GENETIC HEALTH PANEL TESTING RESULTS

Marker by labcorp™

Patient name:	John Smith	**Sample type:**	Blood	**Report date:**	28-JUL-2026
DOB:	01-JAN-1990	**Sample collection date:**	27-JUL-2026	**Invitae #:**	RQ12009617
Sex assigned at birth:	Female	**Sample accession date:**	26-JUL-2026	**Clinical team:**	Aliza Baltimore
Gender:					
Patient ID (MRN):					

Test performed

Sequence analysis and deletion/duplication testing of the 163 genes listed in the Genes Analyzed section.

- Marker Consumer GHP

RESULT: POSITIVE

A clinically significant genetic change was found in the MYBPC3 gene, which is associated with a heart-related condition.

A clinically significant genetic change was found in the PMS2 gene, which is associated with hereditary cancer.

A single clinically significant genetic change was found in the HFE gene, which is associated with being a carrier for a hereditary condition.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
MYBPC3	c.3811C>T (p.Arg1271*)	heterozygous	PATHOGENIC
PMS2	c.123_131del (p.Leu42_Glu44del)	heterozygous	PATHOGENIC
HFE	c.187C>G (p.His63Asp)	heterozygous	Pathogenic (low penetrance)

About this test

This test evaluates 163 genes for variants (genetic changes) that indicate a significantly increased risk of developing certain types of actionable medical genetic conditions. These are disorders for which early detection may enable effective medical interventions and preventive measures. Genetic changes of uncertain significance are not included in this report; however, if additional evidence becomes available to indicate that a previously uncertain genetic change is clinically significant, the laboratory will update this report and provide notification.

Next steps

- This is a medically important result that should be discussed with an appropriate healthcare provider. Genetic counseling is recommended to discuss the implications of this result and potential next steps.
- Please see PMID: 29567486, 29904160, 32698598, 38718139, 27832612, 35363499, 38763377, and 39976316 for management guidelines regarding MYBPC3-related condition(s). Please see NCCN (**www.nccn.org**) for management guidelines regarding PMS2-related condition(s).
- Consider sharing this result with relatives as they may also be at risk. Details on our Family Variant Testing program can be found at **www.invitae.com/family**.

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Patient name: John Smith **DOB:** 01-JAN-1990
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Clinical summary

A Pathogenic variant, c.3811C>T (p.Arg1271*), was identified in MYBPC3.

- Certain genetic changes in the MYBPC3 gene significantly increase the risk for hereditary cardiomyopathy.
- This is a clinically significant result that increases the risk to develop MYBPC3-related conditions.
- Cardiomyopathy refers to a disease of the heart muscle that causes the heart to become weaker and less able to pump blood through the body. This can lead to heart failure or an abnormal heart rhythm (arrhythmia). Individuals with clinically significant genetic changes in the MYBPC3 gene have been reported to have an increased risk for hypertrophic cardiomyopathy or dilated cardiomyopathy. In hypertrophic cardiomyopathy, the heart muscle thickens, becoming stiff and less able to relax and fill with blood. In dilated cardiomyopathy, the heart's main pumping chamber becomes enlarged or weakened (dilated), preventing the heart from contracting normally. Individuals with multiple genetic changes in cardiomyopathy-related genes can have an earlier and/or more severe presentation. Screening and management guidelines exist to help identify and/or treat cardiomyopathy at an earlier stage. It is important to recognize that this result is not a diagnosis of cardiomyopathy and that not all individuals with a genetic change in MYBPC3 will develop cardiomyopathy.
- Since genetic changes are often shared within families, there is a chance that biological relatives may be at risk as well and could consider testing.

A Pathogenic variant, c.123_131del (p.Leu42_Glu44del), was identified in PMS2.

- Certain genetic changes in one copy of the PMS2 gene significantly increase the risk for an autosomal dominant condition known as Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC). If a person carries two clinically significant genetic changes, one in each copy of the PMS2 gene, this may result in an autosomal recessive condition known as constitutional mismatch repair deficiency syndrome (CMMR-D).
- This is a clinically significant result that increases the risk to develop autosomal dominant PMS2-related conditions.
- Individuals with Lynch syndrome due to a change in the PMS2 gene are more likely to develop one or more cancers involving the colon, uterus, ovaries, urinary tract, bladder, biliary tract, brain, and possibly prostate, small bowel, and pancreas. Screening and management guidelines exist to help prevent these cancers and/or identify them at an earlier stage. It is important to recognize that this result is not a diagnosis of cancer and not all individuals with a genetic change in PMS2 will develop cancer.

