently lacking for most inherited conditions.[7]

The complete ACMG SF v3.3 list is presented in Table 1 (and is also presented as an editable spreadsheet in Supplemental Table 1). Three new genes, *ABCD1*, *CYP27A1*, and *PLN,* were added to the v3.3 list, and a brief description of the factors considered in adding each of these genes can be found in Table 2. Three genes, *GCK*, *RUNX1*, and *SLC4A1*, were considered for inclusion on the v3.3 list but were not added. Table 3 provides information on these gene-disease pair decisions, including additional information that was deemed necessary for reconsideration. One nominated gene, *ADA2*, was considered for inclusion on the v3.3 list, but ultimately, a decision by the SFWG to include versus exclude was deferred until additional information from the nomination submitters or other published data are available to inform a vote. No nominations for genes to be considered for removal from the SF list were received.

Considerations for specific phenotypic categories

Genes related to cancer predisposition

Not recommended for addition to the SF v3.3 list: RUNX1

The gene-disease nomination for *RUNX1*-related thrombocytopenia, platelet defects, and risk for hematologic malignancies was previously considered by the SFWG, and a decision to not include it on the SF v.3.1 list was published.[5] The reasons for this decision included the limited data on prevalence and penetrance (especially from genomically ascertained cohorts), the need for confirmation from skin fibroblasts to confirm the germline origin of a variant, and a noncatastrophic clinical presentation and limited evidence-based guidance to ameliorate the risk of myeloid malignancy. Reconsideration of the 2022 decision was requested, given the availability of new data on phenotype and penetrance from a large longitudinal natural history study.[8] In this phenotypically ascertained cohort, the hematologic malignancy risk was high (62% of families), as well as

Table 1 ACMG SF v3.3 genes and associated diseases recommended for return as secondary findings from clinical exome and genome sequencing

Disease	ACMG SF List Version	OMIM Disorder	Gene	Inheritance	Variants to Report[a]
Genes Related to Cancer Predisposition					
Familial adenomatous polyposis (FAP)	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 (JPS)	2.0	174900	*BMPR1A*	AD	All P and LP
Juvenile polyposis syndrome (JPS)/ 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 (HNPCC)	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 (MAP)	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 (PJS)	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 Disease Predisposition					
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*		

(continued)

Table 1 Continued

Disease	ACMG SF List Version	OMIM Disorder	Gene	Inheritance	Variants to Report[a]
Arrhythmogenic right ventricular cardiomyopathy (a subcategory of Arrhythmogenic Cardiomyopathy or ACM)	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	
Dilated cardiomyopathy	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*		
	3.3	609909	*PLN*[d,g]		
Ehlers-Danlos syndrome, vascular type	1.0	130050	*COL3A1*	AD	All P and LP
Familial hypercholesterolemia	1.0	143890	*LDLR*	SD	All P and LP
	1.0	144010	*APOB*	AD	
	1.0	603776	*PCSK9*	AD	
Hypertrophic cardiomyopathy	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*		
Long QT syndrome types 1 and 2	1.0	192500	*KCNQ1*	AD	All P and LP
	1.0	613688	*KCNH2*		
Long QT syndrome 3; Brugada syndrome	1.0	603830, 601144	*SCN5A*[b]	AD	All P and LP
Long QT syndrome types 14-16	3.2	616247	*CALM1*[h]	AD	All P and LP
		616249	*CALM2*[h]	AD	
		618782	*CALM3*[h]	AD	
Genes Related to Inborn Errors of Metabolism					
Biotinidase deficiency	3.0	253260	*BTD*	AR	P and LP (2 variants)
Cerebrotendinous xanthomatosis	3.3	213700	*CYP27A1*	AR	P and LP (2 variants)
Fabry disease	1.0	301500	*GLA*[i]	XL	All hemi, het, homozygous P and LP
Hereditary hemochromatosis	3.0	235200	*HFE*	AR	*HFE* p.C282Y[j] homozygotes only
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)
X-linked adrenoleukodystrophy[k]	3.3	300100	*ABCD1*	XL	All hemi, homozygous or 2 het. P and/or LP
Genes Related to Other Disease Phenotypes					
Hereditary hemorrhagic telangiectasia	3.0	600376	*ACVRL1*	AD	All P and LP
	3.0	187300	*ENG*		
Hereditary TTR amyloidosis	3.1	105210	*TTR*	AD	All P and LP
Malignant hyperthermia	1.0	145600	*RYR1*	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,	*RPE65*	AR	P and LP (2 variants)

