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CLIA: 22D0957540

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Metroplex Pathology Associates
Lakewood Pathology Associates
Cohen Dermatopathology
Therapath Partners

Patient Information:
18113, Donor
DOB: [redacted]
Sex: M
MR#:
Patient#: FT-PT8705340

Partner Information:
Not Tested

Physician:
Kuan, James
ATTN: Kuan, James
Denver Sperm Bank
4915 25th Avenue NE, Ste 204W
Seattle, WA 98105
Phone: (206) 588-1484

Laboratory:
Fulgent Therapeutics LLC
CAP#: 8042697
CLIA#: 05D2043189
Laboratory Director:
Lawrence M. Weiss, MD
Report Date: **Apr 29,2024**

Accession:
FT-7133881
Test#: FT-TS14811995
Specimen Type: Blood (EDTA)
Collected: Apr 11,2024

Accession:
N/A

FINAL RESULTS

Carrier for **ONE** genetic condition
Genetic counseling is recommended.

TEST PERFORMED

Beacon Preconception Carrier Screening - 515 Genes (without X-linked Disorders)
(515 Gene Panel; gene sequencing with deletion and duplication analysis)

Condition and Gene	Inheritance	18113, Donor	Partner
Leukoencephalopathy with vanishing white matter *EIF2B4*	AR	⊕ Carrier c.1462T>C (p.Tyr488His)	N/A

INTERPRETATION:

Notes and Recommendations:

- Based on these results, this individual is positive for a carrier mutation in 1 gene. Carrier screening for the reproductive partner is recommended to accurately assess the risk for any autosomal recessive conditions. A negative result reduces, but does not eliminate, the chance to be a carrier for any condition included in this screen. Please see the supplemental table for details.
- Testing for copy number changes in the SMN1 gene was performed to screen for the carrier status of Spinal Muscular Atrophy. The results for this individual are within the normal range for non-carriers. See Limitations section for more information.
- This carrier screening test does not screen for all possible genetic conditions, nor for all possible mutations in every gene tested. This report does not include variants of uncertain significance; only variants classified as pathogenic or likely pathogenic at the time of testing, and considered relevant for reproductive carrier screening, are reported. Please see the gene specific notes for details. Please note that the classification of variants can change over time.
- Patients may wish to discuss any carrier results with blood relatives, as there is an increased chance that they are also carriers. These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- X-linked genes are not routinely analyzed for male carrier screening tests. Gene specific notes and limitations may be present. See below.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National Society of Genetic Counselors (NSGC; https://www.nsgc.org)

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LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER

Patient	18113, Donor	Partner
Result	Carrier	N/A
Variant Details	***EIF2B4*** (NM_015636.3) c.1462T>C (p.Tyr488His)	N/A

What is Leukoencephalopathy with vanishing white matter?

Leukoencephalopathy with vanishing white matter (also called childhood ataxia with vanishing white matter) is a disorder of the central nervous system. It is characterized by progressive deterioration of the brain substance called white matter, which results in a decline of neurological functions eventually leading to lethargy, coma or death. Clinical progression commonly starts with abnormal or declining motor skills, seizures and spasticity, while intellectual decline and behavioral manifestations, such as delusions and emotional lability usually appear during later stages of the disease. The decline is typically periodic, with intervals of deterioration and external factors such as infections and head injuries, may accelerate the deterioration process. Onset of the decline may be as early as during pregnancy, but symptoms may also develop later in life. Some individuals with homozygous mutations have been described to be asymptomatic as adults. Onset during pregnancy or infancy typically leads to a rapid decline and death within the first two years of life. Severity and prognosis of the disorder are generally correlated with the time of onset, which has been shown to correlated at least to some extent with certain genetic changes.

What is my risk of having an affected child?

Leukoencephalopathy with vanishing white matter is inherited in an autosomal recessive manner. The risk for being a carrier for this condition is very low (carrier frequency less than 1/500). If the patient and the partner are both carriers, the risk for an affected child is 1 in 4 (25%).

What kind of medical management is available?

