Children's Hospital of Philadelphia
Division of Genomic Diagnostics

GENOMIC DIAGNOSTIC LABORATORY
CHOP Medical Exome: Secondary Findings List

Background: The CHOP Medical Exome includes the option for patients and family members to choose to receive secondary findings from the analysis of certain genes/conditions, as recommended by the American College of Genetics and Genomics (ACMG) [Miller 2021, PMID: 34012069]. Reporting of secondary findings is optional. Patients/families can choose whether they would like the laboratory to look for and report secondary findings.

Secondary Findings List: The laboratory updates the Secondary Findings (SF) list periodically based on the recommendations of the ACMG. Exomes ordered *on* or *after* the implementation date of the most current SF list will include analysis/reporting of the related genes/phenotypes on the given list, if indicated by the selection on the patient's consent form. Please see below for the current version of the ACMG SF list that is utilized by the laboratory. The version of the SF list utilized for analysis is indicated on the patient's exome results report.

Please Note: During the period of transition to an updated SF list, the version of the SF list utilized for a specific patient's analysis depends on the date that all necessary materials are received. Exomes ordered prior to the launch date for an updated SF list may undergo analysis of the newer list if all samples are not received by the cutoff date. This difference is because the SF list is a part of the CHOP Medical Exome's bioinformatics pipeline. Therefore, the version of the SF list utilized in the analysis of a patient's exome is dependent on the date the actual pipeline is initiated on a given patient.

Launch Dates for Secondary Finding Lists* Utilized by the CHOP Genomic Diagnostic Laboratory:

Launch Date	List Version	Reference
June, 2014	ACMG v1.0	Green 2013, PMID: 23788249
June 21, 2017	ACMG v2.0	Kalia 2017, PMID: 27854360
April 1, 2022	ACMG v3.0	Miller 2021, PMID: 34012068
August 22, 2022	ACMG v3.1	Miller 2022, PMID: 35802134
April 29, 2024	ACMG v3.2	Miller 2023, PMID: 37347242

*Please see the full list of genes/conditions on each version of the ACMG Secondary Findings List below.

Current ACMG Secondary Findings List v3.2 [Adapted from Miller 2023, PMID: 37347242]

Gene	Gene MIM	Disease/Phenotype	Phenotype Category	Inheritance	SF List Version	Variants to report[a]
APC	611731	Familial adenomatous polyposis	Cancer	AD	1.0	All P and LP
RET[b]	164761	Familial medullary thyroid cancer	Cancer	AD	1.0	All P and LP
RET	164761	Multiple endocrine neoplasia type 2A	Cancer	AD	1.0	All P and LP
RET	164761	Multiple endocrine neoplasia type 2B	Cancer	AD	1.0	All P and LP
BRCA1	113705	Hereditary breast and ovarian cancer	Cancer	AD	1.0	All P and LP
BRCA2	600185	Hereditary breast and ovarian cancer	Cancer	AD	1.0	All P and LP
PALB2	610355	Hereditary breast cancer	Cancer	AD	3.0	All P and LP
SDHD	602690	Hereditary paraganglioma-pheochromocytoma syndrome	Cancer	AD	1.0	All P and LP
SDHAF2	613019	Hereditary paraganglioma-pheochromocytoma syndrome	Cancer	AD	1.0	All P and LP
SDHC	602413	Hereditary paraganglioma-pheochromocytoma syndrome	Cancer	AD	1.0	All P and LP
SDHB	185470	Hereditary paraganglioma-pheochromocytoma syndrome	Cancer	AD	1.0	All P and LP
MAX	154950	Hereditary paraganglioma-pheochromocytoma syndrome	Cancer	AD	3.0	All P and LP
TMEM127	613403	Hereditary paraganglioma-pheochromocytoma syndrome	Cancer	AD	3.0	All P and LP
BMPR1A	601299	Juvenile polyposis syndrome	Cancer	AD	1.0	All P and LP
SMAD4[c]	600993	Juvenile polyposis syndrome	Cancer	AD	1.0	All P and LP
TP53	191170	Li-Fraumeni syndrome	Cancer	AD	1.0	All P and LP
MLH1	120436	Lynch syndrome	Cancer	AD	1.0	All P and LP
MSH2	609309	Lynch syndrome	Cancer	AD	1.0	All P and LP
MSH6	600678	Lynch syndrome	Cancer	AD	1.0	All P and LP
PMS2	600259	Lynch syndrome	Cancer	AD	1.0	All P and LP
MEN1	613733	Multiple endocrine neoplasia type 1	Cancer	AD	1.0	All P and LP
MUTYH	604933	*MUTYH*-associated polyposis	Cancer	AR	1.0	P and LP (2 variants)[a]
NF2	607379	Neurofibromatosis type 2	Cancer	AD	1.0	All P and LP
STK11	602216	Peutz-Jeghers syndrome	Cancer	AD	1.0	All P and LP

