



ACMG STATEMENT

ACMG SF v3.1 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 (SF) in the context of clinical exome and genome

sequencing in 2013, 2017, and 2021.¹⁻³ The ACMG Secondary Findings Working Group (SFWG) and Board of Directors (BOD) 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 SF 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 BOD,² versioning of the SF list was designed to differentiate major vs minor revisions. Major 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 (v4.0, v5.0, etc). Minor revisions reflect the addition or removal of 1 or a few number of genes or variants without any policy change, and 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

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counselors, cardiologists, a bioinformatician, and a bioethicist. Since our last update, we have added 2 new members, one with expertise in biomedical ethics, and another with a research focus on genetic disorders in diverse populations. The SFWG has met at least once monthly via web conferencing to review nomination forms and vote on inclusion or exclusion of gene–phenotype pairs for the ACMG SF v3.1 list. Miller et al.³ provide details on the nomination and review process.

Internal nominations from SFWG committee members and external nominations were considered for SF v3.1. Internal nominations from committee members included *BAG3*, *DES*, *RBM20*, and *TNNC1* associated with dilated cardiomyopathy (DCM) and *RAD51C* and *RAD51D* associated with hereditary breast and ovarian cancer. External nominations were reviewed for *TTR*/hereditary TTR (transthyretin) amyloidosis and *RUNX1*/*RUNX1*-related thrombocytopenia, platelet defects, and risk for hematologic malignancies. No nominations were requested by other professional organizations, but going forward, we will accept this category of requests. The final proposed ACMG SF v3.1 list from the SFWG was sent to the ACMG BOD for review and approval in November 2021.

Recommendations for the ACMG SF V3.1 List

The overall charge 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 v3.1 list is presented in Table 1. In total, 5 new genes were added to the v3.1 list, as shown in Table 2, with a brief description of the factors considered in adding these genes. A list of 3 genes considered for inclusion, but ultimately excluded from the v3.1 list, are outlined in Table 3; these genes could be reviewed again in the future if new data emerge. *TTR* (transthyretin) was previously reviewed by the SFWG for *TTR*-associated amyloidosis and not included on the SF v3.0 list. However, this gene–phenotype pair was reconsidered and included in SF v3.1 because of the availability of new data on population prevalence and US Food and Drug Administration–approved treatments, demonstrating the fluidity of the SF list over time as new information emerges.

Penetrance is another factor that influenced our decision because we recognize that for many genes, the associated risk is an overestimate because of ascertainment from families affected by the disorder. For many genes, penetrance estimates will decrease over time with the availability of data sets that are larger and consist of more diverse populations and are consequently less susceptible to ascertainment bias. Thus, whenever possible, we used lifetime

penetrance estimates derived from larger cohorts that were sequenced regardless of phenotype (ie, ascertained by genotype). As an aside, we also considered penetrance in the context of other variables, such as severity of phenotype and availability of an intervention, precluding our ability to set a strict penetrance threshold.

Considerations for Specific Phenotypic Categories

Genes related to cancer phenotypes

Recommended for addition to the SF v3.1 list: none

The cancer subgroup prioritized new genes for consideration by soliciting nominations from the cancer genetics community and reviewing the recent literature on phenotype, penetrance, and actionability.

Table 3 lists the 3 cancer risk/hematology genes (*RUNX1*, *RAD51C*, and *RAD51D*) that were reviewed and discussed but not included, despite a well-established gene–phenotype relationship. For *RUNX1*, there are published Clinical Genome Resource variant interpretation guidelines and identification of a germline *RUNX1* variant that may alter clinical management.⁴ In this case, platelet infusions may be needed during childbirth and surgery and unnecessary splenectomies may be avoided. There is also an increased risk for myeloid malignancies, as recognized by the World Health Organization.⁵ However, the workgroup voted to not include *RUNX1* for multiple reasons, including (1) as with most genes, there are limited data on penetrance and prevalence from genomically ascertained (vs family- or clinic-based) cohorts, (2) need for confirmation of the germline nature of a *RUNX1* variant, which requires a skin biopsy for culture of fibroblasts (or use of DNA from a hair bulb or cultured mesenchymal stromal cells),⁴ potentially imposing a significant burden on clinicians and patients, and (3) a noncatastrophic clinical presentation. In addition, although the risk of myeloid malignancy is elevated,⁵ evidence-based guidance to ameliorate this risk remains lacking.

