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ACMG STATEMENT

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)

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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.

INTRODUCTION

The American College of Medical Genetics and Genomics (ACMG) previously published guidance for reporting secondary findings in the context of clinical exome and genome sequencing (ES/GS) in 2013 and 2017.[1,2] These recommendations were developed by the ACMG Secondary Findings Maintenance Working Group (SFWG), which was convened by the ACMG Board of Directors (BOD) to evaluate the need for a minimum list of genes that should be evaluated in individuals undergoing clinical ES/GS based on the medical actionability of the associated condition. In the past, policy recommendations concerning what types of variants to return along with lists of which genes to analyze were included. Given the increase in uptake of clinical ES/GS, the ACMG SFWG and BOD have agreed the list of recommended genes should now be updated annually. Policy updates surrounding the purpose, scope, and process for maintaining the ACMG Secondary Findings List are being published separately,[3] and will be updated separately, as needed. It is important to reiterate here that use of the SF results should not be a replacement for indication-based diagnostic clinical genetic testing.

The goal of the SF gene list is to guide clinical laboratories as to which medically actionable genes unrelated to the indication for testing should be evaluated as part of clinical ES/GS, while maintaining a minimum list to balance the interests of patients with the additional burden placed on laboratories providing sequencing. The SFWG members took several aspects of the associated phenotype into consideration to evaluate genes for this list, including the actionability, severity, penetrance, and impact and/or burden of available treatment modalities or screening recommendations. The SFWG was also mindful to recommend genes where the majority of pathogenic variants are detectable by ES/GS. For instance, no gene–phenotype pairs caused by trinucleotide repeats were considered for this list. Even with these restrictions, there are still many gene–phenotype pairs that could be considered for inclusion on the ACMG SF list; however, the SFWG and BOD felt a duty to keep this list to a manageable number. Therefore, members worked toward making compromises by, for example, avoiding inclusion of disorders that would typically be diagnosed clinically, disorders where timing of the diagnosis was not critical for treatment efficacy, or disorders

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where a lifestyle change was the prominent intervention (e.g., avoiding tobacco use). Here, we present the ACMG SF v3.0 list, its development using the policies described in the ACMG SF Policy Statement and our rationale for and against inclusion of considered genes.

WORKING GROUP OPERATIONS

The 2018–2021 SFWG is composed of six biochemical, molecular, and/or cytogenetics clinical laboratory directors, five clinical geneticists of differing subspecialities, two genetic counselors, two cardiologists, one PhD medical geneticist, one pharmacogenomics expert, and one patient advocate. An ACMG board liaison was added to support clear communication of standards and expectations between the Board and the SFWG. The SFWG meets at least monthly via virtual web conferencing and also in-person during the ACMG and American Society of Human Genetics annual conferences to review nomination forms and vote on inclusion or exclusion of gene–phenotype topics. For all meetings, regardless of whether they are virtual or in-person, we follow established ACMG committee and working group policies for review of nominations and voting.

NOMINATION AND REVIEW PROCESS

SFWG members began the nomination and review process by evaluating genes and phenotypes from the SF v2.0 list to assess their appropriateness to remain on the SF v3.0 list. The committee also reconsidered genes that were nominated, but not included, on previous versions of the SF list. The committee then considered gene–phenotype pairs that scored a total of 10 or higher for actionability by the ClinGen Actionability Working Group as of August 2018.[4] Finally, the SFWG used the actionable gene lists from the eMERGE Network and the French Society of Predictive and Personalized Medicine on hereditary cancer genes to identify genes for review.[5,6]

Nominations for gene–phenotype pairs to add to or remove from the SF list were accepted from ACMG members via a nomination form (ACMG Secondary Findings Panel Nomination Form) that was developed through a subcommittee of the SFWG.[7] Internal nominations from SFWG members included *CASQ2*/catecholaminergic polymorphic ventricular tachycardia (CPVT), *DICER1*/*DICER1*-related hereditary cancer, *FLNC*/*FLNC*-related cardiomyopathy, *NOTCH3*/CADASIL, *RPE65*/*RPE65*-related retinopathy, *TRDN*/CPVT and long QT syndrome (LQTS) and *TTN*/cardiomyopathy. All externally submitted nominations were also considered; the committee received nominations for *HNF1A*/MODY3 and *HNF1B*/MODY5, *PRKAR1A*/Carney complex, *SERPINA1*/alpha-1-antitrypsin deficiency and *TTR*/*TTR*-associated amyloidosis.

