ACMGG Secondary Findings 2.0

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Secondary Findings

- In 2013 ACMG *"…Working Group elected to present recommendations in the form of a 'minimum list' of incidental findings to report from clinical sequencing."*
  - *"Disorders for which preventive measures and/or treatments were available and disorders in which individuals with pathogenic mutations might be asymptomatic for long periods of time."*
  - High bar: Known Pathogenic (KP) and Expected Pathogenic (EP) variants

- In 2014 "secondary findings" term was adopted and patients were given "opt-out" option as recommended by the Presidential Commission on Bioethical Issues and surveys among the ACMG members.

- In 2016 the 'minimum list' was updated to 59 genes.

Process for Making Changes to the 56 Genes

- Nominations for genes/conditions to add to, or remove from, the SF list were accepted from ACMG members via a nomination form. Announcements made to ACMG, College of American Pathologists, Association of Molecular Pathologists, American Society of Clinical Oncology, American College of Cardiology membership
- Data collected included phenotypes, prevalence, and reported variants in the gene from ClinVar and the Human Gene Mutation Database.
- Clinical features, likelihood of early clinical diagnosis by a pediatrician/internist, molecular genetic characteristics, clinical genetic testing options, and medical actionability.
- Each form was presented by the submitter or a designee followed by a vote of the committee.
- ACMG Board of Directors voted on the list.

Secondary Findings

- Secondary Findings Working Group Gene Inclusion/Removal Criteria
  1. Severity of disease/nature of the health threat
  2. Likelihood of the disease/health threat materializing (i.e., penetrance)
  3. Efficacy of specific intervention(s)
  4. Overall strength of the current knowledge base about the gene/condition
  5. Acceptability of the proposed intervention based on its risks and benefits

- ClinGen Actionability Working Group
  - "Actionability Evidence Based Summaries" for genes/conditions on the secondary findings list.

Changes in the Secondary Findings List: 56 => 59

ACMG 2013	Gene #
Oncologic	23
Cardiac	20
Aortic Aneurysm Conditions	8
Metabolic/Other	5
Total	56

ACMG 2016	Gene #
Oncologic	25
Cardiac	20
Aortic Aneurysm Conditions	7
Metabolic/Other	7
Total	59

Oncologic
Hereditary paragangliomapheochromocytoma syndrome
Lynch Syndrome
Juvenile Polyposis
Tuberous sclerosis complex
HBOC
Neurofibromatosis Type 2
PTEN hamartoma tumor syndrome
Peutz-Jeghers Syndrome
Retinoblastoma
Li-Fraumeni Syndrome
MEN type 2 / Famillary Medullary Thyroid Cancer
Von Hippel-Lindau syndrome
WT1-related Wilms Tumor
MEN type 1
Familial Adenomatosis Polyposis
MYH-associated poluposis

Cardiac
HCM/DCM
Arrhythmogenic right ventricular cardiomyopathy
Romano-Ward long-QT syndrome types 1,2,and 3, Brugada Syndrome
Catecholaminergic polymorphic ventricular tachycardia
Aortic Aneurysm Conditions
FTAAD
Loeys-Dietz syndrome
Marfan Syndrome
Ehlers-Danlos syndrome, vascular type
Metabolic/Other
Familial hypercholesterolemia
Malignant hyperthermia susceptibility
Wilson Disease
Ornithine transcarbamylase deficiency

Four Genes Added and One Gene Removed from the List

A. Add

Phenotype	MIM disorder	PMID Gene Reviews Entry	Typical age of onset	Gene	MIM gene	Inheritance	Variants to report[a]
Juvenile polyposis	174900	20301642	Child/adult	*BMPR1A* *SMAD4*	601299 600993	AD	KP and EP
Wilson disease	277900	20301685	Child	*ATP7B*	606882	AR[b]	KP and EP
Ornithine transcarbamylase deficiency	311250	24006547	Newborn (male)/ child (female)	*OTC*	300461	XL	KP and EP (hemi, het, hom)

B. Remove

Phenotype	MIM disorder	PMID Gene Reviews Entry	Typical age of onset	Gene	MIM gene	Inheritance	Variants to report
Familial thoracic aortic aneurysms and dissections	613780	20301299	Child	*MYLK*	600922	AD	Not applicable

[a]KP: known pathogenic, sequence variation is previously reported and is a recognized cause of the disorder; EP: expected pathogenic, sequence variation is previously unreported and is of the type that is expected to cause the disorder. [b]We recommend searching only for individuals with biallelic mutations.