After diagnosis with leukoencephalopathy with vanishing white matter, affected individuals should be evaluated and monitored regularly for signs of neurological deterioration. Special care has to be taken to reduce the chances of infections and head injury, to prevent a more rapid disease progression. Physical therapy and rehabilitation as well as treatment of seizures and behavioral anomalies are common.

What mutation was detected?

The detected heterozygous variant was NM_015636.3:c.1462T>C (p.Tyr488His). This variant has been reported in the compound heterozygous state in 2 siblings with ovarioleukodystrophy (PubMed: 12707859). The laboratory classifies this variant as likely pathogenic.

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GENES TESTED:

Beacon Preconception Carrier Screening - 515 Genes (without X-linked Disorders) - 515 Genes

This analysis was run using the Beacon Preconception Carrier Screening - 515 Genes (without X-linked Disorders) gene list. 515 genes were tested with 99.5% of targets sequenced at >20x coverage. For more gene-specific information and assistance with residual risk calculation, see the SUPPLEMENTAL TABLE.

AAAS, ABCA12, ABCA3, ABCA4, ABCB11, ABCB4, ABCC2, ABCC8, ACAD9, ACADM, ACADVL, ACAT1, ACOX1, ACSF3, ADA, ADAMTS2, ADAMTSL4, ADGRG1, ADGRV1, AGA, AGL, AGPS, AGXT, AHI1, AIPL1, AIRE, ALDH3A2, ALDH7A1, ALDOB, ALG1, ALG6, ALMS1, ALPL, AMN, AMT, ANO10, AP1S1, AQP2, ARG1, ARL6, ARSA, ARSB, ASL, ASNS, ASPA, ASS1, ATM, ATP6V1B1, ATP7B, ATP8B1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BCKDHA, BCKDHB, BCS1L, BLM, BLOC1S3, BLOC1S6, BMP1, BRIP1, BSND, CAD, CANT1, CAPN3, CASQ2, CBS, CC2D1A, CC2D2A, CCDC103, CCDC39, CCDC88C, CD3D, CD3E, CD40, CD59, CDH23, CEP152, CEP290, CERKL, CFTR, CHAT, CHRNE, CHRNG, CIITA, CLCN1, CLN3, CLN5, CLN6, CLN8, CLRN1, CNGB3, COL11A2, COL17A1, COL27A1, COL4A3, COL4A4, COL7A1, COX15, CPS1, CPT1A, CPT2, CRB1, CRTAP, CRYL1, CTNS, CTSA, CTSC, CTSD, CTSK, CYBA, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1B1, CYP21A2, CYP27A1, CYP27B1, CYP7B1, DBT, DCAF17, DCLRE1C, DDX11, DGAT1, DGUOK, DHCR7, DHDDS, DLD, DLL3, DNAH11, DNAH5, DNAI1, DNAI2, DNMT3B, DOK7, DUOX2, DYNC2H1, DYSF, EIF2AK3, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, ELP1, EPG5, ERCC2, ERCC6, ERCC8, ESCO2, ETFA, ETFB, ETFDH, ETHE1, EVC, EVC2, EXOSC3, EYS, FAH, FAM161A, FANCA, FANCC, FANCD2, FANCE, FANCG, FANCI, FANCL, FBP1, FBXO7, FH, FKBP10, FKRP, FKTN, FMO3, FOXN1, FOXRED1, FRAS1, FREM2, FUCA1, G6PC, G6PC3, GAA, GALC, GALE, GALK1, GALNS, GALNT3, GALT, GAMT, GATM, GBA, GBE1, GCDH, GCH1, GDF5, GFM1, GHR, GJB2, GJB6, GLB1, GLDC, GLE1, GNE, GNPAT, GNPTAB, GNPTG, GNS, GORAB, GRHPR, GRIP1, GSS, GUCY2D, GUSB, HADH, HADHA, HADHB, HAMP, HAX1, HBA1, HBA2, HBB, HEXA, HEXB, HGSNAT, HJV, HLCS, HMGCL, HMOX1, HOGA1, HPD, HPS1, HPS3, HPS4, HPS5, HPS6, HSD17B3, HSD17B4, HSD3B2, HYAL1, HYLS1, IDUA, IGHMBP2, IKBKB, IL7R, INVS, ITGA6, ITGB3, ITGB4, IVD, JAK3, KCNJ1, KCNJ11, LAMA2, LAMA3, LAMB3, LAMC2, LARGE1, LCA5, LDLR, LDLRAP1, LHX3, LIFR, LIG4, LIPA, LMBRD1, LOXHD1, LPL, LRAT, LRP2, LRPPRC, LYST, MAK, MAN2B1, MANBA, MCEE, MCOLN1, MCPH1, MECR, MED17, MESP2, MFSD8, MKKS, MKS1, MLC1, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MOCS1, MOCS2, MPI, MPL, MPV17, MRE11, MTHFR, MTR, MTRR, MTTP, MUSK, MUT, MVK, MYO15A, MYO7A, NAGA, NAGLU, NAGS, NBN, NCF2, NDRG1, NDUFAF2, NDUFAF5, NDUFS4, NDUFS6, NDUFS7, NDUFV1, NEB, NEU1, NGLY1, NPC1, NPC2, NPHP1, NPHS1, NPHS2, NR2E3, NSMCE3, NTRK1, OAT, OCA2, OPA3, OSTM1, OTOA, OTOF, P3H1, PAH, PANK2, PC, PCBD1, PCCA, PCCB, PCDH15, PCNT, PDHB, PEPD, PET100, PEX1, PEX10, PEX12, PEX13, PEX16, PEX2, PEX26, PEX5, PEX6, PEX7, PFKM, PGM3, PHGDH, PHKB, PHKG2, PHYH, PIGN, PJVK, PKHD1, PLA2G6, PLEKHG5, PLOD1, PMM2, PNPO, POLG, POLH, POMGNT1, POMT1, POMT2, POR, POU1F1, PPT1, PRCD, PRDM5, PRF1, PROP1, PSAP, PTPRC, PTS, PUS1, PYGM, QDPR, RAB23, RAG1, RAG2, RAPSN, RARS2, RDH12, RLBP1, RMRP, RNASEH2A, RNASEH2B, RNASEH2C, RPE65, RPGRIP1L, RTEL1, RXYLT1, RYR1, SACS, SAMD9, SAMHD1, SCO2, SEC23B, SEPSECS, SGCA, SGCB, SGCD, SGCG, SGSH, SKIV2L, SLC12A1, SLC12A3, SLC12A6, SLC17A5, SLC19A2, SLC19A3, SLC1A4, SLC22A5, SLC25A13, SLC25A15, SLC25A20, SLC26A2, SLC26A3, SLC26A4, SLC27A4, SLC35A3, SLC37A4, SLC38A8, SLC39A4, SLC45A2, SLC4A11, SLC5A5, SLC7A7, SMARCAL1, SMN1, SMPD1, SNAP29, SPG11, SPR, SRD5A2, ST3GAL5, STAR, STX11, STXBP2, SUMF1, SUOX, SURF1, SYNE4, TANGO2, TAT, TBCD, TBCE, TCIRG1, TCN2, TECPR2, TERT, TF, TFR2, TG, TGM1, TH, TK2, TMC1, TMEM216, TMEM67, TMPRSS3, TPO, TPP1, TREX1, TRIM32, TRIM37, TRMU, TSEN54, TSFM, TSHB, TSHR, TTC37, TTPA, TULP1, TYMP, TYR, TYRP1, UBR1, UNC13D, USH1C, USH2A, VDR, VLDLR, VPS11, VPS13A, VPS13B, VPS45, VPS53, VRK1, VSX2, WISP3, WNT10A, WRN, XPA, XPC, ZBTB24, ZFYVE26, ZNF469

METHODS:

Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 99.51% and 99.46% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications are analyzed using Fulgent Germline proprietary pipeline for this specimen. Bioinformatics: The Fulgent Germline v2019.2 pipeline was used to analyze this specimen.

