15 Crawford St., STE 100
Needham, MA 02494
(p) 626-350-0537
(f) 626-454-1667
Lab Director: Arash Radfar M.D.
CLIA: 22D0957540

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Patient Information:
18200, Donor
DOB: [redacted]
Sex: M
MR#:
Patient#: FT-PT8835814

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: **Sep 23,2024**

Accession:
FT-6982967
Test#: FT-TS14942804
Specimen Type: Blood (EDTA)
Collected: Sep 04,2024

Accession:
N/A

FINAL RESULTS

4 Carrier for genetic conditions in **multiple** genes.
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	18200, Donor	Partner
Mulibrey nanism *TRIM37*	AR	⊕ Carrier c.1081C>T (p.Arg361*)	N/A
Fumarase deficiency *FH*	AR	⊕ Carrier c.1431_1433dup (p.Lys477dup)	N/A
Congenital ichthyosis *TGM1*	AR	⊕ Carrier c.788G>A (p.Trp263*)	N/A
Alpha thalassemia *HBA2*	AR	⊕ Carrier Whole Gene Deletion (αα/α-)	N/A

INTERPRETATION:

Notes and Recommendations:

- **PLEASE NOTE: While some heterozygous variants in the FH gene have been associated with autosomal dominant hereditary leiomyomatosis and renal cell cancer (HLRCC) (PubMed: 11865300, 20301430, 31444830), the reported variant has not been associated with those findings.**
- Based on these results, this individual is positive for carrier mutations in 4 genes. 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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MULIBREY NANISM

Patient	18200, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***TRIM37*** (NM_015294.6) c.1081C>T (p.Arg361*)	N/A

What is Mulibrey nanism?

Mulibrey nanism is a growth disorder characterized by prenatal onset of poor growth with abnormalities of the heart, muscle liver, eye, and brain. Most affected individuals have a misshapen thorax, small trunk, low muscle tone, pericardial thickening, dysmorphic facies, and enlarged liver.

What is my risk of having an affected child?

TRIM37-related Mulibrey nanism is rare. 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?

Treatment is generally supportive therapies. Surgical cardiac intervention may provide a clinical benefit to reduce the progression of congestive heart failure. Some individuals may develop Wilms tumors and other tumors.

What mutation was detected?

The detected heterozygous variant was NM_015294.6:c.1081C>T (p.Arg361*). This variant is predicted to introduce a premature stop codon at least 50 nucleotides upstream of the canonical donor splice site of the penultimate exon and to result in the loss of function of the protein product due to nonsense-mediated mRNA decay (PubMed: 25741868, 30192042, 27618451, 11532962, 18066079). There's sufficient evidence that loss of function in this gene is a known disease mechanism for mulibrey nanism (PubMed: 28815877, 15108285, 29731032). The laboratory classifies this variant as likely pathogenic.

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FUMARASE DEFICIENCY

Patient	18200, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***FH*** (NM_000143.4) c.1431_1433dup (p.Lys477dup)	N/A

What is Fumarase deficiency?

Fumarase deficiency primarily affects the nervous system, especially the brain. It is typically characterized by early onset hypotonia, profound psychomotor retardation, and brain abnormalities, such as agenesis of the corpus callosum, gyral defects, and ventriculomegaly. Many affected individuals show neonatal distress, metabolic acidosis, and/or encephalopathy. Other symptoms include small head size (microcephaly), severe developmental delay, weak muscle tone (hypotonia), failure to thrive, seizures, enlarged liver and spleen (hepatosplenomegaly), excess red blood cells (polycythemia), deficiency of white blood cells (leukopenia), and/or unusual facies including a prominent forehead, low set ears, small jaw, widely spaced eyes, and depressed nasal bridge.

What is my risk of having an affected child?

Fumarase deficiency is inherited in an autosomal recessive manner. 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?

Expected survival of affected individuals is only a few months of life, although few have lived into early adulthood. There are no known therapeutic strategies at this time to reverse or prevent disease. Supportive treatment should be implemented to treat individuals' specific needs.

What mutation was detected?