(continued)

Table 1 Continued

Disease	ACMG SF List Version	OMIM Disorder	Gene	Inheritance	Variants to Report[a]
Wilson disease	2.0	613794 277900	*ATP7B*	AR	P and LP (2 variants)

AD, autosomal dominant; *AR*, autosomal recessive; *Hemi*, hemizygous; *Het*, heterozygous; *LP*, likely pathogenic; *OMIM*, Online Mendelian Inheritance in Man; *P*, pathogenic; *SD*, semidominant; *TTR*, transthyretin; *XL*, X-linked.

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

[b]Also associated with dilated cardiomyopathy (DCM) as a primary disease.

[c]Also associated with long QT syndrome.

[d]Also associated with hypertrophic cardiomyopathy (HCM).

[e]Pathogenic and likely pathogenic (P/LP) LMNA variants that have any case-level phenotype evidence of association with cardiac disease (eg, DCM, ARVC, ACM, 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]Only truncating variants in the Titin gene (*TTN*tv) should be reported as a secondary finding.

[g]Also associated with arrhythmogenic right ventricular cardiomyopathy (ARVC).

[h]Also associated with catecholaminergic polymorphic ventricular tachycardia.

[i]Gene also applies to the cardiovascular category.

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

[k]A single heterozygous P/LP variant should not be reported.

thrombocytopenia (91%) and abnormal bleeding scores (51%). However, penetrance data in an unselected population still remain unavailable for this gene-disease nomination. In addition, there are still no published *RUNX1*-specific management guidelines and, from an actionability perspective on hematologic neoplasm risk, there remains little evidence that routine complete blood counts (or bone marrow biopsies) is efficacious.[9]

Genes related to cardiovascular predisposition

Recommended for addition to the SF v3.3 list: PLN

Cardiovascular genes continue to be frequently nominated and included on the SF list because of the high morbidity and mortality of heart failure and sudden cardiac death, the ability to treat or prevent these conditions with well-established interventions, the relatively large number of genes associated with cardiovascular phenotypes, and the robust evidence supporting those gene-disease relationships.[10,11] For the SF v3.3 list, 1 gene related to cardiovascular phenotypes, *PLN*, was nominated. Phenotypes associated with this gene that were considered as part of the SFWG review were dilated cardiomyopathy,[12] arrhythmogenic right ventricular cardiomyopathy (ARVC),[13] and hypertrophic cardiomyopathy.[14] There is a relatively common Dutch founder pathogenic *PLN* variant denoted as NM_002667.5(*PLN*):c.37AGA[1], p.(Arg14del) that may be present in up to 10% to 15% of patients with dilated cardiomyopathy or ARVC in The Netherlands; this variant has been reported in individuals from the United States, Canada, and China as well.[15,16] Other missense and null variants have also been associated with disease.[17,18] A large cohort study of 403 *PLN* p.(Arg14del) heterozygotes found a standardized mortality ratio of 1.7 (95% CI, 1.4-2.0) with mortality beginning at age 25 years and recommended genetic and cardiac screening in *PLN* variant heterozygotes beginning in adolescence.[13]

Genes related to inborn errors of metabolism phenotypes

Recommended for addition to the SF v3.3 list: ABCD1, CYP27A1

The X-linked gene, *ABCD1,* was nominated for reconsideration for the SF v3.3 list by 2 individual submitters. This gene was initially nominated for the v3.0 gene list.[4] Pathogenic variants in this gene have been associated with X-linked adrenoleukodystrophy typically in individuals hemizygous for these variants (eg, individuals with a 46,XY karyotype). Cerebral adrenoleukodystrophy (CALD) is characterized by progressive behavioral, cognitive, and neurologic deficits often beginning in childhood. Adrenal insufficiency (AI) is also more commonly seen in both children and adults hemizygous for these variants, and has rarely been reported in individuals heterozygous for these variants (eg, individuals with a 46,XX karyotype).[19] Individuals heterozygous for a pathogenic *ABCD1* variant can be asymptomatic or have adrenomyeloneuropathy (AMN), a condition characterized by spasticity and bowel and bladder dysfunction that has no current disease course altering treatments.[19] Individuals with hemizygous and homozygous variants have also been reported to have the AMN phenotype.[19] Currently, there are 2 main effective treatment options for CALD, including autologous bone marrow transplant with gene therapy and hematopoietic stem cell transplantation.[19,20] At this time, the FDA-approved gene therapy is only available to individuals under 18 years of