  CMMR-D is a rare, childhood-onset condition that increases the chance of developing certain cancers such as leukemia, lymphoma, brain tumors, and very early-onset colorectal cancer. Affected individuals will also typically have light brown birthmarks known as cafe-au-lait spots.
- Since genetic changes are often shared within families, there is a chance that biological relatives may be at risk for the autosomal dominant PMS2-related conditions. Additionally, being a carrier for the autosomal recessive PMS2-related conditions means there is a chance of having children with autosomal recessive PMS2-related conditions.

A Pathogenic (low penetrance) variant, c.187C>G (p.His63Asp), was identified in HFE.

- If a person carries two clinically significant genetic changes, one in each copy of the HFE gene, this may increase the risk for hereditary hemochromatosis (HH).
- This result is associated with being a carrier of autosomal recessive HFE-HH. Carriers typically do not have symptoms of the condition, but may be at risk to have a child with the condition.
- HH is characterized by excessive storage of iron in the skin, liver, pancreas, heart, and joints. Clinical symptoms are usually mild, but in cases of severe or untreated iron depositions, findings may include progressive increase in skin pigmentation, diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis, hypogonadism, osteoporosis, and liver disease, including cirrhosis and/or subsequent liver cancer. It is important to recognize that the genetic changes in HFE, the gene that most commonly causes HH, are known to have reduced penetrance. Reduced penetrance means that not all individuals with these genetic changes will show signs or symptoms of the condition. Penetrance is often higher in men than in women, and increases with age.
- Since genetic changes are often shared within families, there is a chance that biological relatives may be a carrier or at risk for autosomal recessive HFE-HH and could consider testing. The chance of having a child with autosomal recessive HFE-HH depends on whether this individual's partner is also a carrier of the same condition.

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Variant details

MYBPC3, Exon 33, c.3811C>T (p.Arg1271*), heterozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Arg1271*) in the MYBPC3 gene. While this is not anticipated to result in nonsense mediated decay, it is expected to disrupt the last 4 amino acid(s) of the MYBPC3 protein.
- This variant is present in population databases (rs397516042, gnomAD 0.003%).
- This premature translational stop signal has been observed in individuals with hypertrophic cardiomyopathy (PMID: 18533079, 23396983, 33673806; internal data).
- ClinVar contains an entry for this variant (Variation ID: 42744).
- Invitae Evidence Modeling of protein sequence and biophysical properties is not currently available for this gene. Multiple in silico approaches were evaluated; however, none provided predictions meeting internal confidence thresholds. The effect of this variant on MYBPC3 protein function cannot be predicted with sufficient confidence for clinical use.
- Experimental studies are conflicting or provide insufficient evidence to determine the effect of this variant on MYBPC3 function (PMID: 19574547).
- For these reasons, this variant has been classified as Pathogenic.

PMS2, Exon 2, c.123_131del (p.Leu42_Glu44del), heterozygous, PATHOGENIC

- This variant, c.123_131del, results in the deletion of 3 amino acid(s) of the PMS2 protein (p.Leu42_Glu44del), but otherwise preserves the integrity of the reading frame.
- This variant is not present in population databases (gnomAD no frequency).
- This variant has been observed in individual(s) with Lynch syndrome and constitutive mismatch repair deficiency syndrome (PMID: 25980754, 30653781; internal data). In at least one individual the data is consistent with being in trans (on the opposite chromosome) from a pathogenic variant.
- Invitae Evidence Modeling of clinical and family history, age, sex, and reported ancestry of multiple individuals with this PMS2 variant has been performed. This variant is expected to be pathogenic with a positive predictive value of at least 99%. This is a validated machine learning model that incorporates the clinical features of 1,627,235 individuals referred to our laboratory for PMS2 testing.
- ClinVar contains an entry for this variant (Variation ID: 216449).
- Algorithms developed to predict the effect of variants on gene product structure and function are not available or were not evaluated for this variant.
- Experimental studies have shown that this variant affects PMS2 function (PMID: 30653781).
- For these reasons, this variant has been classified as Pathogenic.