RAD51C/D were previously reviewed for inclusion on the ACMG SF v3.0 list regarding their association with ovarian cancer risk and were not included on the basis of penetrance considerations and the absence of effective ovarian cancer screening.³ The recent publication of 2 large population-based case-control studies reporting on the prevalence and risk of breast cancer for *RAD51C/D* led the committee to review these genes again for their association with breast cancer risk.^{6,7} These publications, and others,⁸ have reported a breast cancer risk of up to 30% for women with pathogenic variants in *RAD51C/D*, particularly for truncating variants and in association with ER-negative and triple negative breast cancer. *RAD51C/D*-related breast cancer risk also appears to be increased most significantly for later-onset disease.⁷

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

Phenotype	ACMG SF		Gene	Inheritance	Variants to Report ^a
	List	OMIM Disorder			
Genes related to cancer phenotypes					
FAP	1.0	175100	<i>APC</i>	AD	All P and LP
Familial medullary thyroid cancer	1.0	155240	<i>RET^b</i>	AD	All P and LP
Hereditary breast and/or ovarian cancer	1.0	604370	<i>BRCA1</i>	AD	All P and LP
	1.0	612555	<i>BRCA2</i>		
	3.0	114480	<i>PALB2</i>		
	1.0	168000	<i>SDHD</i>	AD	All P and LP
Hereditary paraganglioma-pheochromocytoma syndrome	1.0	601650	<i>SDHAF2</i>		
	1.0	605373	<i>SDHC</i>		
	1.0	115310	<i>SDHB</i>		
	3.0	171300	<i>MAX</i>		
	3.0	171300	<i>TMEM127</i>		
JPS	2.0	174900	<i>BMPR1A</i>	AD	All P and LP
	2.0		<i>SMAD4^c</i>		
Li–Fraumeni syndrome	1.0	151623	<i>TP53</i>	AD	All P and LP
Lynch syndrome (HNPCC)	1.0	609310	<i>MLH1</i>	AD	All P and LP
		120435	<i>MSH2</i>		
		614350	<i>MSH6</i>		
		614337	<i>PMS2</i>		
Multiple endocrine neoplasia type 1	1.0	131100	<i>MEN1</i>	AD	All P and LP
MAP	1.0	608456	<i>MUTYH</i>	AR	P and LP (2 variants)
Neurofibromatosis type 2	1.0	101000	<i>NF2</i>	AD	All P and LP
PJS	1.0	175200	<i>STK11</i>	AD	All P and LP
<i>PTEN</i> hamartoma tumor syndrome	1.0	158350	<i>PTEN</i>	AD	All P and LP
Retinoblastoma	1.0	180200	<i>RB1</i>	AD	All P and LP
Tuberous sclerosis complex	1.0	191100	<i>TSC1</i>	AD	All P and LP
	1.0	613254	<i>TSC2</i>		
von Hippel-Lindau syndrome	1.0	193300	<i>VHL</i>	AD	All P and LP
<i>WT1</i> -related Wilms tumor	1.0	194070	<i>WT1</i>	AD	All P and LP
Genes related to cardiovascular phenotypes					
Aortopathies	1.0	154700	<i>FBN1</i>	AD	All P and LP
	1.0	609192	<i>TGFBR1</i>		
	1.0	610168	<i>TGFBR2</i>		
	1.0	613795	<i>SMAD3</i>		
	1.0	611788	<i>ACTA2</i>		
	1.0	132900	<i>MYH11</i>		
Arrhythmogenic right ventricular cardiomyopathy (a subcategory of ACM)	1.0	609040	<i>PKP2</i>	AD	All P and LP
	1.0	607450	<i>DSP^d</i>		
	1.0	610476	<i>DSC2</i>		
	1.0	604400	<i>TMEM43</i>		
Catecholaminergic polymorphic ventricular tachycardia	1.0	610193	<i>DSG2</i>		
	1.0	604772	<i>RYR2</i>	AD	All P and LP
	3.0	611938	<i>CASQ2</i>	AR	P and LP (2 variants)
Dilated cardiomyopathy	3.0	615441	<i>TRDN^e</i>	AR	
	1.0	601494	<i>TNNT2^f</i>	AD	All P and LP
	1.0	115200	<i>LMNA^g</i>		See text
	3.0	617047	<i>FLNC^g</i>		
	3.0	604145	<i>TTN^h</i>		
	3.1	613881	<i>BAG3^g</i>		
	3.1	604765	<i>DES^g</i>		
	3.1	613172	<i>RBM20</i>		
Ehlers-Danlos syndrome, vascular type	1.0	130050	<i>COL3A1</i>	AD	All P and LP
	1.0	143890	<i>LDLR</i>	SD	All P and LP
Familial hypercholesterolemia	1.0	144010	<i>APOB</i>	AD	
	1.0	603776	<i>PCSK9</i>	AD	