Table 2 New gene/phenotype pairs for SF v3.3 list

Gene/ Phenotype	Additional Comments
Genes Related to Cardiovascular Disease Predisposition	
PLN	Similar penetrance rates to other sudden cardiac death genes previously on ACMG secondary findings list.
Genes Related to Inborn Errors of Metabolism	
ABCD1	Degenerative condition with time-dependent effective treatment options in individuals with hemizygous variants (eg, 46,XY individuals).
CYP27A1	Rare condition with time-dependent effective treatment options shown to prevent significant neurological disease and early death.

age with the CALD phenotype. Although eligibility for clinical trials may exist for adults, qualifying for ongoing clinical trials is not itself considered sufficient justification to add a condition to the ACMG SF list. Early features of the cerebral phenotype can be missed, and treatment is most effective in early disease stages.[21,22] The treatment of AI is similar to its management when it results from other causes.[21,22]

There was overall consensus to recommend the return of hemizygous P/LP variants. The actionability of ALD is clear, this gene is on the Recommended Uniform Screening Panel (RUSP) and currently is part of nearly all US state newborn screening (NBS) programs. In an effort to keep a minimal list for reporting back SF, the SFWG typically would not recommend gene-disease pairs to the SF list if they are already addressed through NBS programs, and there are no plans to systematically consider additional genes on the RUSP unless nominated for consideration for a future ACMG SF list. In fact, this gene was previously considered for the v3.0 ACMG SF list and not included in part because of NBS. However, for the *ABCD1* gene, there are acknowledged gaps in the screening of individuals at this time because not all states include this gene in their screening programs, and screening for this gene was first initiated in late 2013.[23] Additionally, there were concerns about our current understanding of the penetrance of ALD, given that the disease prevalence estimates have increased from 1 in 14,000 to 1 in 4000 (F. Eichler, personal communication, June 25, 2024) with the initiation of NBS for this disorder.[24] These data raise the question whether individuals are being identified who will not develop complications of ALD or if there are a significant number of undiagnosed or misdiagnosed X-linked ALD cases. Ultimately, the time-limited opportunities for all treatment options and the potential difficulty in making this clinical diagnosis early led to a majority decision to include this gene on the SF v3.3 list in the context of hemizygous, homozygous, and known/assumed compound heterozygous P/LP variants. However, this gene's appropriateness on the ACMG SF minimal list could be reconsidered in the future as more at-risk individuals have access to NBS.

A similarly difficult decision among the SFWG involved whether to report heterozygous (monoallelic) P/LP variants in the *ABCD1* gene. The SFWG has previously recommended reporting heterozygous P/LP variants in X-linked genes including *GLA* and *OTC* because of the likelihood of individuals harboring heterozygous variants manifesting a treatable phenotype in a large number of individuals. However, P/LP variants in the *ABCD1* gene are less likely to cause a treatable phenotype (ie, CALD and/or AI) in individuals heterozygous for these variants, with most of these individuals being at risk for AMN.[19-21] As part of its mission, the SFWG aims to avoid the inclusion of reportable findings that are untreatable in the majority of cases and/or for the sake of informing reproductive risk. Therefore, the group voted not to report heterozygous P/LP variants.

The *CYP27A1* gene was nominated in association with the phenotype of cerebrotendinous xanthomatosis (CTX). This rare autosomal recessive condition is characterized by the presence of infantile or juvenile onset chronic diarrhea, bilateral juvenile cataracts in a substantial number of cases, xanthomas that can be present in the second and third decades of life, and progressive neurological dysfunction among other variable manifestations.[25] To date, this condition has not been included on the RUSP. An oral therapy, chenodeoxycholic acid (CDCA), which is FDA approved

Table 3 Genes not recommended for SF v3.3 list

Gene/Disease	Category	Additional Comments
ADA2/deficiency of adenosine deaminase 2	Other	Decision deferred because of lack of penetrance data in genomically ascertained populations.
GCK/glucokinase-related monogenic diabetes	Other	Lack of phenotype severity with no recommended treatment, and prevention of overtreatment is beyond the scope of this list.
RUNX1/*RUNX1*-related familial platelet disorder with associated myeloid malignancies	Cancer predisposition	Lack of demonstrated efficacy data for cancer screening or bleeding prophylaxis in individuals with *RUNX1* disease-associated variants.
SLC4A1/hereditary spherocytosis type 4/ovalocystosis, SA type/AD renal tubular acidosis	Other	Lack of phenotypic severity with more severe presentations likely being diagnosed clinically in early childhood.