LIMITATIONS:

General Limitations

These test results and variant interpretation are based on the proper identification of the submitted specimen, accuracy of any stated familial relationships, and use of the correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributors, genetic or

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otherwise, to future pregnancies, and negative results do not rule out the genetic risk to a pregnancy. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (https://www.genenames.org) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the available clinical and family history information for this individual, collected published information, and Alamut annotation available at the time of reporting. This assay is not designed or validated for the detection of low-level mosaicism or somatic mutations. This assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions other than specified genes. DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) may not be detected by this test. Unless otherwise indicated, no additional assays have been performed to evaluate genetic changes in this specimen. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic alterations in both sequencing and deletion/duplication analyses. Deletion/duplication analysis can identify alterations of genomic regions which include one whole gene (buccal swab specimens and whole blood specimens) and are two or more contiguous exons in size (whole blood specimens only); single exon deletions or duplications may occasionally be identified, but are not routinely detected by this test. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not. Unless otherwise indicated, deletion/duplication analysis has not been performed in regions that have been sequenced by Sanger.

Gene Specific Notes and Limitations

ALG1: Due to the interference by highly homologous regions, our current testing method has less sensitivity to detect variants in exons 6-13 of the ALG1 gene (NM_019109.4). *CEP290:* Copy number analysis for exons 8-13 and exons 39-42 may have reduced sensitivity in the CEP290 gene. Confirmation of these exons are limited to individuals with a positive personal history of CEP290-related conditions and/or individuals carrying a pathogenic/likely pathogenic sequence variant. *CFTR:* Analysis of the intron 8 polymorphic region (e.g. IVS8-5T allele) is only performed if the p.Arg117His (R117H) mutation is detected. Single exon deletion/duplication analysis is limited to deletions of previously reported exons: 1, 2, 3, 11, 19, 20, 21. Analysis of the intron 8 polymorphic region (e.g. IVS8-5T allele) is only performed if the p.Arg117His (R117H) mutation is detected. Single exon deletion/duplication analysis is limited to deletions of previously reported exons: 1, 2, 3, 11, 19, 20, 21. CFTR variants primarily associated with CFTR-related isolated congenital bilateral absence of the vas deferens and CFTR-related pancreatitis are not included in this analysis. CFTR variants with insufficient evidence of being cystic fibrosis mutations will not be reported either. *CRYL1:* As mutations in the CRYL1 gene are not known to be associated with any clinical condition, sequence variants in this gene are not analyzed. However, to increase copy number detection sensitivity for large deletions including this gene and a neighboring on gene on the panel (GJB6, also known as connexin 30), this gene was evaluated for copy number variation. *CYP11B1:* The current testing method is not able to reliably detect certain pathogenic variants in this gene due to the interference by highly homologous regions. This analysis is not designed to detect or rule-out copy-neutral chimeric CYP11B1/CYP11B2 gene. *CYP11B2:* The current testing method is not able to reliably detect certain pathogenic variants in this gene due to the interference by highly homologous regions. This analysis is not designed to detect or rule-out copy-neutral chimeric CYP11B1/CYP11B2 gene. *CYP21A2:* Significant pseudogene interference and/or reciprocal exchanges between the CYP21A2 gene and its pseudogene, CYP21A1P, have been known to occur and may impact results. As such, the relevance of variants reported in this gene must be interpreted clinically in the context of the clinical findings, biochemical profile, and family history of each patient. LR-PCR is not routinely ordered for NM_000500.9:c.955C>T (p.Gln319Ter). Individuals with c.955C>T (p.Gln319Ter) will be reported as a Possible Carrier indicating that the precise nature of the variant has not been determined by LR-PCR and that the variant may occur in the CYP21A2 wild-type gene or in the CYP21A1P pseudogene. The confirmation test is recommended if the second reproductive partner is tested positive for variants associated with classic CAH. *DDX11:* Due to the interference by highly homologous regions, our current testing method has less sensitivity to detect variants in the DDX11 gene. *DUOX2:* The current testing method is not able to reliably detect variants in exons 6-8 of the DUOX2 gene (NM_014080.5) due to significant interference by the highly homologous gene, DUOX1. *FANCD2:* Due to pseudogene interference, copy-number-variants within exon 14-17 of the FANCD2 gene (NM _033084.4) are not evaluated and detection of single-nucleotide variants and small insertions/deletions in this region is not guaranteed. *GALT:* In general, the D2 "Duarte" allele is not reported if detected, but can be reported upon request. While this allele can cause positive newborn screening results, it is not known to cause clinical symptoms in any state. See GeneReviews for more information: https://www.ncbi.nlm.nih.gov/books/NBK1518/ *GBA:* Significant pseudogene interference and/or reciprocal exchanges between the GBA gene and its pseudogene, GBAP1, have been known to occur and may impact results. As such, the relevance of variants reported in this gene must be interpreted clinically in the context of this individual's clinical findings, biochemical profile, and family history. The current testing method cannot detect copy-neutral rearrangements between the pseudogene and the functional gene, which have been reported in very rare cases of Gaucher disease (PubMed: 21704274). *HBA1:* Significant interference