Based on their expertise, SFWG members were split into one of four subgroups (hereditary cancer, inborn errors of metabolism (IEM), cardiovascular, or miscellaneous) and pared down the final list of genes for review by the full SFWG. However, all nominations from the community were put forth for full review and consideration.

Genes that underwent full review were presented to the entire SFWG by a member of the corresponding subgroup. Nomination forms were circulated to the membership prior to meetings and presented by one member for consideration. After discussion, a motion to include or exclude the gene from the v3.0 list was made and seconded, which prompted a vote requiring consensus to include or exclude genes from the SF v3.0 list.

The final proposed ACMG SF v3.0 list from the SFWG was sent to the ACMG BOD for ratification with a summary of the SFWG discussion, voting outcome, and a recommendation for the suggested update to the SF minimum list. The BOD reviewed each recommendation on a gene-by-gene basis in November 2020.

RECOMMENDATIONS FOR THE ACMG SF V3.0 LIST

The overall goal of the SFWG is to recommend a minimum list of genes that places limited excess burden on patients and clinical laboratories while maximizing the potential to reduce morbidity and mortality when ES/GS is being performed. Table 1 includes the complete list of genes on the v3.0 list. A searchable, and sortable, list is available in Supplemental Table 1. No genes were removed between the v2.0 and v3.0 lists. There is a total of 73 genes on the SF v3.0 list. A list of newly added genes to the v3.0 list is shown in Table 2. A list of genes considered for inclusion, but ultimately excluded from the v3.0 list are outlined in Table 3. A number of genes have been placed on a "watchlist" to review for future versions of the SF list, particularly those that lack sufficient data as to their penetrance.

CONSIDERATIONS FOR SPECIFIC PHENOTYPE CATEGORIES

Genes related to cancer phenotypes

The cancer subgroup prioritized new genes for consideration by selecting 13 genes underlying seven hereditary cancer phenotypes. Relevant, recent literature on phenotype, penetrance, and actionability was curated from a gene-focused search of OMIM, GeneReviews, and PubMed, as well as the expertise of the subgroup. Technical issues of sequencing the genes were reviewed with relevant members of the SFWG.

Recommended for addition to the SF v3.0 list. A recent, international study of individuals heterozygous for a *PALB2* pathogenic variant from 524 families estimated that the absolute risk of developing breast cancer by age 80 years varies from 52% (95% CI: 42–62%) for a female with an unaffected mother at age 50 years and unaffected maternal grandmother at age 70 years to 76% (95% CI: 69–83%) for a female with two affected first-degree relatives.[8] Quantified risks of developing ovarian cancer and pancreatic cancer risk were much lower. Pediatric cancer (osteosarcoma, leukemia, brain tumors, and soft-tissue sarcoma) has also been reported in *PALB2* heterozygotes, but absolute risk is uncertain.[9] Management of risk in individuals heterozygous for pathogenic *PALB2* variants is similar to that for the *BRCA1* and *BRCA2* genes; however, given the overall lower range of *PALB2*-associated risk in breast and ovarian cancer, individualized estimates are important for management decisions.[10]

Germline variants in *MAX* and *TMEM127* are rare (1–2% each) causes of hereditary paraganglioma/pheochromocytoma, a well-established phenotype on the ACMG SF list.[11] A large, longitudinal international investigation showed a high penetrance for pathogenic variants in both genes, although data is still limited.[12]

Not recommended for addition to the SF v3.0 list. As listed in Table 3, several cancer genes were reviewed and discussed but not included on the ACMG SF list for numerous reasons, even for genes with well-established phenotypes. For example, the workgroup voted not to include *SDHA* gene due to poor analytical specificity related to high sequence homology, although other genes that cause hereditary paraganglioma/pheochromocytoma are included on the list. Other technical difficulties were noted for genes such as *EPCAM* associated with Lynch syndrome and *GREM1*-associated polyposis, where routine detection of common deletions or duplications could be difficult at this time by ES/GS in many laboratories. Lower penetrance was also an important consideration, especially in genes such as *RAD51C*, *RAD51D*, and *BRIP1* that predispose to risk for ovarian cancer, given the uncertainties in how best to manage risk, difficulty of surveillance, and morbidity of intervention. For other genes (*BAP1*, *DICER1*, *POLE*, *POLD1*), there remains uncertainty about phenotype, risk, and penetrance.