AD, autosomal dominant; *SA*, Southeast Asian.

for another indication but used off label in CTX and has received FDA medical necessity determination, has been shown to normalize biochemical abnormalities, halt disease progression in many cases, and prevent symptoms of CTX in children.[26-28] Although treatment is appropriate at any age, late-treated adults with significant disease burden may not experience improvement in neurological symptoms; however, progression of symptoms might be prevented.[27,29] An alternative therapy, cholic acid is FDA approved for use in CTX and has been used in infants with CTX exhibiting cholestasis or in rare instances of infants with transaminasemia from chenodeoxycholic acid. There is little long-term experience with its chronic use in CTX.[30,31] Given the availability of effective timely treatment that has been shown to prevent debilitating neurological symptoms and early death, the *CYP27A1* gene has been added to the SF v3.3 list.

Genes related to other phenotypes

Not recommended for addition to the SF list: ADA2, GCK, and SLC4A1

The *ADA2* gene was nominated for inclusion on the SF v3.3 list because of its association with deficiency of adenosine deaminase 2. The nomination noted that, although there are other genes associated with similar phenotypes that could be considered for addition, pathogenic variants in *ADA2* posed particular diagnostic challenges because of variable expressivity. This autosomal recessive complex systemic autoinflammatory disorder involving vasculopathy, immune dysfunction, and hematologic abnormalities tends to demonstrate intra- and interfamilial phenotypic variability, including age of onset and severity.[32] There is evidence that use of antitumor necrosis factor agents can prevent strokes and that such treatment would be recommended for all individuals with biallelic pathogenic *ADA2* variants, even if asymptomatic.[33-35] Additionally, standard-of-care recommendations for treating a stroke, such as anticoagulants or thrombolysis agents, could lead to hemorrhagic strokes in individuals with this condition.[36] Although the actionability of this condition does not appear to be in question, there is currently an absence of data on the penetrance of this disorder in genomically ascertained individuals. This point is of significant concern because all individuals with biallelic pathogenic variants would be recommended to remain on lifelong treatment while asymptomatic. In the absence of more comprehensive penetrance data from genomically ascertained individuals, the SFWG deferred moving forward with a vote on whether or not to include this gene on the ACMG SF list. Therefore, this gene was not included on the ACMG SF v3.3 list.

The nomination for the *GCK* gene, associated with glucokinase-related monogenic diabetes, was an interesting twist from typical motivations for nominating genes for the SF list. This condition is typically discovered incidentally during diabetes screening and is associated with a mild hyperglycemia with no recommendations for treatment.[37] The impetus for nominating this gene for the SF list was an attempt to reduce the known issue with overtreatment of this condition, especially during pregnancy. Individuals detected to have mild hyperglycemia on routine HbA1c screenings are often not genetically tested and can be misclassified as type 1 or 2 diabetics and treated as such.[38,39] In addition, because the evidence for actionability of this finding is mainly in the setting of individuals who have clinically apparent hyperglycemia, the SFWG thought that the genetic evaluation for *GCK* is more appropriate to be performed in the primary context in the setting of hyperglycemia. Therefore, although the SFWG agreed that *GCK* is an important gene for consideration, it was determined that this reasoning is beyond the scope of the intent of the ACMG SF list because this list has generally not included genes in which the actionability is solely avoidance of a treatment or exposure.

A current exception to this conclusion is the *RYR1* gene, which was included on the original ACMG SF list, for which the recommendation is avoidance of certain anesthetics. However, the consequence of this exposure can be sudden death, which makes pathogenic gain-of-function variants in *RYR1* of higher priority for return of results. Finally, the SFWG noted that the *GCK* gene could be considered on population screening panels.