PTEN	601728	*PTEN* hamartoma tumor syndrome	Cancer	AD	1.0	All P and LP
RB1	614041	Retinoblastoma	Cancer	AD	1.0	All P and LP
TSC1	605284	Tuberous sclerosis complex	Cancer	AD	1.0	All P and LP
TSC2	191092	Tuberous sclerosis complex	Cancer	AD	1.0	All P and LP
VHL	608537	Von Hippel-Lindau syndrome	Cancer	AD	1.0	All P and LP
WT1	607102	*WT1*-related Wilms tumor	Cancer	AD	1.0	All P and LP
DSC2	125645	Arrhythmogenic right ventricular cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
DSG2	125671	Arrhythmogenic right ventricular cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
DSP	125647	Arrhythmogenic right ventricular cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
PKP2	602861	Arrhythmogenic right ventricular cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
TMEM43	612048	Arrhythmogenic right ventricular cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
SCN5A	600163	Brugada syndrome	Cardiovascular	AD	1.0	All P and LP
CASQ2	114251	Catecholaminergic polymorphic ventricular tachycardia	Cardiovascular	AR	3.0	P and LP (2 variants)[a]
RYR2	180902	Catecholaminergic polymorphic ventricular tachycardia	Cardiovascular	AD	1.0	All P and LP
TRDN	603283	Catecholaminergic polymorphic ventricular tachycardia	Cardiovascular	AR	3.0	All P and LP
BAG3[d]	613881	Dilated Cardiomyopathy	Cardiovascular	AD	3.1	All P and LP
DES[d]	604765	Dilated Cardiomyopathy	Cardiovascular	AD	3.1	All P and LP
DSP	125647	Dilated cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
FLNC[d]	102565	Dilated cardiomyopathy	Cardiovascular	AD	3.0	All P and LP
LMNA[d]	150330	Dilated cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
MYH7	160760	Dilated cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
RBM20	613172	Dilated Cardiomyopathy	Cardiovascular	AD	3.1	All P and LP
SCN5A	600163	Dilated cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
TNNT2	191045	Dilated cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
TTN[e]	188840	Dilated cardiomyopathy (truncating variants only)	Cardiovascular	AD	3.0	P and LP (truncating variants only)
COL3A1	120180	Ehlers-Danlos syndrome, vascular type	Cardiovascular	AD	1.0	All P and LP
APOB	107730	Familial hypercholesterolemia	Cardiovascular	AD	1.0	All P and LP

