

ACMG update to secondary findings gene list adds five genes, including one linked to heart failure

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The American College of Medical Genetics and Genomics (ACMG) has released an update to the recommended minimum gene list for the

reporting of secondary findings (SF). In 2021, the ACMG Board of Directors and Secondary Findings Working Group (SFWG) declared that the College would update the list (SF v3.0) annually. Today's update (SF v3.1) adds five new genes—four associated with dilated cardiomyopathy predisposition and one associated with hereditary transthyretin amyloidosis, a cause of heart failure.

The paper "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)" represents the work of an expanded SFWG since the last update, with the addition of an expert in biomedical ethics and another in genetic disorders in diverse populations. The paper is being published in ACMG's official journal, *Genetics in Medicine*.

"The v3.1 list is the first of our ongoing yearly updates and embodies our working group's goals of maintaining a minimum list of actionable results that will impact patients and their families in a positive way," said lead author and co-chair of the ACMG SFWG, David T. Miller, MD, Ph.D., FACMG.

Christa L. Martin, Ph.D., FACMG and co-chair of the SFWG added, "We recognize that ethical issues are important in genomics and diversity is also a continued priority for the College, therefore we added two new members to the SFWG, one with expertise in biomedical ethics and another with expertise in genetic disorders in diverse populations. Their contributions were instrumental to this update."

Guidance from the original ACMG policy statement on incidental (updated later to the current term, "secondary") findings in 2013 established that clinical laboratories performing exome or [genome sequencing](#) should report a "minimum list" of known pathogenic or expected pathogenic variants in a defined set of genes considered

medically actionable, even when unrelated to the primary medical reasons for testing. In May 2021, the ACMG's SFWG issued "ACMG SF v3.0 List for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing: a Policy Statement of the American College of Medical Genetics and Genomics," which included 73 genes and was the most cited article that ACMG published last year.

The ACMG SF v3.1 adds five genes

While cardiovascular genes have been represented on the SF list since its first iteration due to the morbidity and mortality of heart failure (HF) and sudden cardiac death (SCD), for SF v3.1 the SFWG voted to include four additional genes associated with dilated cardiomyopathy (DCM) predisposition: TNNC1, RBM20, BAG3 and DES. The decision is based on evidence that all four genes significantly predispose individuals to DCM at a similar or greater level of risk for morbidity and mortality as other DCM genes already included in previous iterations of the list.

The fifth and final gene added to the SF v3.1 list is TTR (transthyretin). Previously reviewed by the SFWG for TTR-associated amyloidosis but not included on the SF v3.0 list, TTR was reconsidered and included in this update due to the availability of new data on population prevalence and FDA-approved treatments.

In its discussion on TTR, the SFWG found subtle differences related to the application of its established criteria in the context of genetic variants that are more common in ancestry groups that are underrepresented in genomics research. The SFWG considered comments submitted by the community observing that hereditary transthyretin amyloidosis (hATTR) shares a number of features with hereditary hemochromatosis, a condition with an associated gene (HFE) that is already on SF v3.0. Both conditions are progressive infiltrative diseases that result in end-organ damage, including cardiomyopathy.

However, while the most common pathogenic variants in hereditary hemochromatosis are present in individuals of European descent, the most common pathogenic variant in TTR occurs with particularly high frequency in individuals with West African ancestry.

While the rarity of a condition and the penetrance of pathogenic variants are factors that the SFWG considers when adding a gene or class of genetic variants to the list, the authors state that the working group "determined that genes associated with conditions that disproportionately affect one 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."

Genes considered but excluded from ACMG SF v3.1

The paper also provides background on three [cancer risk](#)/hematology genes that were considered but eventually excluded from the SF v3.1 update: RUNX1, RAD51C and RAD51D.

The workgroup voted to not include RUNX1 for three reasons stated in the paper, including limited data on penetrance and prevalence from genomically ascertained (as opposed to family- or clinic-based) cohorts.

RAD51C/D were previously reviewed for inclusion on the ACMG SF v3.0 list regarding their association with ovarian cancer risk. Due to the release of two recent large population breast cancer studies, the workgroup revisited these genes with regard to breast cancer risk. Rationale is provided for omitting RAD51C/D. The SFWG is already discussing other moderate penetrance breast cancer genes and has established criteria to "maintain a minimum list of [genes](#) for recommended return" and to "treat like cases alike."

More information: David T. Miller et al, 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), *Genetics in Medicine* (2022). [DOI: 10.1016/j.gim.2022.04.006](https://doi.org/10.1016/j.gim.2022.04.006)

David T. Miller et al, Correction to: ACMG SF v3.0 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), *Genetics in Medicine* (2021). [DOI: 10.1038/s41436-021-01278-8](https://doi.org/10.1038/s41436-021-01278-8)

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