The *SLC4A1* gene was nominated for consideration with several phenotypes to be included on the SF gene list, including hereditary spherocytosis type 4, ovalocystosis, SA type, and autosomal dominant distal renal tubular acidosis. There were concerns that the severity of these disorders, if discovered as a SF, may not rise to the level of other conditions currently on the list. The SFWG recognizes that severe presentations can be observed, but these cases typically manifest and can be identified in early childhood. In addition, there do not appear to be genotype/phenotype correlations that would allow laboratories to determine which variants should be considered for which condition(s), and the penetrance of these conditions is largely unclear.[40] Finally, there is a lack of surveillance guidelines for individuals who carry P/LP variants in the *SLC4A1* gene.[40]

Conclusion

The ACMG SFWG reviewed 7 genes as part of their annual review for updating the ACMG SF gene list. Three genes (*ABCD1*, *CYP27A1*, and *PLN*) were recommended for addition to the SF v3.3 list, whereas *GCK*, *RUNX1*, and *SLC4A1* were not recommended for addition to the list at this time. Additional information was deemed necessary before moving to a final vote for the *ADA2* gene.

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/93256282335156). 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 to include or remove genes going forward.

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Conflict of Interest

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Additional Information

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"The ACMG Secondary Findings v3.3 list is provided here in spreadsheet format for content searchability, but has not been validated for clinical testing pipeline use to ensure the accuracy of data (e.g. gene symbols, OMIM numbers, etc)."

Gene	Gene MIM	Disease/Phentyope	Disorder MIM	Phenotype Category	Inheritance	SF List Version	Variants to report
ABCD1	300371	X-linked adrenoleukodystrophy	300100	Metabolic	XL	3.3	All hemi or homozygous P and LP or 2 het. P/LP variants
ACTA2	102620	Familial thoracic aortic aneurysm	611788	Cardiovascular	AD	1.0	All P and LP
ACTC1	102540	Hypertrophic cardiomyopathy	612098	Cardiovascular	AD	1.0	All P and LP
ACVRL1	601284	Hereditary hemorrhagic telangiectasia	600376	Other	AD	3.0	All P and LP
APC	611731	Familial adenomatous polyposis	175100	Cancer	AD	1.0	All P and LP
APOB	107730	Familial hypercholesterolemia	144010	Cardiovascular	AD	1.0	All P and LP
ATP7B	606882	Wilson disease	277900	Other	AR	2.0	P and LP (2 variants)
BAG3	603883	Dilated cardiomyopathy	613881	Cardiovascular	AD	3.1	All P and LP
BAG3	603883	Myofibrillar myopathy	612954	Cardiovascular	AD	3.1	All P and LP
BMPR1A	601299	Juvenile polyposis syndrome	174900	Cancer	AD	1.0	All P and LP
BRCA1	113705	Hereditary breast and ovarian cancer	604370	Cancer	AD	1.0	All P and LP
BRCA2	600185	Hereditary breast and ovarian cancer	612555	Cancer	AD	1.0	All P and LP
BTD	609019	Biotinidase deficiency	253260	Metabolic	AR	3.0	P and LP (2 variants)
CACNA1S	114208	Malignant hyperthermia	601887	Other	AD	1.0	All P and LP
