Genetics in Medicine (2022) 24, 1407–1414

ELSEVIER

Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

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)

ARTICLE INFO

Article history:
Received 29 March 2022
Accepted 1 April 2022
Available online 17 June 2022

Keywords:
Exome sequencing
Genome sequencing
Incidental findings
Secondary findings

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

The Board of Directors of the American College of Medical Genetics and Genomics approved this statement on February 28, 2022.
*Correspondence: ACMG. *E-mail address:* documents@acmg.net
A full list of authors and affiliations appears at the end of the paper.

doi: https://doi.org/10.1016/j.gim.2022.04.006

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 List Version	OMIM Disorder	Gene	Inheritance	Variants to Report[a]
Genes related to cancer phenotypes					
FAP	1.0	175100	*APC*	AD	All P and LP
Familial medullary thyroid cancer	1.0	155240	*RET*[b]	AD	All P and LP
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*		
JPS	2.0	174900	*BMPR1A*	AD	All P and LP
	2.0		*SMAD4*[c]		
Li–Fraumeni syndrome	1.0	151623	*TP53*	AD	All P and LP
Lynch syndrome (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
MAP	1.0	608456	*MUTYH*	AR	P and LP (2 variants)
Neurofibromatosis type 2	1.0	101000	*NF2*	AD	All P and LP
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 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 ACM)	1.0	609040	*PKP2*	AD	All P and LP
	1.0	607450	*DSP*[d]		
	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*[e]	AR	
Dilated cardiomyopathy	1.0	601494	*TNNT2*[f]	AD	All P and LP
	1.0	115200	*LMNA*[g]		See text
	3.0	617047	*FLNC*[g]		
	3.0	604145	*TTN*[h]		
	3.1	613881	*BAG3*[g]		
	3.1	604765	*DES*[g]		
	3.1	613172	*RBM20*		
	3.1	611879	*TNNC1*		
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	

(continued)

Table 1 Continued

Phenotype	ACMG SF List Version	OMIM Disorder	Gene	Inheritance	Variants to Report[a]
Hypertrophic cardiomyopathy[i]	1.0	192600	*MYH7*[d]	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*[j]		
	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*[d]	AD	All P and LP
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*[k]	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[l] homozygotes only
Hereditary hemorrhagic telangiectasia	3.0	600376	*ACVRL1*	AD	All P and LP
	3.0	187300	*ENG*		
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, 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

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.

[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 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.

[b]Also associated with multiple endocrine neoplasia type 2.

[c]Also associated with hereditary hemorrhagic telangiectasia.

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

[e]Also associated with long QT syndrome.

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

[g]Also associated with a skeletal myopathy (ie, myofibrillar myopathy).

[h]Only loss-of-function variants should be reported as a secondary finding.

[i]Individuals with primary HCM may present in late stage disease with a DCM phenotype.

[j]Pathogenic variants in this gene are associated with a metabolic storage disease that mimics HCM, but also can involve skeletal muscle.

[k]Gene also applies to the cardiovascular category.

[l]Transcript 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	
BAG3/cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list; also associated with skeletal myopathy
DES/cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list; also associated with skeletal myopathy
RBM20/cardiomyopathy	Clear screening guidelines endorsed by ACMG; missense in 5 codons are known P/LP; few examples of LoF that are P/LP
TNNC1/cardiomyopathy	Similar prevalence/penetrance rates to other DCM genes already on ACMG SF list
Genes related to miscellaneous phenotypes	
TTR/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
RAD51C/breast and ovarian cancer	Cancer	Moderate risk of primarily later-onset breast cancer and low penetrance for ovarian cancer
RAD51D/breast and ovarian cancer	Cancer	Moderate risk of primarily later-onset breast cancer and low penetrance for ovarian cancer
RUNX1/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

We are grateful to the Clinical Genome Resource Actionability Working Group for their evaluations of the genes that we reviewed. We would also like to acknowledge the input of external experts to inform our reviews of *TTR* and *RUNX1*, including Mathew Maurer, Columbia University (*TTR*); Christopher Haggerty, Geisinger (*TTR*); Brendan Carry, Geisinger (*TTR*); Janina Jeff, Illumina, Inc (*TTR*); Lucy Godley, The University of Chicago (*RUNX1*); and David Wu, University of Washington (*RUNX1*).