The detected heterozygous variant was NM_000143.4:c.1431_1433dup (p.Lys477dup). This variant, p.Lys477dup, results in an in-frame insertion of one amino acid.This variant has been previously reported as homozygous or compound heterozygous in multiple patients with fumarase deficiency (PubMed: 36672771, 9300800, 9635293, 16510303, 23612258, 16151915).Functional studies of patient derived cells compound heterozygous for this variant and another loss-of-function FH variant have significantly reduced fumarate hydratase enzyme activity (0-20%), compared to wild-type cells (PubMed: 9300800, 9635293, 15987702, 16151915, 24182348).This variant is one of the most common mutations associated with fumarase deficiency, however, none of the published FH deficient cases are homozygous for p.Lys477dup (PubMed: 9635293, 16510303, 9300800, 24182348). Moreover, two presumably unaffected homozygous individuals are reported in the gnomAD database. While p.Lys477dup is associated with fumarase deficiency when compound heterozygous with a second disease mutation in the FH gene, additional evidence is needed to define the risk of disease in individuals homozygous for this variant. The laboratory classifies this variant as likely pathogenic.

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CONGENITAL ICHTHYOSIS

Patient	18200, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***TGM1*** (NM_000359.3) c.788G>A (p.Trp263*)	N/A

What is Congenital ichthyosis?

Autosomal recessive congenital ichthyosis (ARCI) is an inherited skin condition characterized by the disruption of the proper formation of proteins that are found in the outer layer of the skin (epidermis). Onset typically occurs at birth with a variable presentation of symptoms. Affected individuals are typically born with a tight, clear sheath covering their skin called a collodion membrane. This membrane will typically dry and peel off within the first few weeks of life, leaving scaly skin. Affected individuals are at increased risk for infections, dehydration, and respiratory problems, as well as abnormal hair loss, nail dystrophy, and decreased ability to sweat.

What is my risk of having an affected child?

Congenital ichthyosis is inherited in an autosomal recessive manner. The risk for being a carrier for Congenital ichthyosis is 1/224. 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?

While there remains no cure for congenital ichthyosis, the prognosis is good with early treatment. Management of symptoms includes moist environments with petroleum-based ointments to keep the skin hydrated. Regular surveillance is recommended to actively prevent infection, dehydration and overheating, and corneal drying.

What mutation was detected?

The detected heterozygous variant was NM_000359.3:c.788G>A (p.Trp263*). This variant is predicted to introduce a premature stop codon at least 50 nucleotides upstream of the canonical donor splice site of the penultimate exon and to result in the loss of function of the protein product due to nonsense-mediated mRNA decay (PubMed: 25741868, 30192042, 27618451, 11532962, 18066079). There is sufficient evidence that loss of function in this gene is a known disease mechanism for autosomal recessive congenital ichthyosis (PubMed: 31168818, 30578701, 18948357, 19241467, 11298529). This variant has been previously reported in homozygous and compound heterozygous state in multiple patients with congenital ichthyosis, and is considered a founder mutation in the Tunisian population (PubMed: 9544844, 27025581, 23192619, 34983512). This variant is classified as "Pathogenic" in ClinVar, with multiple submitters in agreement (Variation ID: 419403). The laboratory classifies this variant as pathogenic.

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ALPHA THALASSEMIA

Patient	18200, Donor	Partner
Result	⊕ Carrier	N/A
Variant Details	***HBA2*** (NM_000517.5) Whole Gene Deletion (αα/α-)	N/A

What is Alpha thalassemia?

Alpha thalassemia is a blood disorder that reduces the production of a protein called hemoglobin. This reduction in the amount of hemoglobin can prevent enough oxygen from reaching the body's tissues. Affected individuals may have anemia, which can cause pale skin, weakness, fatigue, and more serious complications. There are two distinct types of alpha thalassemia: the more severe type is known as Hb Bart syndrome, and the milder form is called HbH disease. Hb Bart syndrome is characterized by hydrops fetalis, a condition in which excess fluid builds up in the body before birth. Additional signs and symptoms can include severe anemia, hepatosplenomegaly (swollen liver and spleen), heart defects, and abnormalities of the urinary system or genitalia. As a result of these serious health problems, most babies with this condition are stillborn or die soon after birth. Hb Bart syndrome can also cause serious complications for women during pregnancy, including preeclampsia, premature delivery, and abnormal bleeding. HbH disease causes mild to moderate anemia, hepatosplenomegaly, and jaundice. Some affected individuals also have bone changes such as overgrowth of the upper jaw and an unusually prominent forehead.

See the table below for a description of the diseases associated with different combinations of HBA1 and HBA2 mutations.

