

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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8 2025 23 6 2025 27 8 494325 101454 101454 21 05 2025 23 06 2026 23 06 2026 05 08 2025 23 06 2026 This file is available for text mining. It may also be used consistent with the principles of fair use under the copyright law. exome sequencing genome sequencing incidental findings secondary findings pmc-status-qastatus 0 pmc-status-live yes pmc-status-embargo no pmc-status-released yes pmc-prop-open-access no pmc-prop-olf no pmc-prop-manuscript yes pmc-prop-open-manuscript yes pmc-prop-legally-suppressed no pmc-prop-has-pdf yes pmc-prop-has-supplement yes pmc-prop-pdf-only no pmc-prop-suppress-copyright no pmc-prop-is-real-version no pmc-prop-is-scanned-article no pmc-prop-preprint no pmc-prop-in-epmc yes 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. 1 – 7 The ACMG Secondary Findings Working Group (SFWG) and Board of Directors (BOD) have agreed that the list of recommended genes should be updated annually, and 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.

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, CA. Among other agenda items, the SFWG reviewed nomination forms and voted on inclusion or exclusion of gene-disease nominations to update the ACMG Secondary Findings (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 one 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), ovalocytosis, 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 Board of Directors 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>).

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 potentials 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 secondary finding for adult-onset conditions. 3 While 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 is available to inform a vote. No nominations for genes to be considered for removal from the SF list were received.

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 non-catastrophic 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, hematologic malignancy risk was high (62% of families), as was thrombocytopenia (91%) and abnormal bleeding scores (51%). However, penetrance data in an unselected population still remains 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 CBCs (or bone marrow biopsies) is efficacious. 9

Cardiovascular genes continue to be frequently nominated and included on the SF list due to 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, one 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 10–15% of patients with DCM or ARVC in the Netherlands; this variant has been reported in individuals from the USA, 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) carriers 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 carriers beginning in adolescence. 13

The X-linked gene, ABCD1, was nominated for reconsideration for the SF v3.3 list by two 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 (X-ALD) 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 two 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 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 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 due to NBS. However, for the ABCD1 gene, there are acknowledged gaps in the screening of individuals at this time, as 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 1/14,000 to 1/4,000 (F. Eichler, personal communication, June 25, 2024) with the initiation of newborn screening for this disorder. 24 This data raises 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 potential difficulty 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) pathogenic and likely pathogenic (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 due to 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), that is FDA approved for another indication but used off label in CTX and 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 CDCA. 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 CPY27A1 gene has been added to the SF v3.3 list.

The ADA2 gene was nominated for inclusion on the SF v3.3 list due to its association with deficiency of adenosine deaminase 2 (DADA2). The nomination noted that while there are other genes associated with similar phenotypes that could be considered for addition, pathogenic variants in ADA2 posed particular diagnostic challenges due to variable expressivity. This autosomal recessive complex systemic autoinflammatory disorder involving vasculopathy, immune dysfunction and hematologic abnormalities tends to demonstrate intra- and inter-familial phenotypic variability, including age of onset and severity. 32 There is evidence that use of anti-tumor 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 since 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 (GCK-MODY), 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, since 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, since this list has generally not included genes where 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, ovalocytosis, Southeast Asian (SA) type and autosomal dominant distal renal tubular acidosis. There were concerns that the severity of these disorders, if discovered as a secondary finding, 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 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

The ACMG SFWG reviewed seven 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, while 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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The Board of Directors of the American College of Medical Genetics and Genomics approved this statement on 24 February 2025.

The online version of this article contains supplementary material , which is available to authorized users.

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

AD, autosomal dominant; AR, autosomal recessive; Hemi, hemizygous; Het, heterozygous; LP, likely pathogenic; MIM, Mendelian Inheritance of Man; P pathogenic; SD semidominant; XL X-linked.

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 two 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 amelioration of disease is available. Variants of uncertain significance should not be reported in any gene.

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

Also associated with hypertrophic cardiomyopathy (HCM).

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.

Only truncating variants in the Titin gene (TTN tv) should be reported as a secondary finding.

Also associated with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Also associated with catecholaminergic polymorphic ventricular tachycardia

Gene also applies to the cardiovascular category.

Transcript for the HFE gene is NM_000410.3 .

A single heterozygous P/LP variants should not be reported.

New gene/phenotype pairs for SF v3.3 list