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from highly homologous regions in exons 1-2 of the HBA1 gene has been recognized to occur, potentially impeding the assay's technical capability to detect pathogenic alterations during sequencing analyses. *HBA2:* Significant interference from highly homologous regions in exons 1-2 of the HBA2 gene has been recognized to occur, potentially impeding the assay's technical capability to detect pathogenic alterations during sequencing analyses. *HSD17B4:* Copy number analysis for exons 4-6 may have reduced sensitivity in the HSD17B4 gene. Confirmation of these exons are limited to individuals with a positive personal history of D-bifunctional protein deficiency and Perrault syndrome and/or individuals carrying a pathogenic/likely pathogenic sequence variant. *LMBRD1:* Copy number analysis for exons 9-12 may have reduced sensitivity in the LMBRD1 gene. Confirmation of these exons are limited to individuals with a positive personal history of combined methylmalonic aciduria and homocystinuria and/or individuals carrying a pathogenic/likely pathogenic sequence variant. *MTHFR:* As recommended by ACMG, the two common polymorphisms in the MTHFR gene - c.1286A>C (p.Glu429Ala, also known as c.1298A>C) and c.665C>T (p.Ala222Val, also known as c.677C>T) - are not reported in this test due to lack of sufficient clinical utility to merit testing (PubMed: 23288205). *NEB:* This gene contains a 32-kb triplicate region (exons 82-105) which is not amenable to sequencing and deletion/duplication analysis. *NPHS2:* If detected, the variant NM_014625.3:c.686G>A (p.Arg229Gln) will not be reported as this variant is not significantly associated with disease when homozygous or in the compound heterozygous state with variants in exons 1-6 of NPHS2. *OTOA:* Due to pseudogene interference, our current testing method is not able to reliably detect variants in exons 20-28 (NM_144672.3) in the OTOA gene. *SMN1:* The current testing method detects sequencing variants in exon 7 and copy number variations in exons 7-8 of the SMN1 gene (NM_022874.2). Sequencing and deletion/duplication analysis are not performed on any other region in this gene. About 5%-8% of the population have two copies of SMN1 on a single chromosome and a deletion on the other chromosome, known as a [2+0] configuration (PubMed: 20301526). The current testing method cannot directly detect carriers with a [2+0] SMN1 configuration but can detect linkage between the silent carrier allele and certain population-specific single nucleotide changes. As a result, a negative result for carrier testing greatly reduces but does not eliminate the chance that a person is a carrier. Only abnormal results will be reported. *TERT:* The TERT promoter region is analyzed for both sequencing and copy number variants. *TYR:* Due to the interference by highly homologous regions, our current testing method has less sensitivity to detect variants in exons 4-5 of the TYR gene (NM_000372.5). *VPS45:* LoF is not a known disease mechanism *WRN:* Due to the interference by highly homologous regions within the WRN gene, our current testing method has less sensitivity to detect variants in exons 10-11 of WRN (NM_000553.6).

SIGNATURE:

Yan Meng, Ph.D., CGMB, FACMG on **4/29/2024**
Laboratory Director, Fulgent

DISCLAIMER:

This test was developed and its performance characteristics determined by Fulgent Therapeutics LLC CAP #8042697 CLIA #05D2043189; 4399 Santa Anita Ave., El Monte, CA, 91731. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. For assistance with interpretation of these results, healthcare professionals may contact us directly at **626-350-0537** or by email at **info@fulgentgenetics.com**. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.