Carrier Status of Partner 1	Carrier Status of Partner 2	Risk for a child with HbH disease (- -/-α)	Risk for a child with Hb Bart syndrome (- -/- -)
alpha thalassemia trait cis (αα/- -)	alpha thalassemia trait trans (α-/α-) or (-α/-α)	50%	No risk
	alpha thalassemia trait cis (αα/- -)	Residual Risk	25%
	silent carrier (αα/α-) or (αα/-α)	25%	Residual Risk
alpha thalassemia trait trans (α-/α-) or (-α/-α)	alpha thalassemia trait trans (α-/α-) or (-α/-α)	Residual Risk	Residual Risk
	silent carrier (αα/α-) or (αα/-α)	Residual Risk	Residual Risk
silent carrier (αα/α-) or (αα/-α)	silent carrier (αα/α-) or (αα/-α)	Residual Risk	Residual Risk

Note that carriers for single heterozygous deletions of HBA1 or HBA2 are commonly referred to as silent carriers (PubMed: 20301608).

What is my risk of having an affected child?

Generally, each person has two copies of the *HBA1* gene and two copies of the *HBA2* gene, or four copies (alleles) in total. The different forms of alpha thalassemia result from the loss of some or all of these alleles: Hb Bart syndrome results from the loss of all four alleles, while HbH disease results from the loss of three alleles. Alpha thalassemia is inherited in an autosomal recessive manner, which means that if one parent is a carrier for a loss of two alleles on one chromosome and a second parent is a carrier of a loss of one or more alleles on one chromosome, there is a 1 in 4 (25%) risk of having an affected child.

What kind of medical management is available?

There is currently no cure for alpha thalassemia. Medical management of Hb Bart syndrome is limited but may include blood transfusions or a stem cell transplant. For HbH disease, management can vary based on the severity of symptoms. Mild forms may have little effect on daily life, and management for such cases can include supplementation of iron or folic acid. Management for more severe cases usually requires regular transfusions. Untreated, the prognosis for HbH disease is poor, with a shortened lifespan of up to age 5 years. However, when treated, individuals with HbH disease may have a lifespan that approaches normal.

What mutation was detected?

The detected variant was a whole gene deletion (αα/α-) in the HBA2 gene (NM_000517.5). The detected mutation was a whole

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gene deletion in one of four alleles comprising the alpha globin locus. These results are consistent with having three functional copies of alpha-globin (αα/α-). If your partner is also a carrier for alpha thalassemia, there is an increased risk to have a child with HbH disease, but not hydrops fetalis. Genetic counseling is recommended. Individuals with a single alpha globin gene defect (αα/α-) are carriers and clinically asymptomatic. Deletions of HBA2 are common in many human populations (PubMed: 20301608, 25390741). The laboratory classifies this variant as 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 99.4% 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, 99.50% and 99.42% 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

15 Crawford St., STE 100
Needham, MA 02494
(p) 626-350-0537
(f) 626-454-1667
Lab Director: Arash Radfar M.D.
CLIA: 22D0957540

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:

Geetu Mendiratta-Vij, PhD, FACMG, CGMBS on **9/23/2024**
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

Patient Information	Specimen Information	Client Information
18200, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Fasting: U Phone: 303.970.5897 Patient ID: 18200 Health ID: 8573035126683842	Specimen: DV191085N Requisition: 0000138 Collected: 08/13/2024 / 11:05 MDT Received: 08/13/2024 / 21:45 MDT Reported: 08/22/2024 / 20:04 MDT	Client #: 70413924 DN99999 DENVER SPERM BANK 1601 E 19TH AVE STE 4500 DENVER, CO 80218-1289

COMMENTS: FASTING:UNKNOWN

Cytogenetic Report

CHROMOSOME ANALYSIS, BLOOD - 14596 Lab:EZ

CHROMOSOME ANALYSIS, BLOOD

Order ID: 24-383567
Specimen Type: Blood
Clinical Indication: GAMETE DONOR, RULE OUT CHROMOSOME

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.

Mark A. Micale, PhD, FACMG, [site SJC6]

Electronic Signature: 8/22/2024 9:23 PM

PERFORMING SITE:
EZ QUEST DIAGNOSTICS/NICHOLS SJC, 33608 ORTEGA HWY, SAN JUAN CAPISTRANO, CA 92675-2042 Laboratory Director: IRINA MARAMICA,MD,PHD,MBA, CLIA: 05D0643352