Table 1. ACMG SF v3.0 gene and associated phenotypes recommended for return as secondary findings from clinical exome and genome sequencing.

Phenotype	ACMG SF list version	MIM disorder	Gene	Inheritance	Variants to report[a]
Genes related to cancer phenotypes					
Familial adenomatous polyposis	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*		
Juvenile polyposis syndrome	2.0	174900	*BMPR1A*	AD	All P and LP
	2.0	175050	*SMAD4*[c]		
Li–Fraumeni syndrome	1.0	151623	*TP53*	AD	All P and LP
Lynch syndrome	1.0	609310	*MLH1*	AD	All P and LP
	1.0	120435	*MSH2*		
	1.0	614350	*MSH6*		
	1.0	614337	*PMS2*		
Multiple endocrine neoplasia type 1	1.0	131100	*MEN1*	AD	All P and LP
MUTYH-associated polyposis	1.0	608456	*MUTYH*	AR	P and LP (2 variants)
Neurofibromatosis type 2	1.0	101000	*NF2*	AD	All P and LP
Peutz–Jeghers syndrome	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	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
	3.0	615441	*TRDN*[e]		(2 variants)
Dilated cardiomyopathy	1.0	601494	*TNNT2*[f]	AD	All P and LP
	1.0	115200	*LMNA*		See text
	3.0	617047	*FLNC*		
	3.0	604145	*TTN*[g]		
Ehlers–Danlos syndrome, vascular type	1.0	130050	*COL3A1*	AD	All P and LP
Familial hypercholesterolemia	1.0	143890	*LDLR*	AD	All P and LP
	1.0	144010	*APOB*	AD	
	1.0	603776	*PCSK9*		

Table 1 continued

Phenotype	ACMG SF list version	MIM disorder	Gene	Inheritance	Variants to report[a]
Hypertrophic cardiomyopathy[h]	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*[i]		
	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*[j]	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.Cys282Tyr homozygotes only[k]
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 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)

AD autosomal dominant, *AR* autosomal recessive, *LP* likely pathogenic, *P* pathogenic, *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 two likely pathogenic and/or pathogenic variants (or an apparently homozygous variant) to meet threshold for reporting even when phase is undetermined, as follow-up family variant testing can often resolve phase or confirm homozygosity. Finally, P/LP variants within genes associated with X-linked phenotypes that are apparently hemizygous (hemi), heterozygous (het), compound heterozygous, or homozygous should be reported, as 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]Only loss-of-function variants should be reported as a secondary finding.
[h]Individuals with primary HCM may present in late stage disease with a DCM phenotype.
[i]Pathogenic variants in this gene are associated with metabolic storage disease that mimics a HCM, but also can involve skeletal muscle.
[j]Gene also applies to the cardiovascular category.
[k]Transcript for the *HFE* gene is NM_000410.3.

Genes related to cardiovascular phenotypes

Cardiovascular genes have been represented on the SF list since its inception, due to the morbidity and mortality of sudden cardiac death (SCD) and heart failure (HF), which can both be treated or prevented with well-established interventions.[13,14]

Primary arrhythmia risk, which leads to presyncope, syncope, and SCD, arises in genes encompassed by the channelopathies. With established risk, the use of antiarrhythmic medications or implantable cardioverter defibrillators (ICDs) 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, itself a morbid and mortal condition, but one that is highly amenable to medical and device therapies. With this in mind, the SFWG reviewed the evidence for nominated cardiovascular genes with a particular focus on the medical actionability of a potential SF, the penetrance

Table 2. New gene–phenotype pairs for secondary findings (SF) list.