(continued)

Table 1 Continued

Phenotype	ACMG SF		Gene	Inheritance	Variants to Report ^a
	List	Version			
Hypertrophic cardiomyopathy ⁱ	1.0	192600	<i>MYH7</i> ^d	AD	All P and LP
	1.0	115197	<i>MYBPC3</i>		
	1.0	613690	<i>TNNI3</i>		
	1.0	115196	<i>TPM1</i>		
	1.0	608751	<i>MYL3</i>		
	1.0	612098	<i>ACTC1</i>		
	1.0	600858	<i>PRKAG2</i> ^j		
	1.0	608758	<i>MYL2</i>		
Long QT syndrome types 1 and 2	1.0	192500	<i>KCNQ1</i>	AD	All P and LP
	1.0	613688	<i>KCNH2</i>		
Long QT syndrome 3, Brugada syndrome	1.0	603830, 601144	<i>SCN5A</i> ^d	AD	All P and LP
Genes related to inborn errors of metabolism phenotypes					
Biotinidase deficiency	3.0	253260	<i>BTD</i>	AR	P and LP (2 variants)
Fabry disease	1.0	301500	<i>GLA</i> ^k	XL	All hemi, het, homozygous P and LP
Ornithine transcarbamylase deficiency	2.0	311250	<i>OTC</i>	XL	All hemi, het, homozygous P and LP
Pompe disease	3.0	232300	<i>GAA</i>	AR	P and LP (2 variants)
Genes related to miscellaneous phenotypes					
Hereditary hemochromatosis	3.0	235200	<i>HFE</i>	AR	<i>HFE</i> p.C282Y ^l homozygotes only
Hereditary hemorrhagic telangiectasia	3.0	600376	<i>ACVRL1</i>	AD	All P and LP
	3.0	187300	<i>ENG</i>		
Malignant hyperthermia	1.0	145600	<i>RYR1</i>	AD	All P and LP
	1.0	601887	<i>CACNA1S</i>		
Maturity-onset of diabetes of the young	3.0	600496	<i>HNF1A</i>	AD	All P and LP
<i>RPE65</i> -related retinopathy	3.0	204100, 613794	<i>RPE65</i>	AR	P and LP (2 variants)
	2.0	277900	<i>ATP7B</i>		
Wilson disease	2.0	277900	<i>ATP7B</i>	AR	P and LP (2 variants)
Hereditary TTR amyloidosis	3.1	105210	<i>TTR</i>	AD	All P and LP

ACM, arrhythmogenic cardiomyopathy; *ACMG*, American College of Medical Genetics and Genomics; *AD*, autosomal dominant; *AR*, autosomal recessive; *FAP*, familial adenomatous polyposis; *hemi*, hemizygous; *het*, heterozygous; *HNPCC*, hereditary nonpolyposis colorectal cancer; *JPS*, juvenile polyposis syndrome; *LP*, likely pathogenic; *MAP*, *MUTYH*-associated polyposis; *P*, pathogenic; *PJS*, Peutz-Jeghers syndrome; *SD*, semidominant; *TTR*, transthyretin; *XL*, X-linked.