HFE, Exon 2, c.187C>G (p.His63Asp), heterozygous, Pathogenic (low penetrance)

- This sequence change replaces histidine, which is basic and polar, with aspartic acid, which is acidic and polar, at codon 63 of the HFE protein (p.His63Asp).
- This variant is present in population databases (rs1799945, gnomAD 14%), and has an allele count higher than expected for a pathogenic variant.
- This missense change has been observed in individual(s) with hemochromatosis (PMID: 11358905, 11399207, 16132052, 24729993). It has also been observed to segregate with disease in related individuals.
- ClinVar contains an entry for this variant (Variation ID: 10).
- Invitae Evidence Modeling of protein sequence and biophysical properties (such as structural, functional, spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) has been performed for this missense variant. However, the output from this modeling did not meet the statistical confidence thresholds required to predict the impact of this variant on HFE protein function.
- Experimental studies have shown that this missense change affects HFE function (PMID: 9162021, 9356458, 12429850, 14673107).
- In summary, this variant is reported to cause disease. However, as this variant is associated with a lower penetrance than other pathogenic alleles in the HFE gene, it has been classified as Pathogenic (low penetrance).

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Genes analyzed

This table represents a complete list of genes analyzed for this individual. Genes listed in this table may also have additional reported clinical associations outside of the conditions listed. Additional information about gene-condition associations can be found at **http://www.omim.org**. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

Cancer-related genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
APC*	NM_000038.5	Gastrointestinal, endocrine, nervous system/brain cancer, and sarcoma
ATM*	NM_000051.3	Breast, gynecologic, gastrointestinal, and prostate cancer
AXIN2	NM_004655.3	Gastrointestinal cancer
BAP1	NM_004656.3	Renal/urinary tract and skin cancer
BARD1	NM_000465.3	Breast cancer
BMPR1A	NM_004329.2	Gastrointestinal cancer
BRCA1	NM_007294.3	Breast, gynecologic, gastrointestinal, and prostate cancer
BRCA2	NM_000059.3	Breast, gynecologic, gastrointestinal, prostate, and skin cancer
BRIP1	NM_032043.2	Gynecologic cancer
CDC73	NM_024529.4	Endocrine and renal/urinary tract cancer
CDH1	NM_004360.3	Breast and gastrointestinal cancer, blepharocheilodontic syndrome
CDK4	NM_000075.3	Skin cancer
CDKN1B	NM_004064.4	Endocrine and gastrointestinal cancer
CDKN2A (p14ARF)	NM_058195.3	Skin and nervous system/brain cancer
CDKN2A (p16INK4a)	NM_000077.4	Skin and gastrointestinal cancer
CHEK2	NM_007194.3	Breast, endocrine, and prostate cancer
DICER1*	NM_177438.2	Endocrine, gynecologic, lung, nervous system/brain, renal/urinary tract cancer, and sarcoma
EGFR	NM_005228.3	Lung cancer
EPCAM*	NM_002354.2	Gastrointestinal, gynecologic, renal/urinary tract, nervous system/brain, prostate, and skin cancer
FH*	NM_000143.3	Renal/urinary tract, endocrine, nervous system/brain cancer, and sarcoma
FLCN	NM_144997.5	Renal/urinary tract cancer
GREM1*	NM_013372.6	Gastrointestinal cancer
HOXB13	NM_006361.5	Prostate cancer
KIT	NM_000222.2	Gastrointestinal cancer and sarcoma, immune condition, skin condition
LZTR1	NM_006767.3	Nervous system/brain cancer, Noonan spectrum disorders
MAX*	NM_002382.4	Endocrine and nervous system/brain cancer, polydactyly-macrocephaly syndrome
MEN1*	NM_130799.2	Endocrine, gastrointestinal, and nervous system/brain cancer, endocrine condition
MET*	NM_001127500.1	Renal/urinary tract cancer, skeletal condition
MITF	NM_000248.3	Skin cancer, Waardenburg syndrome
MLH1*	NM_000249.3	Gastrointestinal, gynecologic, renal/urinary tract, nervous system/brain, prostate, and skin cancer
MSH2*	NM_000251.2	Gastrointestinal, gynecologic, renal/urinary tract, nervous system/brain, prostate, and skin cancer
MSH3*	NM_002439.4	Gastrointestinal cancer
MSH6*	NM_000179.2	Gastrointestinal, gynecologic, renal/urinary tract, nervous system/brain, prostate, and skin cancer
MUTYH	NM_001128425.1	Gastrointestinal cancer
NF1*	NM_000267.3	Breast, endocrine, gastrointestinal, nervous system/brain cancer, and sarcoma
NF2	NM_000268.3	Nervous system/brain cancer
NTHL1	NM_002528.6	Gastrointestinal cancer
PALB2	NM_024675.3	Breast, gynecologic, gastrointestinal, and prostate cancer
PDGFRA	NM_006206.4	Gastrointestinal cancer and sarcoma
PMS2*	NM_000535.5	Gastrointestinal, gynecologic, renal/urinary tract, nervous system/brain, prostate, and skin cancer
POLD1*	NM_002691.3	Gastrointestinal cancer and MDPL syndrome
POLE	NM_006231.3	Gastrointestinal cancer
POT1	NM_015450.2	Skin and nervous system/brain cancer, and sarcoma
PRKAR1A	NM_002734.4	Endocrine, nervous system/brain cancer, and sarcoma, acrodysostosis
PTCH1	NM_000264.3	Skin, nervous system/brain cancer, and sarcoma
PTEN*	NM_000314.4	Breast, gynecologic, gastrointestinal, endocrine, renal/urinary tract, nervous system/brain, and skin cancer
RAD51C	NM_058216.2	Breast and gynecologic cancer
RAD51D	NM_002878.3	Breast and gynecologic cancer
RB1*	NM_000321.2	Retinoblastoma, skin cancer, and sarcoma
RET	NM_020975.4	Endocrine and nervous system/brain cancer, gastrointestinal condition