Gene–phenotype	Key considerations
Genes related to cancer phenotypes	
MAX/hereditary paraganglioma/pheochromocytoma	Penetrance met threshold to include with other PGL/PCC genes
PALB2/hereditary breast cancer	Risk of breast cancer risk meets penetrance threshold
TMEM127/hereditary paraganglioma/pheochromocytoma	Penetrance met threshold to include with other PGL/PCC genes
Genes related to cardiovascular phenotypes	
CASQ2/catecholaminergic polymorphic ventricular tachycardia (CPVT)	Risk of sudden death with preventive interventions available
FLNC/cardiomyopathy	Risk of sudden death with preventive interventions available
TRDN/catecholaminergic polymorphic ventricular tachycardia (CPVT) & long QT syndrome	Risk of sudden death with preventive interventions available
TTN/cardiomyopathy	Risk of sudden death with preventive interventions available
Genes related to inborn errors of metabolism phenotypes	
BTD/biotinidase deficiency	Features can be nonspecific; highly effective treatment in children and adults
GAA/Pompe disease	Availability of effective enzyme replacement therapy in infantile and later-onset cases
Genes related to miscellaneous phenotypes	
ACVRL1/hereditary hemorrhagic telangiectasia	Potential morbidity meets penetrance threshold and has efficacious intervention
ENG/hereditary hemorrhagic telangiectasia	Potential morbidity meets penetrance threshold and has efficacious intervention
HFE/hereditary hemochromatosis (*HFE* p.C282Y homozygotes only)	Potential morbidity meets penetrance threshold and has efficacious intervention
HNF1A/maturity-onset diabetes of the young (MODY3)	Accounts for 30–50% of known MODY cases likely to respond to low dose sulfonylureas; early treatment may prevent complications
RPE65/*RPE65*-related retinopathy	Availability of gene therapy treatment that may be more efficacious earlier in disease progression

PGL/PCC paraganglioma/pheochromocytoma.

and expressivity of the given gene, and the potential burden on providers and clinical laboratories should the gene be included.

Recommended for addition to the SF v3.0 list. There is strong evidence that pathogenic and likely pathogenic (P/LP) variants in *FLNC* significantly predispose individuals to high-risk dilated and arrhythmogenic cardiomyopathies; these often first manifest as sudden cardiac death.[15–17] The SFWG voted to include this gene based on its high penetrance, severity of the phenotype if untreated, and the strong potential benefit of intervention based on returning P/LP variants in this gene as a SF.

TTN, the largest single gene in the human genome, has long been associated with dilated cardiomyopathy, and clinical intervention based on *TTN* variants that are P/LP can afford significant benefit to patients and their families. However, both its considerable length and high variant burden previously have stymied attempts to measure penetrance and made interpretation of *TTN* variants a challenge for clinical laboratories and clinicians alike. For these reasons, *TTN* had been previously considered by the SFWG, but ultimately not recommended for inclusion. Since the last iteration of the guidelines, however, new data on penetrance and expressivity derived from large population cohorts necessitated that the SFWG reconsider this gene.[18] This new evidence indicated significant risk for cardiomyopathy among those with *TTN* truncating variants (TTNtv), specifically TTNtv in exons that are highly expressed. Further, TTNtv variants are far less frequent than missense variants in *TTN* (TTNtv found in 0.5–1% of the overall population) and thus identification and reporting of TTNtv variants was considered warranted and with limited burden to clinical laboratories in the assessment of this large gene. As such, the SFWG voted to include *TTN* on the current iteration of the list, with the critical caveat that *only TTN truncating variants* be returned as SF.

Pathogenic variants in the *CASQ2* gene are associated with autosomal recessive catecholaminergic polymorphic ventricular tachycardia (CPVT), which commonly presents in childhood or adolescence. As with other forms of CPVT, the clinical presentation is heralded by sudden death during exercise. Patients are otherwise asymptomatic at rest and have normal structural hearts on cardiac imaging. Exercise treadmill testing provokes the typical polymorphic ventricular arrhythmia characteristic of CPVT. Treatment is highly effective, either in the form of antiarrhythmic medical therapy, or with ICD in some cases. This condition is often lethal when unrecognized, and as such the SFWG voted to include *CASQ2* to the SF list for LP/P variants detected in *trans* or apparently homozygous variants.

TRDN is associated with autosomal recessive CPVT or an atypical form of long QT syndrome, depending on the appearance of the resting ECG. Common to all presentations is an early age of onset (<10 years) of exercise-induced sudden cardiac death. In some cases, evidence of skeletal myopathy coexists with the cardiac manifestations. Early recognition of this condition may lead to appropriate intervention in the form

Table 3. Genes not selected for secondary findings (SF) list v3.0 and reasoning.