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

Funding and support listed here did not support development of this document unless included in the Acknowledgments section. N.S.A.-H. was previously employed by the Regeneron Genetics Center, has received an honorarium from Genentech, and is a member of the scientific advisory

board of Allelica, Inc. W.K.C. is a member of the scientific advisory board of Regeneron Genetics Center. D.T.M. has received honoraria from Ambry Genetics and PreventionGenetics LLC. D.R.S. is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute, Rockville, MD, United States, and also performs contract clinical telehealth services for Genome Medical, Inc in accordance with relevant National Cancer Institute ethics policies. All other authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2021.04.006) contains supplementary material, which is available to authorized users.

Authors

David T. Miller[1], Kristy Lee[2], Noura S. Abul-Husn[3], Laura M. Amendola[4], Kyle Brothers[5], Wendy K. Chung[6], Michael H. Gollob[7], Adam S. Gordon[8], Steven M. Harrison[9], Ray E. Hershberger[10], Teri E. Klein[11], Carolyn Sue Richards[12], Douglas R. Stewart[13], Christa Lese Martin[14]; on behalf of the ACMG Secondary Findings Working Group[15,*]

Affiliations

[1]Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA; [2]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Departments of Medicine and Genetics and Genomic Sciences, Institute for Genomic Health, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Illumina Inc, San Diego, CA; [5]Department of Pediatrics, University of Louisville, Louisville, KY; [6]Departments of Pediatrics and Medicine, Columbia University, New York, NY; [7]Division of Cardiology, Department of Physiology, University of Toronto, Toronto, Ontario, Canada; [8]Department of Pharmacology, Center for Genetic Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; [9]Ambry Genetics, Aliso Viejo, CA; [10]Divisions of Human Genetics and Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University, Columbus, OH; [11]Departments of Biomedical Data Science and Medicine, Stanford University, Stanford, CA; [12]Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland, OR; [13]Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD; [14]Autism & Developmental Medicine Institute, Geisinger, Danville, PA; [15]American College of Medical Genetics and Genomics, Bethesda, MD

References

1. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565–574. http://doi.org/10.1038/gim.2013.73.
2. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017;19(2):249–255. http://doi.org/10.1038/gim.2016.190.
3. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1391–1398. http://doi.org/10.1038/s41436-021-01171-4.
4. Luo X, Feurstein S, Mohan S, et al. ClinGen Myeloid Malignancy Variant Curation Expert Panel recommendations for germline RUNX1 variants. *Blood Adv*. 2019;3(20):2962–2979. http://doi.org/10.1182/bloodadvances.2019000644.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. http://doi.org/10.1182/blood-2016-03-643544.
6. Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med*. 2021;384(5):440–451. http://doi.org/10.1056/NEJMoa2005936.
7. Dorling L, Carvalho S, Allen J, et al. Breast cancer risk genes—association analysis in more than 113,000 women. *N Engl J Med*. 2021;384(5):428–439. http://doi.org/10.1056/NEJMoa1913948.
8. Yang X, Song H, Leslie G, et al. Ovarian and breast cancer risks associated with pathogenic variants in RAD51C and RAD51D. *J Natl Cancer Inst*. 2020;112(12):1242–1250. http://doi.org/10.1093/jnci/djaa030.
9. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy-a Heart Failure Society of America practice guideline. *J Card Fail*. 2018;24(5):281–302. http://doi.org/10.1016/j.cardfail.2018.03.004.
10. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138(13):e272–e391. http://doi.org/10.1161/CIR.0000000000000549.
11. Brauch KM, Karst ML, Herron KJ, et al. Mutations in ribonucleic acid binding protein gene cause familial dilated cardiomyopathy. *J Am Coll Cardiol*. 2009;54(10):930–941. http://doi.org/10.1016/j.jacc.2009.05.038.
12. Filippello A, Lorenzi P, Bergamo E, Romanelli MG. Identification of nuclear retention domains in the RBM20 protein. *FEBS Lett*. 2013;587(18):2989–2995. http://doi.org/10.1016/j.febslet.2013.07.018.
13. Mogensen J, Murphy RT, Shaw T, et al. Severe disease expression of cardiac troponin C and T mutations in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 2004;44(10):2033–2040. http://doi.org/10.1016/j.jacc.2004.08.027.
14. Jordan E, Peterson L, Ai T, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144(1):7–19. http://doi.org/10.1161/CIRCULATIONAHA.120.053033.
15. Myers VD, Gerhard GS, McNamara DM, et al. Association of variants in BAG3 with cardiomyopathy outcomes in African American individuals. *JAMA Cardiol*. 2018;3(10):929–938. http://doi.org/10.1001/jamacardio.2018.2541.
16. Brodehl A, Gaertner-Rommel A, Milting H. Molecular insights into cardiomyopathies associated with desmin (DES) mutations. *Biophys Rev*. 2018;10(4):983–1006. http://doi.org/10.1007/s12551-018-0429-0.
17. Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure

among individuals of African or Hispanic/Latino Ancestry. *JAMA*. 2019;322(22):2191–2202. http://doi.org/10.1001/jama.2019.17935.

18. Jacobson DR, Alexander AA, Tagoe C, et al. The prevalence and distribution of the amyloidogenic transthyretin (TTR) V122I allele in Africa. *Mol Genet Genomic Med*. 2016;4(5):548–556. http://doi.org/10.1002/mgg3.231.
19. Gurdasani D, Barroso I, Zeggini E, Sandhu MS. Genomics of disease risk in globally diverse populations. *Nat Rev Genet*. 2019;20(9):520–535. http://doi.org/10.1038/s41576-019-0144-0.
20. Smith CE, Fullerton SM, Dookeran KA, et al. Using genetic technologies to reduce, rather than widen, health disparities. *Health Aff (Millwood)*. 2016;35(8):1367–1373. http://doi.org/10.1377/hlthaff.2015.1476.
21. Miller DT, Lee K, Chung WK, et al. 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). *Genet Med*. 2021;23(8):1381–1390. Published correction appears in *Genet Med*. 2021;23(8):1582–1584. https://doi.org/10.1038/s41436-021-01172-3.

"The ACMG Secondary Findings v3.1 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
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	Miscellaneous	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	Miscellaneous	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	Miscellaneous	AD	1.0	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
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	Miscellaneous	AD	3.0	All P and LP
FBN1	134797	Marfan syndrome	154700	Cardiovascular	AD	1.0	All P and LP
FLNC	102565	Dilated 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 Cardiovascular	AR	3.0	P and LP (2 variants)
GLA	300644	Fabry disease	301500	Metabolic	XL	1.0	All hemi, het, homozygous P and LP
HFE	613609	Hereditary hemochromatosis (c.845G>A; p.C282Y homozygotes only)	235200	Miscellaneous	AR	3.0	p.C282Y homozygotes only
HNF1A	142410	Maturity-Onset of Diabetes of the Young	600496	Miscellaneous	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	Neurofibromatosis type 2	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
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	Miscellaneous	AR	3.0	P and LP (2 variants)
RYR1	180901	Malignant hyperthermia	145600	Miscellaneous	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	Miscellaneous	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	Miscellaneous	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

Disclaimer: This statement is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. Adherence to this statement is completely voluntary and does not necessarily assure a successful medical outcome. This statement should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, clinicians should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this statement. Clinicians also are advised to take notice of the date this statement was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.