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SDHA*	NM_004168.3	Endocrine, nervous system/brain, and gastrointestinal cancer, sarcoma, mitochondrial disorder
SDHAF2	NM_017841.2	Endocrine and nervous system/brain cancer
SDHB	NM_003000.2	Endocrine, nervous system/brain, renal/urinary tract, and gastrointestinal cancer, sarcoma
SDHC*	NM_003001.3	Endocrine, nervous system/brain, renal/urinary tract, and gastrointestinal cancer, sarcoma
SDHD	NM_003002.3	Endocrine, nervous system/brain, and gastrointestinal cancer, sarcoma
SMAD4	NM_005359.5	Gastrointestinal cancer, hereditary hemorrhagic telangiectasia, aortopathy, Myhre syndrome
SMARCA4	NM_001128849.1	Gynecologic, nervous system/brain, and renal/urinary tract cancer, Coffin-Siris syndrome
SMARCB1	NM_003073.3	Nervous system/brain and renal/urinary tract cancer, Coffin-Siris syndrome
STK11	NM_000455.4	Breast, gynecologic, gastrointestinal, lung, and testicular cancer
TMEM127	NM_017849.3	Endocrine and nervous system/brain cancer
TP53	NM_000546.5	Breast, gynecologic, gastrointestinal, endocrine, nervous system/brain, renal/urinary tract, prostate, skin, and hematologic cancer, sarcoma
TSC1*	NM_000368.4	Endocrine, gastrointestinal, renal/urinary tract, and nervous system/brain cancer
TSC2	NM_000548.3	Endocrine, gastrointestinal, renal/urinary tract, and nervous system/brain cancer
VHL	NM_000551.3	Endocrine, gastrointestinal, renal/urinary tract, and nervous system/brain cancer
WT1	NM_024426.4	Renal/urinary tract cancer