Gene–phenotype	Category	Additional comments
Technical concerns		
EPCAM-associated Lynch syndrome	Cancer	Concern that deletions or duplications would be difficult to detect by NGS
GREM1-related polyposis	Cancer	Concern that duplication would be difficult to detect with NGS and overall limited information about this gene
HNF1B-related maturity-onset diabetes of the young (MODY5)	Miscellaneous	Accounts for ~5% of known MODY with ~50% of cases associated with deletions difficult to detect on exome sequencing
SDHA/hereditary paraganglioma/ pheochromocytoma	Cancer	Concerns about presence of many pseudogenes that could lead to false positive results that would require labs to perform extensive validation work
Penetrance concerns		
BRIP1/RAD51C/RAD51D-related ovarian cancer	Cancer	Lack of effective surveillance modalities for ovarian cancer also a consideration
DICER1-associated tumors	Cancer	Challenges in *DICER1* missense variant interpretation
HFE-related hemochromatosis (except for *HFE* p.C282Y homozygotes)	Miscellaneous	Penetrance is driven by the p.Cys282Tyr variant, and not other variants in HFE
TTR-amyloidosis	Miscellaneous	Also considered that sudden death was rare, thus allowing time for clinical diagnosis
Clinical management concerns		
ABCD1 X-linked adrenoleukodystrophy	IEM	Severe cases have early onset and would be diagnosed by newborn screening; no specific treatment in adulthood
BAP1-related tumors	Cancer	Small number of families reported to date and no established consensus management recommendations as of time reviewed
COL5A1-associated Ehlers–Danlos syndrome	Miscellaneous	Not considered highly actionable
GCH1-related dopa-responsive dystonia	Miscellaneous	Concern that diagnosis of the classic phenotype is relatively straightforward and that the treatment efficacy was not dependent on the timing of initiation
HMBS-associated acute intermittent porphyria	Miscellaneous	Concern that avoidance of exposures and delays in diagnosis could be out of scope for the ACMG SF list
MEFV-associated familial Mediterranean fever	Miscellaneous	Concern about clinical management of acute episodes being primarily supportive, and diagnosis could then be made through diagnostic testing
NOTCH3/CADASIL	Miscellaneous	Not considered highly actionable
POLD1/POLE-related polyposis	Cancer	Rarity of known pathogenic variants that could be reported and uncertain risks of extracolonic cancers
PRKAR1A/Carney complex	Miscellaneous	Concerns about penetrance and questions about actionability
SERPINA1-related alpha-1-antitrypsin deficiency	Miscellaneous	Concern that avoidance of exposures could be out of scope for the ACMG SF list

ACMG American College of Medical Genetics and Genomics, *IEM* inborn errors of metabolism, *NGS* next-generation sequencing.

of antiarrhythmic therapy or ICD. In view of the early onset of disease and lethality, the SFWG voted to include *TRDN* to the SF list for the recessive state in which two LP/P variants are detected in *trans* or apparently homozygous variants.

Not recommended for addition to the SF v3.0 list. As with many other SF genes, population-based penetrance estimates are lacking for most cardiovascular genes, particularly those derived from population cohorts not ascertained for cardiovascular phenotypes. As such evidence continues to amass, we recognize that some additional "watchlist" genes not included here may meet the standard for inclusion. This includes genes associated with dilated cardiomyopathy (e.g., *BAG3, DES, RBM20, TNNC1*), which have evidence showing similar or greater risk of morbidity and mortality as other cardiomyopathy genes already included. Additionally, *CALM1*, *CALM2*, and *CALM3*, three separate genes all encoding the identical protein, have accumulated evidence supporting their cause of an atypical form of LQTS presenting in the neonatal period or early childhood, at times associated with developmental delay and seizure. As this condition usually does not escape diagnosis, and the role of variants in these three genes in adult disease presentations remains unclear, these genes have not yet been added to the SF list. The workgroup's new policy to update the guidelines more regularly will facilitate a stringent but more agile approach to review emerging evidence for these genes and for their overall suitability for inclusion on the SF list.

Genes related to phenotypes associated with inborn errors of metabolism

When considering IEM, the SFWG first considered the broader question of whether all genes and disorders on the Recommended Uniform Screening Panel (RUSP) should be reviewed and considered for inclusion.[19] Newborn screening (NBS) for disorders on the RUSP is recommended by the Department of Health and Human Services. Most states test for the majority of the recommended disorders, and some states test for additional disorders. The abundance of data associated with state screening

programs, including validity of testing methodologies employed currently, are already in place and have been so for many years for many IEMs.[20] Assays to measure analytes are generally more clinically sensitive to identify an IEM than molecular analysis for secondary findings, with likely limited yield for the latter if the patient had NBS. A secondary consideration noted by the SFWG would be the added cost for analysis and counseling that would be associated with the addition of more than 30 disorders to the SF list.