CALM1	114180	Long-QT syndrome type 14	616247	Cardiovascular	AD	3.2	All P and LP
CALM1	114180	Catecholaminergic polymorphic ventricular tachycardia	614916	Cardiovascular	AD	3.2	All P and LP
CALM2	114182	Long-QT syndrome type 15	616249	Cardiovascular	AD	3.2	All P and LP
CALM2	114182	Catecholaminergic polymorphic ventricular tachycardia	616249	Cardiovascular	AD	3.2	All P and LP
CALM3	114183	Long-QT syndrome type 16	618782	Cardiovascular	AD	3.2	All P and LP
CALM3	114183	Catecholaminergic polymorphic ventricular tachycardia	618782	Cardiovascular	AD	3.2	All P and LP
CASQ2	114251	Catecholaminergic polymorphic ventricular tachycardia	611938	Cardiovascular	AR	3.0	P and LP (2 variants)
COL3A1	120180	Ehlers-Danlos syndrome, vascular type	130050	Cardiovascular	AD	1.0	All P and LP
CYP27A1	213700	Cerebrotendinous xanthomatosis	213700	Metabolic	AR	3.3	P and LP (2 variants)
DES	125660	Dliated cardiomyopathy	604765	Cardiovascular	AD	3.1	All P and LP
DES	125660	Myofibrillar myopathy	601419	Cardiovascular	AD	3.1	All P and LP
DSC2	125645	Arrhythmogenic right ventricular cardiomyopathy	610476	Cardiovascular	AD	1.0	All P and LP
DSG2	125671	Arrhythmogenic right ventricular cardiomyopathy	610193	Cardiovascular	AD	1.0	All P and LP
DSP	125647	Arrhythmogenic right ventricular cardiomyopathy	607450	Cardiovascular	AD	1.0	All P and LP
DSP	125647	Dilated cardiomyopathy	615821	Cardiovascular	AD	1.0	All P and LP
ENG	131195	Hereditary hemorrhagic telangiectasia	187300	Other	AD	3.0	All P and LP
FBN1	134797	Marfan syndrome	154700	Cardiovascular	AD	1.0	All P and LP
FLNC	102565	Dilated cardiomyopathy	n/a	Cardiovascular	AD	3.0	All P and LP
FLNC	102565	Hypertrophic cardiomyopathy	617047	Cardiovascular	AD	3.0	All P and LP
FLNC	102565	Myofibrillar myopathy	609524	Cardiovascular	AD	3.0	All P and LP
GAA	606800	Pompe disease	232300	Metabolic	AR	3.0	P and LP (2 variants)
GLA	300644	Fabry disease	301500	Cardiovascular Metabolic	XL	1.0	All hemi, het, homozygous P and LP
HFE	613609	Hereditary hemochromatosis (c.845G>A; p.C282Y homozygotes only)	235200	Other	AR	3.0	p.C282Y homozygotes only
HNF1A	142410	Maturity-Onset of Diabetes of the Young	600496	Other	AD	3.0	All P and LP
KCNH2	152427	Long-QT syndrome type 2	613688	Cardiovascular	AD	1.0	All P and LP
KCNQ1	607542	Long-QT syndrome type 1	192500	Cardiovascular	AD	1.0	All P and LP
LDLR	606945	Familial hypercholesterolemia	143890	Cardiovascular	AD	1.0	All P and LP
LMNA	150330	Dilated cardiomyopathy	115200	Cardiovascular	AD	1.0	All P and LP
MAX	154950	Hereditary paraganglioma-pheochromocytoma syndrome	171300	Cancer	AD	3.0	All P and LP
MEN1	613733	Multiple endocrine neoplasia type 1	131100	Cancer	AD	1.0	All P and LP
MLH1	120436	Lynch syndrome	609310	Cancer	AD	1.0	All P and LP
MSH2	609309	Lynch syndrome	120435	Cancer	AD	1.0	All P and LP
MSH6	600678	Lynch syndrome	614350	Cancer	AD	1.0	All P and LP
MUTYH	604933	*MUTYH* -associated polyposis	608456	Cancer	AR	1.0	P and LP (2 variants)
MYBPC3	600958	Hypertrophic cardiomyopathy	115197	Cardiovascular	AD	1.0	All P and LP
MYH11	160745	Familial thoracic aortic aneurysm	132900	Cardiovascular	AD	1.0	All P and LP
MYH7	160760	Hypertrophic cardiomyopathy	192600	Cardiovascular	AD	1.0	All P and LP