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Cardiovascular-related genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
ACTA2	NM_001613.2	Aortopathy
ACTC1*	NM_005159.4	Cardiomyopathy, congenital heart disease, skeletal condition
ACTN2*	NM_001103.3	Cardiomyopathy, neuromuscular condition
ACVRL1	NM_000020.2	Hereditary hemorrhagic telangiectasia, pulmonary arterial hypertension
APOB	NM_000384.2	Familial hypercholesterolemia, familial hypobetalipoproteinemia
BAG3	NM_004281.3	Cardiomyopathy, neuromuscular condition
BMPR2	NM_001204.6	Pulmonary arterial hypertension
CACNA1C*	NM_000719.6;NM_001129840.1	Arrhythmia, Timothy syndrome
CALM1	NM_006888.4	Arrhythmia
CALM2	NM_001743.4	Arrhythmia
CALM3	NM_005184.2	Arrhythmia
CASQ2	NM_001232.3	Arrhythmia
CAV1	NM_001753.4	Pulmonary arterial hypertension, lipodystrophy
COL3A1*	NM_000090.3	Aortopathy
COL5A1	NM_000093.4	Connective tissue disorder
COL5A2	NM_000393.3	Connective tissue disorder
CSRP3	NM_003476.4	Cardiomyopathy
DES	NM_001927.3	Arrhythmia, cardiomyopathy, neuromuscular condition
DMD	NM_004006.2	Cardiomyopathy, neuromuscular condition
DSC2	NM_024422.4	Arrhythmia, cardiomyopathy
DSG2	NM_001943.3	Arrhythmia, cardiomyopathy
DSP	NM_004415.2	Arrhythmia, cardiomyopathy
ENG*	NM_000118.3	Hereditary hemorrhagic telangiectasia
FBN1	NM_000138.4	Marfan syndrome, lipodystrophy, connective tissue disorder, skeletal conditions
FHL1	NM_001449.4	Cardiomyopathy, neuromuscular condition
FLNC*	NM_001458.4	Arrhythmia, cardiomyopathy, neuromuscular conditions
GDF2	NM_016204.2	Hereditary hemorrhagic telangiectasia, pulmonary arterial hypertension
GLA	NM_000169.2	Fabry disease
HCN4	NM_005477.2	Arrhythmia, cardiomyopathy, aortopathy
JUP	NM_002230.2	Arrhythmia, cardiomyopathy
KCNE1	NM_000219.5	Arrhythmia
KCNH2	NM_000238.3	Arrhythmia
KCNJ2	NM_000891.2	Arrhythmia, Andersen-Tawil syndrome
KCNQ1	NM_000218.2	Arrhythmia
LAMP2	NM_002294.2	Danon disease
LDLR	NM_000527.4	Familial hypercholesterolemia
LDLRAP1	NM_015627.2	Familial hypercholesterolemia
LMNA	NM_170707.3	Arrhythmia, cardiomyopathy, neuromuscular conditions, progeria, lipodystrophy, and others
MYBPC3	NM_000256.3	Cardiomyopathy
MYH11	NM_001040113.1	Aortopathy, gastrointestinal condition
MYH7	NM_000257.3	Cardiomyopathy, neuromuscular condition
MYL2	NM_000432.3	Cardiomyopathy
MYL3	NM_000258.2	Cardiomyopathy
MYLK	NM_053025.3	Aortopathy
PCSK9*	NM_174936.3	Familial hypercholesterolemia
PKP2	NM_004572.3	Arrhythmia, cardiomyopathy
PLN	NM_002667.3	Arrhythmia, cardiomyopathy
PRKAG2	NM_016203.3	Arrhythmia, cardiomyopathy
PRKG1	NM_006258.3	Aortopathy
PROC	NM_000312.3	Hereditary thrombophilia
PROS1	NM_000313.3	Hereditary thrombophilia
RBM20	NM_001134363.2	Arrhythmia, cardiomyopathy
RYR2	NM_001035.2	Arrhythmia, cardiomyopathy
SCN5A	NM_198056.2	Arrhythmia, cardiomyopathy
SERPINC1	NM_000488.3	Hereditary thrombophilia
SGCD	NM_000337.5	Neuromuscular condition
SMAD3	NM_005902.3	Aortopathy
SMAD9	NM_001127217.2	Pulmonary arterial hypertension
TCAP	NM_003673.3	Cardiomyopathy
TGFB2	NM_003238.3	Aortopathy, skeletal condition
TGFB3	NM_003239.3	Aortopathy
TGFBR1	NM_004612.2	Aortopathy, skin tumors
TGFBR2	NM_003242.5	Aortopathy
TMEM43	NM_024334.2	Arrhythmia, cardiomyopathy
TNNC1	NM_003280.2	Cardiomyopathy
TNNI3	NM_000363.4	Cardiomyopathy
TNNT2	NM_001001430.2	Cardiomyopathy
TPM1	NM_001018005.1	Cardiomyopathy
TRDN	NM_006073.3	Arrhythmia
TTN*	NM_001267550.2	Cardiomyopathy, neuromuscular condition
TTR	NM_000371.3	Hereditary transthyretin-mediated amyloidosis
VCL	NM_014000.2	Cardiomyopathy