The SFWG, therefore, considered the following when deciding whether to review and approve an IEM for inclusion in the secondary findings list: (1) the existence of a juvenile or later-onset form of the disorder and that early or presymptomatic diagnosis of late-onset disease is unlikely for disorders recently added to the RUSP, (2) that the late-onset form should be highly medically actionable, and (3) that there appear to be a significant number of undiagnosed cases in the population.

Recommended for addition to the SF v3.0 list. Biotinidase deficiency, due to pathogenic variants in the *BTD* gene, was reviewed based on its high actionability score in ClinGen.[21] Its addition is recommended based on the severity of clinical symptoms in a significant proportion of undiagnosed older individuals at risk for disease, ease of confirmatory diagnosis by enzyme assay, and effectiveness and ease of treatment with lifelong oral biotin.[22]

Pompe disease caused by recessive pathogenic variants in the acid α-glucosidase (*GAA*) gene was added to the RUSP in 2015. However, as of October 2020, only 23 states and Washington, DC were performing NBS for the disorder.[23] Although the number of states screening is likely to increase over time, NBS may fail to diagnose later-onset, milder forms of the disorder. Given the availability of FDA-approved effective enzyme replacement therapy (ERT), we recommend adding *GAA*/Pompe as a SF to facilitate detection of later-onset cases and in older individuals who were not screened as newborns.[24,25]

While Fabry disease was included in the original SF recommendations under the disease category of cardiomyopathy, the workgroup recommends that the gene–phenotype association be broadened in affected males and females to include all P/LP variants associated with any disease manifestation(s), including significant risk for stroke and renal disease.[26,27]

Not recommended for addition to the SF v3.0 list. X-linked adrenoleukodystrophy (ALD) was added to the RUSP in 2016. As of October 2020, 18 states and Washington, DC perform NBS for ALD.[23] The classic cerebral form of the disorder in affected males is associated with an early onset (4–8 years) and rapid progression of disease. While treatment is available in the form of hematopoietic stem cell transplantation with early stage cerebral disease, it is associated with significant morbidity and mortality and success depends upon early treatment.[28,29] Therapy for later-onset cases in affected males and females is currently supportive. For these reasons, the SFWG assessed that, at the present time, NBS should be the focus, allowing presymptomatic diagnosis and the opportunity for more timely medical treatment and appropriate counseling. With NBS, it is unlikely many additional individuals would be diagnosed as a secondary finding.

The review and possible inclusion of additional lysosomal storage disorders was briefly discussed by the SFWG, particularly for forms with later onset. However, the SFWG decided that inclusion on NBS panels for some (such as Hurler syndrome), as well as the low likelihood of presymptomatic diagnosis and/or effective treatment for others, did not warrant their inclusion at this time.

For additional IEMs on the NBS list, such as organic acidemias and fatty acid oxidation disorders, the SFWG decided that insufficient numbers of additional asymptomatic patients would be secondarily diagnosed to warrant addition.

Genes related to miscellaneous phenotypes

The SFWG also reviewed nominations for genes that cause phenotypes outside of the core disease review groups. This subgroup reviewed 13 genes associated with 11 different phenotypes, and ultimately approved 4 genes to be added to the v3.0 list.

Recommended for addition to the SF v3.0 list. Hereditary hemorrhagic telangiectasia (HHT) was considered for inclusion on the ACMG SF v3.0 list, and it was ultimately decided that the *ACVRL1* and *ENG* genes should be included. We acknowledge that the *SMAD4* gene also contributes to this phenotype; however, this gene was previously placed on the list due to its association with juvenile polyposis syndrome. The HHT phenotype was added to the SF list largely due to disease severity, medical management recommendations, and disease penetrance.[30] Inclusion of the *GDF2* gene, which is also associated with HHT, was not considered at this time due to the small number of reported cases.[31] Of note, the *ACVRL1* and *ENG* gene have also been considered associated with hereditary pulmonary hypertension; however, review for association with the HHT phenotype only was used to include these genes on the v3.0 list.[32–35]