Actionability Criteria

Semi-quantitative Metric (SQM)

Category	Levels	Level of Evidence
Severity	3 - sudden death 2 - possible death or major morbidity 1 - modest morbidity 0 - minimal or no morbidity	NA
Likelihood of Disease	3 - >40% chance 2 - 5-39% chance 1 - 1-4% chance 0 - <1% chance or unknown	A = substantial evidence B = moderate evidence C = minimal evidence D = poor evidence E = expert contributed evidence
Efficacy of Intervention	3 - highly effective 2 - moderately effective 1 - minimally effective 0 - ineffective/no intervention IN* – ineffective/no intervention	A = substantial evidence B = moderate evidence C = minimal evidence D = poor or conflicting evidence E = expert contributed evidence
Nature of Intervention	3 - low risk/medically acceptable/ low intensity intervention 2 - moderately acceptable/risk/ intensive interventions 1 - greater risk/less acceptable/ substantial interventions 0 - high risk/poor acceptable/ intensive or no intervention	NA

Rational for Adding/Subtracting Genes

Gene	Disease	Rationale
BMPR1A SMAD4	Juvenile Polyposis	• Possible death or major morbidity • High penetrance • Highly effective intervention • Moderately acceptable medical risk during interventions
ATP7B	Wilson Disease	• Possible death or major morbidity • High penetrance • Highly effective intervention • Moderately acceptable medical risk during interventions
OTC	Ornithine transcabamylase deficiency	• Possible death or major morbidity • Nearly full penetrance in males; 20 to 30% in heterozygous females. • Moderately effective intervention • Low-moderately acceptable medical risk during interventions

MYLK	FTAAD	• Rarity of known pathogenic variants
		• Lack of effective confirmatory test, screening modality, or intervention to prevent morbidity or mortality from FTAAD
		  • Aortic dissection related to variants in MYLK often presents without a history of aortic enlargement, the intervention of echocardiogram may be falsely reassuring and may not prevent sudden cardiac death.
		  • There is insufficient evidence on the appropriate age to begin medications and the efficacy of this intervention to reduce dynamic stress on the aorta.

Juvenile Polyposis (BMPR1A and SMAD4)

- An individual with a KP/EP variant in BMPR1A has a more than 90% chance of developing polyps and a 10–50% lifetime risk of developing cancer.
- The majority of patients with clinical features of the disease have colon polyps by age 20, and colon cancer typically develops by the mid-40s.
- Screening via endoscopy with histological confirmation of juvenile-type polyps is readily available, highly sensitive, effective at reducing morbidity, and presents minimal risk or burden.
- Although most individuals with a BMPR1A variant have a positive family history, many cases remain undetected because GI cancer screening is not routine in the general population before age 50.
- Penetrance of KP/EP variants in SMAD4 is estimated to be approximately 20% for colon cancer by age 35 and nearly 70% by age 65, with the average age of onset reported to be in the early 40s.
- Gastric cancer occurs in approximately 21% of patients with gastric polyps. Screening via colonoscopy and upper GI endoscopy for polyps are effective interventions for risk reduction.

Wilson Disease (ATP7B)

- Morbidity among homozygotes directly correlates with copper deposition in the liver, brain, and eye.
- The disease is progressive, and, if left untreated, premature death is likely. In some cases, liver failure may be the presenting sign.
- Given its long recognition as a Mendelian disorder, it is reasonable to consider Wilson disease to be at least relatively highly penetrant. Expressivity is variable.
- Treatment for Wilson disease involves administration of copper chelating agents and/or zinc to block intestinal absorption of copper; treatment is extremely effective when administered prior to the onset of symptoms.
- Sanger sequencing of the ATP7B gene is considered confirmatory in asymptomatic patients. In symptomatic patients, in addition to Sanger sequencing, the results of serum ceruloplasmin, serum copper concentration, and 14-hour urine copper excretion can be diagnostic.
- The ClinGen Actionability scoring process generated a high actionability score of 10/12 for copper chelation and zinc therapy in the treatment of ATP7B associated liver disease and/or neuropsychiatric disease.

Ornithine Transcarbamylase Deficiency (OTC)

- Penetrance in hemizygous males is nearly 100%, although cases in which there is partial expression of the mutated allele with residual enzyme activity often present later with milder symptoms. In heterozygous females, penetrance estimates range from approximately 20 to 30%. The phenotype among affected females varies widely from mild to severe, depending primarily on the pattern of X-inactivation of the gene in hepatocytes.
- Interventions exist to prevent crises and ameliorate outcomes, including protein restriction in the diet and medications that remove ammonia by alternate metabolic pathways. These treatments are most useful in symptomatic heterozygous females and among males with later onset or partial disease.
- Medical management may also include the potential for prolonged hospitalization during illness as well as dialysis for acute crises with hyperammonemia to help prevent or minimize brain damage. For males with severe disease who present in the neonatal period, and for some males and females with later-onset disease, liver transplantation is recommended due to the high risk for recurrent hyperammonemia, subsequent neurological deterioration, and/or death.
- OTC deficiency is included on newborn screening panels in only some states; however, males with severe disease often become ill in the first 2–3 days of life, when newborn screening results are not yet available

Familial Thoracic Aortic Aneurysms (MYLK)

- Rarity of known pathogenic variants
- Lack of effective confirmatory test, screening modality, or intervention to prevent morbidity or mortality from FTAAD
  - Aortic dissection related to variants in MYLK often presents without a history of aortic enlargement, the intervention of echocardiogram may be falsely reassuring and may not prevent sudden cardiac death.
  - There is insufficient evidence on the appropriate age to begin medications and the efficacy of this intervention to reduce dynamic stress on the aorta.

Secondary Findings Committee Members

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