Other genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
ABCD1	NM_000033.3	X-linked adrenoleukodystrophy
ATP7B	NM_000053.3	Wilson disease
BTD	NM_000060.3	Biotinidase deficiency
CACNA1S	NM_000069.2	Malignant hyperthermia susceptibility, neuromuscular conditions
CAV3	NM_033337.2	Neuromuscular condition
CRYAB	NM_001885.2	Cataracts, neuromuscular condition
EMD	NM_000117.2	Neuromuscular condition
F11	NM_000128.3	Bleeding condition
F2	NM_000506.3	Bleeding condition
F5	NM_000130.4	Bleeding condition
F9	NM_000133.3	Bleeding condition
G6PD	NM_001042351.2	Glucose-6-phosphate dehydrogenase deficiency
GAA	NM_000152.3	Glycogen storage disease
GCH1	NM_000161.2	Neuromuscular condition
HAMP	NM_021175.2	Hereditary hemochromatosis
HFE	NM_000410.3	Hereditary hemochromatosis
HJV	NM_213653.3	Hereditary hemochromatosis
HMBS	NM_000190.3	Acute intermittent porphyria
HNF1A	NM_000545.5	Maturity-onset diabetes of the young
HNF1B	NM_000458.3	Renal cysts and diabetes syndrome
MEFV	NM_000243.2	Familial Mediterranean fever
OTC	NM_000531.5	Ornithine transcarbamylase deficiency
RPE65	NM_000329.2	Retinal dystrophy
RYR1	NM_000540.2	Malignant hyperthermia susceptibility, neuromuscular conditions
SERPINA1	NM_000295.4	Alpha-1 antitrypsin deficiency
SLC40A1	NM_014585.5	Hereditary hemochromatosis
TFR2	NM_003227.3	Hereditary hemochromatosis

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with >=50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated in the Genes Analyzed table. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed. Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Confirmation of the presence and location of reportable variants is performed as needed based on stringent criteria using one of several validated orthogonal approaches (PubMed ID 30610921). Sequencing is performed by Labcorp Genetics, Inc (1400 16th Street, San Francisco, CA 94103, #05D2040778). Confirmatory sequencing is performed by Labcorp Genetics, Inc (1400 16th Street, San Francisco, CA 94103, #05D2040778). RNA sequencing is performed by Labcorp Genetics, Inc (1400 16th Street, San Francisco, CA 94103, #05D2040778).

  The following additional analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. For C9orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Interpretation Reference Ranges: Benign (Normal Range): <25 repeat units, Uncertain: 25-30 repeat units, Pathogenic (Full Mutation): >=31 repeat units (PMID: 21944779, 22406228, 23111906, 28689190, 31315673, 33168078, 33575483). A second round of RP-PCR utilizing a non-overlapping set of primers is used to confirm the initial call in the case of suspected allele sizes of 22 or more repeats. For RNA analysis of the genes indicated in the Genes Analyzed table, complementary DNA is synthesized by reverse transcription from RNA derived from a blood specimen and enriched for specific gene sequences using capture hybridization. After high-throughput sequencing using Illumina technology, the output reads are aligned to a reference sequence (genome build GRCh37; custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test specimen is assessed quantitatively and compared to the usage seen in control specimens. Abnormal exon junction usage is evaluated as evidence in the Sherloc variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above, the presence of the variant is confirmed by targeted DNA sequencing.