We assessed two nominated genes for maturity-onset diabetes of the young (MODY). MODY is somewhat atypical and can therefore be difficult to correctly diagnose among diabetic patients and may go undiagnosed for many years. Untreated or poorly controlled diabetes, including MODY, leads to complications including cardiovascular disease, renal disease, neuropathy, and retinopathy. Therefore, early and effective treatment is important. MODY3 is associated with pathogenic variants in *HNF1A*, which accounts for approximately 30–65% of MODY cases. MODY3 does not require insulin treatment and responds well to low dose oral sulfonylureas, typically lower doses than are customary for most type 2 diabetics.[36] Furthermore, newborns can have transient neonatal hyperinsulinemic hypoglycemia that can lead to lifelong disabilities if hypoglycemia is not quickly recognized and treated. More than 95% of *HNF1A* pathogenic variants are detectable with ES. In contrast, MODY5 due to variants in *HNF1B* accounts for only <5% of MODY, and ~50% of pathogenic variants in *HNF1B* are due to deletions that are not readily detected by ES if copy-number analysis is not included.[37] For this reason, only *HNF1A* was recommended for the SF list at this time.

The SFWG concluded that only the *HFE* p.Cys282Tyr variant associated with hereditary hemochromatosis should be reported from ES/GS testing and only when found in the homozygous state after deliberation. The SFWG recognized the lower penetrance levels for all other genotypes in the *HFE* gene, such as *HFE* p.His63Asp/p.Cys282Tyr compound heterozygotes and *HFE* p.His63Asp homozygotes. Newer studies show penetrance rates of severe iron overload to be as high as 35% and severe liver disease in 9–24% among male p.Cys282Tyr homozygotes, including larger studies without ascertainment bias.[38] There is a highly effective follow-up laboratory testing (i.e., serum transferrin–iron saturation assay) that can indicate who would benefit from undergoing phlebotomy and/or iron chelation treatment.[39] Additionally, this condition can easily escape detection before significant organ damage occurs, which can be prevented should treatment be initiated before significant iron overload takes place.

RPE65-associated retinopathy was nominated for inclusion on the v3.0 list due to recent availability of an FDA-approved gene replacement therapy. Individuals with biallelic pathogenic variants in *RPE65* have a range of age of onset that is likely dependent on severity and combination of biallelic variants, but can be associated with symptoms, including nystagmus, at or shortly after birth.[40] As the condition progresses, individuals experience a decrease in their visual field and deterioration of color vision and central visual acuity. Milder forms may present later in childhood or early adulthood, and symptoms of early

retinal deterioration can be missed or overlooked. Lack of treatment over time causes devastating vision impairment or complete loss. While ongoing long-term data are still being collected, the therapy depends on viable retinal cells, and thus, may be more advantageous if administered earlier rather than later in the disease course.[41,42] Therefore, the SFWG felt there was the potential for significant benefit to patients by adding this gene to the SF gene list.

Not recommended for addition to the SF v3.0 list. The SFWG received nominations for *TTR*-associated amyloidosis due to the availability of newer FDA-approved treatments. However, the SFWG did not ultimately recommend inclusion of this gene on the current list due to concerns of incomplete penetrance and that most patients develop recognizable disease-related symptoms allowing for diagnosis and treatment prior to late-stage disease. As part of this decision, the SFWG referenced a cardinal principle that the SF list should not be a replacement for indication-based diagnostic genetic testing.

The SFWG questioned the actionability of *COL5A1*-associated Ehlers–Danlos syndrome, *PRKAR1A*/Carney complex, and *NOTCH3*/CADASIL. The SFWG decided that including gene phenotypes such as *HMBS*-associated acute intermittent porphyria and *SERPINA1*/alpha-1-antitrypsin deficiency with interventions involving environmental exposures or behavior modification was beyond the scope of this list.

GCH1-associated dopa-responsive dystonia was also thought to be beyond the scope of the list using the rationale that its clinical presentation would likely prompt an individual to seek a diagnosis, and while an effective treatment is available, the timing of its initiation does not appear to compromise its effectiveness. *MEFV*-associated familial Mediterranean fever was ultimately not included on the list due to concerns about there being a low chance of having a SF reported out that later becomes downgraded to a new classification that would be below the threshold for reporting, which could be burdensome to patients. Finally, the *HNF1B*/MODY5 was not included for reasons described in detail above.