^aVariants 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 because 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, heterozygous, or homozygous should be reported because 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.

^bAlso associated with multiple endocrine neoplasia type 2.

^cAlso associated with hereditary hemorrhagic telangiectasia.

^dAlso associated with dilated cardiomyopathy (DCM) as a primary disease.

^eAlso associated with long QT syndrome.

^fAlso associated with hypertrophic cardiomyopathy (HCM).

^gAlso associated with a skeletal myopathy (ie, myofibrillar myopathy).

^hOnly loss-of-function variants should be reported as a secondary finding.

ⁱIndividuals with primary HCM may present in late stage disease with a DCM phenotype.

^jPathogenic variants in this gene are associated with a metabolic storage disease that mimics HCM, but also can involve skeletal muscle.

^kGene also applies to the cardiovascular category.

^lTranscript for the *HFE* gene is NM_000410.3.

Discussions related to the inclusion of other moderate penetrance breast cancer genes (eg, *ATM* and *CHEK2*) on the SF list are ongoing in the context of our goals to maintain a minimum list of genes for recommended return and to consistently apply the principle of treat like cases alike (see later). Thus, the committee decided not to add *RAD51C/D* to the SF v3.1 list.

Genes related to cardiovascular phenotypes

Recommended for addition to the SF v3.1 list: *TNNC1*, *RBM20*, *BAG3*, *DES*

Cardiovascular genes have been represented on the SF list since its inception, owing to the morbidity and mortality of heart failure and sudden cardiac death (SCD), which can

Table 2 New gene/phenotype pairs for SF v3.1 list

Gene/Phenotype	Additional Comments
Genes related to cardiovascular phenotypes	
<i>BAG3</i> /cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list; also associated with skeletal myopathy
<i>DES</i> /cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list; also associated with skeletal myopathy
<i>RBM20</i> /cardiomyopathy	Clear screening guidelines endorsed by ACMG; missense in 5 codons are known P/LP; few examples of LoF that are P/LP
<i>TNNC1</i> /cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list
Genes related to miscellaneous phenotypes	
<i>TTR</i> /hereditary TTR (transthyretin) amyloidosis	Nonspecific features leading to potential morbidity (heart failure); availability of treatment that may be more efficacious earlier in disease progression; high prevalence in individuals with West African ancestry

ACMG, American College of Medical Genetics and Genomics; DCM, dilated cardiomyopathy; LoF, loss of functions; LP, likely pathogenic; P, pathogenic.

both be treated or prevented with well-established interventions.^{9,10}

Primary arrhythmia risk, which may lead to presyncope, syncope, and SCD, arises in genes encompassed by the channelopathies. With established risk, the use of antiarrhythmic medications or implantable cardioverter defibrillators can greatly reduce the risk of SCD and morbidity. The cardiomyopathies, classified as diseases of the myocardium, can also cause lethal arrhythmias. The cardiomyopathies also lead to heart failure, which is not only a morbid and mortal condition in itself but also one that may be attenuated in disease progression by medical and device therapies. With this in mind, the SFWG reviewed the evidence for nominated cardiovascular genes with a particular focus on the actionability of a potential SF, the penetrance and expressivity of the given gene (data that are limited in unselected populations), and the potential burden on providers and clinical laboratories, should the gene be included.

For v3.1, the SFWG voted to include 4 additional genes associated with DCM predisposition (*TNNC1*, *RBM20*, *BAG3*, and *DES*); review of evidence for all 4 genes showed a similar or greater risk of morbidity and mortality as other DCM genes already included in previous iterations.

Pathogenic and likely pathogenic (P/LP) variants in *RBM20* significantly predispose individuals to high-risk DCM.¹¹ Importantly, there is a stretch of 5 amino acids (p.Arg634-p.Pro638) that is important for nuclear

localization of the protein, and the majority of the known DCM causing missense variants in *RBM20* are located in this region.^{11,12} It is unknown if missense variants outside this domain in *RBM20* are causative for DCM. The SFWG voted to include this gene on the basis of the severity of the phenotype if untreated and the strong potential benefit of intervention based on returning P/LP variants in this gene as an SF.