To view the supplemental table describing the carrier frequencies, detection rates, and residual risks associated with the genes on this test please visit the following link:
Beacon Expanded Carrier Screening Supplemental Table

INVITAE

INVITAE PROACTIVE TESTING RESULTS

Patient name:	Donor 18113	**Sample type:**	Saliva	**Report date:**	04-MAR-2024
DOB:	[redacted]	**Sample collection date:**	23-FEB-2024	**Invitae #:**	RQ6233946
Sex assigned at birth:	Male	**Sample accession date:**	27-FEB-2024	**Clinical team:**	Guadalupe Martinez Dr. James Kuan
Gender:					
Patient ID (MRN):					

Test performed

Sequence analysis and deletion/duplication testing of the 65 genes listed in the Genes Analyzed section.

- Invitae Cancer Screen

RESULT: NEGATIVE

This test did not identify any genetic variation that is currently recognized as clinically significant.

About this test

This test evaluates 65 genes for variants (genetic changes) that indicate a significantly increased risk of developing certain types of cancer. These are disorders for which effective medical interventions and preventive measures are known and available. 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, Invitae will update this report and provide notification.

Next steps

- You can request a referral for genetic counseling to further discuss this test result and to review your family health history. A complete family history may point to health risks not evaluated by this test. It is important to note that while this test has found no genetic risk factors for certain types of conditions, at least a baseline, population-level risk remains for developing these types of disorders and age-appropriate screenings are still recommended.

- Register your test at **www.invitae.com/patients** to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.

Laboratory Director: Jeana DaRe, PhD, FACMG
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Clinical summary

There were no known, clinically significant genetic changes identified that confer a genetic predisposition to, or carrier status for, certain types of cancer tested with this panel (see complete list of genes and conditions evaluated below). However, other types of risk based on factors including personal and family history, genetic causes not evaluated with this test, lifestyle, or other environmental influences may still be of clinical significance.