Pharmacogenomic genes/variants

The current SF list includes *RYR1*, and we considered several issues related to the possibility of adding additional pharmacogenetics (PGx) variants as secondary findings. The clinical validity and utility of PGx testing has been demonstrated in many studies to aid drug therapy, and guidelines for implementation are currently available from international PGx consortia such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG).[43–45] ES/GS genotypes could potentially be a cost-effective method to generate useful PGx profiles, which can then be used preemptively to guide drug dose and choice. However, several critical PGx variants or haplotypes cannot be captured through exome-based testing, and generating haplotypes requires additional data processing that is not part of a standard ES informatics pipeline. Therefore, we evaluated these technical limitations as part of the SF gene nomination process.

The difficulties for the laboratory to report clinically actionable variants in these genes arise from multiple issues: (1) many of the clinically relevant variants reside in promoter, intronic, or untranslated regions that are not captured using current methodology (e.g., the key variant for warfarin dosing [−1639G>A in *VKORC1*] is in the promoter region; the increased function CYP2C19*17 allele is also characterized by a promoter variant [−806C>T] that results in increased gene expression); (2) copy-number variants (CNVs), repeats, and gene hybrids have been challenging to assess with current ES technology (e.g., *CYP2D6* CNVs that define the ultrarapid metabolizer phenotype); (3) for some genes and variants there is still controversy regarding genotype/phenotype correlations; and (4) as many PGx guidelines describe haplotypes, testing often requires genotyping multiple positions/regions and types of variation within the same gene, complicating the analysis and reporting, especially when phase cannot be easily determined. Some phenotypes may not be determined accurately due to a lack of coverage and missing CNV information depending on the assay design (e.g., a number of *CYP2D6* alleles include SNPs at multiple positions and may also involve duplication, deletion, and large-scale gene rearrangements (hybrid). Rare *CYP2D6* variants also may not be included in the genotype testing used by some laboratories, which could result in errors in diplotype/phenotype calls as well as false negative findings.

Other challenges not specific for ES include (1) lack of evidence and guidance for combining results from multiple PGx genes beyond what has been covered by existing CPIC guidelines; (2) the majority of published PGx research is conducted with European ancestry-dominant cohorts, lacking evidence from diverse patient populations (thus, the guidance based on alleles common in European ancestry–majority cohorts may not be appropriate/generalizable for other ethnicities); (3) ambiguity in PGx testing results, i.e., variants with unknown or uncertain significance; and (4) the large number of patients taking multiple medications (polypharmacy) that may have synergistic or antagonistic effects on each other, and thus affect interpretation of PGx results.

In the future, it may be possible for a workgroup to develop a universal and easily implemented method for analysis and interpretation of PGx variants that can be utilized by all diagnostic laboratories. We encourage ongoing research to document (1) the reliable identification of alleles (and proper phasing) based on standard ES/GS; (2) spectrum of PGx variants outside of European ancestry populations; (3) the time and effort required within the laboratory; (4) the time and effort required in clinics, including educational needs for clinicians who are not already familiar with this type of testing in terms of what they need to know to properly consent and return results; (5) how the results will be documented in the medical record in order to be accessible in the distant future; and (6) how often persons receiving these results will use them in medication choices.

CONCLUSIONS

With the publication of the accompanying SF policy statement, we have separated this secondary findings gene list update, which describes the rationale supporting how genes are selected for addition to or removal from the secondary findings list. This dual publication approach was done intentionally with a primary goal of providing more frequent updates to the actual SF gene list. Going forward, we foresee updates to the general policy only as needed and may be expected to occur every few years. In contrast, updates to the gene 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 update laboratory and reporting processes. For example, 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 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.[7] We hope that the detailed descriptions of our decision process during the preparation of this update will help the community to better understand the types of genes and variants that we consider appropriate for this list to guide nominations going forward.

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COMPETING INTERESTS

S.J.B. is a contractor to GeneDx, a subsidiary of OPKO, through Bale Genetic Consulting, LLC. W.K.C. is a member of the scientific advisory board of Regeneron Genetic 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), and also performs contract clinical telehealth services for Genome Medical, Inc. in accordance with relevant NCI ethics policies. The other authors declare no competing interests.

ADDITIONAL INFORMATION

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