Similarly, P/LP variants in *TNNC1*, *BAG3*, and *DES* also significantly predispose individuals to DCM.¹³⁻¹⁶ Owing to the severity of the DCM phenotype if untreated and the strong potential benefit of intervention based on returning P/LP variants in this gene, the SFWG voted to include these 3 genes on the list.

Genes related to other phenotypes

Recommended for addition to the SF list: *TTR*

The working group has established criteria that it uses in determining whether a gene should be added to the SF gene list. Although the SFWG is not revising those criteria, the working group's discussion on *TTR* uncovered important nuances related to the application of these criteria in the context of genetic variants that are more common in ancestry groups that are underrepresented in genomics research. The working group is inclined to treat like cases alike, a principle that has both scientific and ethical dimensions. Specifically, when a gene is placed on the list,

Table 3 Genes not selected for SF v3.1 list

Gene/Phenotype	Category	Additional Comments
<i>RAD51C</i> /breast and ovarian cancer	Cancer	Moderate risk of primarily later-onset breast cancer and low penetrance for ovarian cancer
<i>RAD51D</i> /breast and ovarian cancer	Cancer	Moderate risk of primarily later-onset breast cancer and low penetrance for ovarian cancer
<i>RUNX1</i> /RUNX1-related thrombocytopenia, platelet defects, and risk for hematologic malignancies	Hematology/cancer	Limited data on prevalence and penetrance, especially from genomically ascertained cohorts; need for confirmation from skin fibroblast to confirm germline origin of variant

genes with substantially similar features should also be considered. As mentioned earlier, this principle was also part of the discussions when reviewing DCM-related genes and the cancer risk genes *RAD51C/D*. In the context of *TTR*, the working group considered comments submitted by the community observing that hereditary transthyretin amyloidosis shares a number of features with hereditary hemochromatosis, in that both conditions are progressive infiltrative diseases that result in end-organ damage, including cardiomyopathy. Because of the insidious and nonspecific nature of its symptoms, hereditary transthyretin amyloidosis remains an under-recognized but treatable cause of heart failure.¹⁷

A relevant difference between these conditions relates to the populations most frequently affected. The most common pathogenic variants in *HFE* are present in individuals of European descent, whereas the most common pathogenic variant in *TTR* worldwide, p.Val142Ile (p.V142I), has a particularly high frequency (1%-2.5%) in individuals with West African ancestry and is a common cause of heart failure in persons of African descent.¹⁸ This difference is of critical importance because the rarity and penetrance of pathogenic variants are considered relevant characteristics in the working group's deliberations on adding a gene-condition pair to the SF gene list. Specifically, when pathogenic variants are exceptionally rare or the penetrance is low (or when these values are unknown), the case for adding a gene to the SF gene list is weakened. As the SFWG has noted previously, however, there is no firm cutoff for either frequency or penetrance.

Although the rarity of a condition and the penetrance of pathogenic variants are factors that we consider in adding a gene or class of genetic variants to the list, the SFWG determined that genes associated with conditions that disproportionately affect 1 or more minoritized group will not be penalized if they are rare or have lower penetrance in the US population as a whole. In other words, we assess rarity and penetrance in the context of specific populations so as not to perpetuate or exacerbate existing disparities in genomic medicine.^{19,20} From an ethical perspective, then, the working group takes an equity approach (considering what each population needs to maximize health) rather than an equality approach (treating each population identically). To foster equity, the working group is committed to identifying genes and genetic variants that disproportionately affect diverse, historically underrepresented populations in an effort to reduce health disparities.

Conclusion

With the recent publication of the SF policy statements for reporting of SF and updating the SF gene list,^{3,21} 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 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.

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 on the basis of 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. 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.

Acknowledgments

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In memoriam

We would like to acknowledge our sadness at the loss of one of our dear colleagues and ACMG Secondary Findings Working Group members, Kent McKelvey, who passed in January 2022 after a prolonged illness. Kent persevered through his illness with cheery optimism and an unwavering dedication to community service, and we will miss him dearly.

Conflict of Interest

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Additional Information

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