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)
AIP	NM_003977.3	Familial isolated pituitary adenoma (FIPA)
APC*	NM_000038.5	Colorectal, Endocrine, Gastric, Nervous System/ Brain and Pancreatic Cancer, Sarcoma
ATM*	NM_000051.3	Breast, Ovarian, Pancreatic, Prostate Cancer
AXIN2	NM_004655.3	Colorectal Cancer
BAP1	NM_004656.3	BAP1 tumor predisposition syndrome
BARD1	NM_000465.3	Breast Cancer
BMPR1A	NM_004329.2	Colorectal, Gastric and Pancreatic Cancer
BRCA1	NM_007294.3	Breast, Gynecologic, Pancreatic and Prostate Cancer
BRCA2	NM_000059.3	Breast, Gynecologic, Pancreatic and Prostate Cancer, Melanoma
BRIP1	NM_032043.2	Breast and Gynecologic Cancer
CDC73	NM_024529.4	Endocrine and Renal/Urinary Tract Cancer
CDH1	NM_004360.3	Breast, Colorectal and Gastric Cancer
CDK4	NM_000075.3	Melanoma
CDKN1B	NM_004064.4	Multiple endocrine neoplasia type 4 (MEN4)
CDKN2A (p14ARF)	NM_058195.3	Nervous System/Brain Cancer, Melanoma
CDKN2A (p16INK4a)	NM_000077.4	Pancreatic Cancer, Melanoma
CHEK2	NM_007194.3	Breast, Colorectal, Endocrine, Prostate Cancer
DICER1*	NM_177438.2	Endocrine, Gynecologic, Nervous System/Brain and Renal/Urinary Tract, Lung Cancer, Sarcoma
EGFR	NM_005228.3	EGFR-related predisposition to lung cancer, Neonatal inflammatory skin and bowel disease
EPCAM*	NM_002354.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
FH*	NM_000143.3	Renal/Urinary Tract, Endocrine Cancer
FLCN	NM_144997.5	Renal/Urinary Tract Cancer
GREM1*	NM_013372.6	Colorectal Cancer
HOXB13	NM_006361.5	Prostate Cancer
KIT	NM_000222.2	Gastrointestinal Tumor or Cancer, Blood Cancer
LZTR1	NM_006767.3	Noonan spectrum disorders (NSDs) / RASopathies, Schwannomatosis
MAX*	NM_002382.4	Endocrine Cancer
MEN1*	NM_130799.2	Endocrine, Nervous System/Brain and Pancreatic Cancer
MET*	NM_001127500.1	Renal/Urinary Tract Cancer
MITF	NM_000248.3	Melanoma
MLH1*	NM_000249.3	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MSH2*	NM_000251.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MSH3*	NM_002439.4	Colorectal Cancer
MSH6*	NM_000179.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MUTYH	NM_001128425.1	Colorectal Cancer
NF1*	NM_000267.3	Breast, Endocrine, Gastric and Nervous System/ Brain Cancer
NF2	NM_000268.3	Nervous System/Brain Cancer
NTHL1	NM_002528.6	Colorectal Cancer
PALB2	NM_024675.3	Breast and Pancreatic Cancer
PDGFRA	NM_006206.4	Gastrointestinal Tumor or Cancer
PMS2*	NM_000535.5	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
POLD1*	NM_002691.3	Colorectal Cancer
POLE	NM_006231.3	Colorectal Cancer
POT1	NM_015450.2	POT1 tumor predisposition syndrome
PRKAR1A	NM_002734.4	Endocrine and Nervous System/Brain Cancer
PTCH1	NM_000264.3	Nervous System/Brain and Skin Cancer
PTEN*	NM_000314.4	Breast, Colorectal, Endocrine, Gynecologic, Nervous System/Brain and Renal/Urinary Tract Cancer, Melanoma
RAD51C	NM_058216.2	Breast, and Gynecologic Cancer
RAD51D	NM_002878.3	Breast, and Gynecologic Cancer
RB1*	NM_000321.2	Melanoma, Retinoblastoma, Sarcoma
RET	NM_020975.4	Endocrine Cancer
SDHA*	NM_004168.3	Endocrine, Gastrointestinal Tumor or Cancer

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
SDHAF2	NM_017841.2	Endocrine Cancer
SDHB	NM_003000.2	Endocrine, Gastrointestinal Tumor or Cancer, Renal/ Urinary Tract Cancer
SDHC*	NM_003001.3	Endocrine, Gastrointestinal Tumor or Cancer, Renal/ Urinary Tract Cancer
SDHD	NM_003002.3	Endocrine, Gastrointestinal Tumor or Cancer, Renal/ Urinary Tract Cancer
SMAD4	NM_005359.5	Colorectal, Gastric and Pancreatic Cancer
SMARCA4	NM_001128849.1	Gynecologic Cancer
SMARCB1	NM_003073.3	Nervous System/Brain and Renal/Urinary Tract Cancer
STK11	NM_000455.4	Breast, Gastrointestinal, Gynecologic, Testicular, Lung, and Pancreatic Cancer
TMEM127	NM_017849.3	Endocrine Cancer
TP53	NM_000546.5	Breast, Endocrine, Gastrointestinal, Genitourinary, Gynecologic, Hematologic, Nervous System/Brain and Skin Cancer, Sarcoma
TSC1*	NM_000368.4	Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
TSC2	NM_000548.3	Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
VHL	NM_000551.3	Endocrine, Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
WT1	NM_024426.4	Renal/Urinary Tract Cancer

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 Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). Confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). RNA sequencing is performed by Invitae Corporation (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 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 (**http://exac.broadinstitute.org**), gnomAD (**http://gnomad.broadinstitute.org**), and dbSNP (**http://ncbi.nlm.nih.gov/SNP**).
- 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/**.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" 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. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed 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. Interpretations are made on the assumption that any clinical information provided, including specimen identity, is accurate. Invitae's 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 for variants in the first donor site of each gene.