- A portion of the analytic workflow, sequencing of DNA libraries, was performed at the Invitae clinical core sequencing facility (CLIA #None) located at None.
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at **http://www.ncbi.nlm.nih.gov/pubmed**.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC, gnomAD, and dbSNP.
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at **http://www.ncbi.nlm.nih.gov/medgen**. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance in Man (OMIM). Search by OMIM number at **http://omim.org/**.
- The laboratory uses information from individuals undergoing testing to inform variant interpretation. If "internal data" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

Limitations

Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. This test detects insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. In some situations, single-exon copy number events may not be confidently determined due to inherent

sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination. Genomic DNA derived from tissue cultured for extended periods of time are at increased risk for cell culture artifacts. Interpretations are made on the assumption that any clinical information provided, including specimen identity, is accurate. RNA analysis is not designed for use as a stand-alone diagnostic method and cannot determine absolute RNA levels. Results from the RNA analysis may not be informative for interpreting copy number events. Additionally, sensitivity to detect RNA splicing events may be reduced in regions that do not meet RNA detection thresholds, which may include variants in the first donor site of each gene and complex events, among others.

ACTC1: Sequencing analysis for exons 6 includes only cds +/- 10 bp. ACTN2: Deletion/duplication analysis is not offered for exon 9. APC: Sequencing analysis for exons 5 includes only cds +/- 10 bp. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. CACNA1C: Deletion/duplication and sequencing analysis is not offered for exons 44-45. COL3A1: Deletion/duplication analysis is not offered for exons 23-24. DICER1: Sequencing analysis for exons 22 includes only cds +/- 10 bp. ENG: Sequencing analysis for exons 7 includes only cds +/- 10 bp. EPCAM: Sequencing analysis is not offered for this gene. FH: Sequencing analysis for exons 9 includes only cds +/- 10 bp. FLNC: Deletion/duplication analysis is not offered for exon 47. Sensitivity and specificity for single nucleotide variants, insertions and deletions in exons 47-48 may be reduced due to the presence of segmental duplications overlapping the region. GREM1: Promoter region duplication testing only. MAX: Sequencing analysis for exons 2 includes only cds +/- 10 bp. MEN1: Sequencing analysis for exons 2 includes only cds +/- 10 bp. MET: Sequencing analysis for exons 12 includes only cds +/- 10 bp. MLH1: Sequencing analysis for exons 12 includes only cds +/- 10 bp. MSH2: Analysis includes the exon 1-7 inversion (Boland mutation). Sequencing analysis for exons 2, 5 includes only cds +/- 10 bp. MSH3: Sequencing analysis of the repeat region of exon 1 (5:79950697-79950765) is not offered. MSH6: Sequencing analysis for exons 7, 10 includes only cds +/- 10 bp. NF1: Sequencing analysis for exons 2, 7, 25, 41, 48 includes only cds +/- 10 bp. PCSK9: Sequencing analysis for exons 9 includes only cds +/- 10 bp. PMS2: Sequencing analysis for exons 7 includes only cds +/- 10 bp. POLD1: Sequencing analysis for exon 22 includes only cds +/- 10 bp and exon 27 includes only cds +-0 bp. PTEN: Sequencing analysis for exons 8 includes only cds +/- 10 bp. RB1: Sequencing analysis for exons 15-16 includes only cds +/- 10 bp. SDHA: Deletion/duplication analysis is not offered for this gene and sequencing analysis is not offered for exon 14. Sequencing analysis for exons 6-8 includes only cds +/- 10 bp. SDHC: Sequencing analysis for exons 2, 6 includes only cds +/- 10 bp. TSC1: Sequencing analysis for exons 21 includes only cds +/- 10 bp. TTN: Exons 45-46, 147, 149, 164, 172-201 (NM_001267550.2) are excluded from analysis. TTN variants are included in the primary report based on functional effect and/or location. A complete list of variants of uncertain significance, likely benign and benign variants in TTN is available upon request. Variants are named relative to the NM_001267550.2 (meta) transcript. Variants in the coding sequence and intronic boundaries of the clinically relevant NM_133378.4 (N2A) and fetal isoforms are reported (PMID: 25589632, 29598826, 29691892, 31660661), with the exception of the PEVK tandem repeat region (172-198) (PMID: 28040389).

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Labcorp Genetics. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

This report has been reviewed and approved by:

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