MYH7	160760	Dilated cardiomyopathy	613426	Cardiovascular	AD	1.0	All P and LP
MYL2	160781	Hypertrophic cardiomyopathy	608758	Cardiovascular	AD	1.0	All P and LP
MYL3	160790	Hypertrophic cardiomyopathy	608751	Cardiovascular	AD	1.0	All P and LP
NF2	607379	*NF2* -related schwannomatosis	101000	Cancer	AD	1.0	All P and LP
OTC	300461	Ornithine transcarbamylase deficiency	311250	Metabolic	XL	2.0	All hemi, het, homozygous P and LP
PALB2	610355	Hereditary breast cancer	114480	Cancer	AD	3.0	All P and LP
PCSK9	607786	Familial hypercholesterolemia	603776	Cardiovascular	AD	1.0	All P and LP
PKP2	602861	Arrhythmogenic right ventricular cardiomyopathy	609040	Cardiovascular	AD	1.0	All P and LP
PLN	172405	Dilated cardiomyopathy	609909	Cardiovascular	AD	3.3	All P and LP
PMS2	600259	Lynch syndrome	614337	Cancer	AD	1.0	All P and LP
PRKAG2	602743	Hypertrophic cardiomyopathy	600858	Cardiovascular Metabolic	AD	1.0	All P and LP
PTEN	601728	*PTEN* hamartoma tumor syndrome	158350	Cancer	AD	1.0	All P and LP
RB1	614041	Retinoblastoma	180200	Cancer	AD	1.0	All P and LP
RBM20	613171	Dliated cardiomyopathy	613172	Cardiovascular	AD	3.1	All P and LP
RET	164761	Familial medullary thyroid cancer	155240	Cancer	AD	1.0	All P and LP
RET	164761	Multiple endocrine neoplasia type 2A	171400	Cancer	AD	1.0	All P and LP
RET	164761	Multiple endocrine neoplasia type 2B	162300	Cancer	AD	1.0	All P and LP
RPE65	180069	*RPE65* -related retinopathy	204100, 613794	Other	AR	3.0	P and LP (2 variants)
RYR1	180901	Malignant hyperthermia	145600	Other	AD	1.0	All P and LP
RYR2	180902	Catecholaminergic polymorphic ventricular tachycardia	604772	Cardiovascular	AD	1.0	All P and LP
SCN5A	600163	Long QT syndrome type 3	603830	Cardiovascular	AD	1.0	All P and LP
SCN5A	600163	Brugada syndrome	601144	Cardiovascular	AD	1.0	All P and LP
SCN5A	600163	Dilated cardiomyopathy	601154	Cardiovascular	AD	1.0	All P and LP
SDHAF2	613019	Hereditary paraganglioma-pheochromocytoma syndrome	601650	Cancer	AD	1.0	All P and LP
SDHB	185470	Hereditary paraganglioma-pheochromocytoma syndrome	115310, 171300	Cancer	AD	1.0	All P and LP
SDHC	602413	Hereditary paraganglioma-pheochromocytoma syndrome	605373	Cancer	AD	1.0	All P and LP
SDHD	602690	Hereditary paraganglioma-pheochromocytoma syndrome	168000, 171300	Cancer	AD	1.0	All P and LP
SMAD3	603109	Loeys-Dietz syndrome	613795	Cardiovascular	AD	1.0	All P and LP
SMAD4	600993	Juvenile polyposis syndrome	174900	Cancer	AD	1.0	All P and LP
SMAD4	600993	Hereditary hemorrhagic telangiectasia	175050	Other	AD	1.0	All P and LP
STK11	602216	Peutz-Jeghers syndrome	175200	Cancer	AD	1.0	All P and LP
TGFBR1	190181	Loeys-Dietz syndrome	609192	Cardiovascular	AD	1.0	All P and LP
TGFBR2	190182	Loeys-Dietz syndrome	610168	Cardiovascular	AD	1.0	All P and LP
TMEM127	613403	Hereditary paraganglioma-pheochromocytoma syndrome	171300	Cancer	AD	3.0	All P and LP
TMEM43	612048	Arrhythmogenic right ventricular cardiomyopathy	604400	Cardiovascular	AD	1.0	All P and LP
TNNC1	191040	Dilated cardiomyopathy	611879	Cardiovascular	AD	3.1	All P and LP
TNNI3	191044	Hypertrophic cardiomyopathy	613690	Cardiovascular	AD	1.0	All P and LP
TNNT2	191045	Dilated cardiomyopathy	601494	Cardiovascular	AD	1.0	All P and LP
TNNT2	191045	Hypertrophic cardiomyopathy	115195	Cardiovascular	AD	1.0	All P and LP
TP53	191170	Li-Fraumeni syndrome	151623	Cancer	AD	1.0	All P and LP
TPM1	191010	Hypertrophic cardiomyopathy	115196	Cardiovascular	AD	1.0	All P and LP
TRDN	603283	Catecholaminergic polymorphic ventricular tachycardia	615441	Cardiovascular	AR	3.0	All P and LP
TRDN	603283	Long QT syndrome	n/a	Cardiovascular	AR	3.0	All P and LP
TSC1	605284	Tuberous sclerosis complex	191100	Cancer	AD	1.0	All P and LP
TSC2	191092	Tuberous sclerosis complex	613254	Cancer	AD	1.0	All P and LP
TTN	188840	Dilated cardiomyopathy (truncating variants only)	604145	Cardiovascular	AD	3.0	P and LP (truncating variants only)
TTR	176300	Hereditary transthyretin-related amyloidosis	105210	Other	AD	3.1	All P and LP
VHL	608537	Von Hippel-Lindau syndrome	193300	Cancer	AD	1.0	All P and LP
WT1	607102	*WT1* -related Wilms tumor	194070	Cancer	AD	1.0	All P and LP

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