LDLR	606945	Familial hypercholesterolemia	Cardiovascular	AD	1.0	All P and LP
PCSK9	607786	Familial hypercholesterolemia	Cardiovascular	AD	1.0	All P and LP
ACTA2	102620	Familial thoracic aortic aneurysm	Cardiovascular	AD	1.0	All P and LP
MYH11	160745	Familial thoracic aortic aneurysm	Cardiovascular	AD	1.0	All P and LP
ACTC1	102540	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
MYBPC3	600958	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
MYH7	160760	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
MYL2	160781	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
MYL3	160790	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
TNNC1	613243	Hypertrophic Cardiomyopathy	Cardiovascular	AD	3.1	All P and LP
TNNI3	191044	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
TNNT2	191045	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
TPM1	191010	Hypertrophic cardiomyopathy	Cardiovascular	AD	1.0	All P and LP
SMAD3	603109	Loeys-Dietz syndrome	Cardiovascular	AD	1.0	All P and LP
TGFBR1	190181	Loeys-Dietz syndrome	Cardiovascular	AD	1.0	All P and LP
TGFBR2	190182	Loeys-Dietz syndrome	Cardiovascular	AD	1.0	All P and LP
TRDN	603283	Long QT syndrome	Cardiovascular	AD	3.0	All P and LP
CALM1	616247	Long QT syndrome 14	Cardiovascular	AD	3.2	All P and LP
CALM2	616249	Long QT syndrome 15	Cardiovascular	AD	3.2	All P and LP
CALM3	618782	Long QT syndrome 16	Cardiovascular	AD	3.2	All P and LP
SCN5A	600163	Long QT syndrome type 3	Cardiovascular	AD	1.0	All P and LP
KCNQ1	607542	Long-QT syndrome type 1	Cardiovascular	AD	1.0	All P and LP
KCNH2	152427	Long-QT syndrome type 2	Cardiovascular	AD	1.0	All P and LP
FBN1	134797	Marfan syndrome	Cardiovascular	AD	1.0	All P and LP
GLA	300644	Fabry disease	Cardiovascular Metabolic	XL	1.0	All hemi, het, homozygous P and LP
PRKAG2	602743	Hypertrophic cardiomyopathy	Cardiovascular Metabolic	AD	1.0	All P and LP
BTD	609019	Biotinidase deficiency	Metabolic	AR	3.0	P and LP (2 variants)[a]
OTC	300461	Ornithine transcarbamylase deficiency	Metabolic	XL	2.0	All hemi, het, homozygous P and LP
GAA	606800	Pompe disease	Metabolic	AR	3.0	P and LP (2 variants)[a]
HFE[f]	613609	Hereditary hemochromatosis (c.845G>A; p.C282Y homozygotes only)	Miscellaneous	AR	3.0	p.C282Y homozygotes only

ACVRL1	601284	Hereditary hemorrhagic telangiectasia	Miscellaneous	AD	3.0	All P and LP
ENG	131195	Hereditary hemorrhagic telangiectasia	Miscellaneous	AD	3.0	All P and LP
SMAD4	600993	Hereditary hemorrhagic telangiectasia	Miscellaneous	AD	1.0	All P and LP
TTR	176300	Hereditary Transthyretin-related amyloidosis	Miscellaneous	AD	3.1	P and LP
CACNA1S	114208	Malignant hyperthermia	Miscellaneous	AD	1.0	All P and LP
RYR1	180901	Malignant hyperthermia	Miscellaneous	AD	1.0	All P and LP
HNF1A	142410	Maturity-Onset of Diabetes of the Young	Miscellaneous	AD	3.0	All P and LP
RPE65	180069	*RPE65*-related retinopathy	Miscellaneous	AR	3.0	P and LP (2 variants)[a]
ATP7B	606882	Wilson disease	Miscellaneous	AR	2.0	P and LP (2 variants)[a]

Table Key: MIM Mendelian Inheritance in Man (https://www.omim.org), AD autosomal dominant, AR autosomal recessive, LP likely pathogenic, P pathogenic, XL X-linked.

Note: Genes/conditions included on a prior version of the list are also included in all subsequent versions unless otherwise specified. Therefore, any genes/conditions listed as version 1 in the SF Version List column above are also included on version SF List v2 and v3, while those listed as version 3 were not included in the prior versions of the list.

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 2a and b.
c. Also associated with hereditary hemorrhagic telangiectasia.
d. Also associated with a skeletal myopathy (I.e., myofibrillar myopathy).
e. Only loss-of-function variants in the A-band should be reported as a secondary finding.
f. Transcript for the *HFE* gene is NM_000410.3.