APC: Sequencing analysis for exons 5 includes only cds +/- 10 bp. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. DICER1: Sequencing analysis for exons 22 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. 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. MSH6: Sequencing analysis for exons 7, 10 includes only cds +/- 10 bp. PMS2: Sequencing analysis for exons 7 includes only cds +/- 10 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. GREM1: Promoter region duplication testing only. POLD1: Sequencing analysis for exon 22 includes only cds +/- 10 bp and exon 27 includes only cds +-0 bp. MSH3: Sequencing analysis of the repeat region of exon 1 (5:79950697-79950765) is not offered. NF1: Sequencing analysis for exons 2, 7, 25, 41, 48 includes only cds +/- 10 bp.

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 Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (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 released utilizing a validated procedure approved by:

Jeana DaRe

Jeana DaRe, Ph.D., FACMG
Laboratory Director

jd_0835_pr

INVITAE

NEGATIVE RESULTS GUIDE

What negative results mean for you

Your genetic test results were negative. This means that no significant genetic changes ("pathogenic variants" or "mutations") were found. Your risk for disease could still be influenced by a combination of unidentified genetic, personal, lifestyle and/or environmental risk factors.

Create a plan with your healthcare provider

Whether or not you develop a disease is not determined by your genetics alone. It is still important to share your genetic test results with your healthcare provider so they can help you make informed medical decisions.

What negative results mean for your family

Your genetic test was negative, however, your family members have their own unique genetic makeup. Genetic testing can help them understand their overall chance of developing a genetic disease.

We (and others) are here to help

Although your test didn't find any genetic changes, you may still have questions about your results or your personal or family medical history. A genetic counselor can help.

Log in to your patient portal (invitae.com) to view your results, search for a local or Invitae genetic counselor, or join Invitae's Patient Insight Network (PIN), a community where you can connect with other patients and share your experience.

This information in this results guide is meant to be used along with your genetic test results and other health information. It is not meant to replace a discussion with your healthcare provider and should not be considered or interpreted as medical advice.

1400 16th Street, San Francisco, CA 94103 • www.invitae.com • 800-436-3037 • 415-276-4164

18113,DONOR

DOB: [redacted] Age: [redacted]
Sex: M Fasting: U
Phone: (303) 970-5897
Patient ID: 18113

Specimen: DV767065M
Requisition: 0000096
Report Status: FINAL / SEE REPORT

Collected: 04/11/2024 11:11
Received: 04/11/2024 22:02
Reported: 04/24/2024 13:36

Client #: 70413924
BERRY,ANDREW
DENVER SPERM BANK
1601 E 19TH AVE STE 4500
DENVER, CO 80218-1289
Phone: (303) 970-5897

FASTING:UNKNOWN

CHROMOSOME ANALYSIS, BLOOD (FINAL)

Lab: EZ

Analyte	Value	
CHROMOSOME ANALYSIS, BLOOD (29770-5)	**See Below**	FINAL

```
Order ID:                 24-171666

Specimen Type:            Blood

Clinical Indication:      GAMETE DONOR

RESULT:
NORMAL MALE KARYOTYPE

INTERPRETATION:
Chromosome analysis revealed normal G-band patterns within
the limits of standard cytogenetic analysis.

Please expect the results of any other concurrent study in a
separate report.


NOMENCLATURE:
46,XY

ASSAY INFORMATION:
Method:                   G-Band (Digital Analysis: MetaSyst
Cells Counted:            20
Band Level:               450
Cells Analyzed:           5
Cells Karyotyped:         5

This test does not address genetic disorders that cannot be
detected by standard cytogenetic methods or rare events such
as low level mosaicism or subtle rearrangements.

Lauren Walters-Sen, PhD, FACMG         (800) NICHOLS-4307, [

Electronic Signature:             4/24/2024 2:38 PM
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Performing Sites

EZ Quest Diagnostics/Nichols SJC-San Juan Capistrano,, 33608 Ortega Hwy, San Juan Capistrano, CA 92675-2042 Laboratory Director: Irina Maramica MD,PhD,MBA

Key

Priority Out of Range | Out of Range | (PEND) Pending Result | (PRE) Preliminary Result | (FINAL) Final Result | (RE) Reissued Result