



Donor 5163

Genetic Testing Summary

Fairfax Cryobank recommends reviewing this genetic testing summary with your healthcare provider to determine suitability.

Last Updated: 12/10/21

Donor Reported Ancestry: French, Spanish, German, Irish

Jewish Ancestry: No

Genetic Test*	Result	Comments/Donor's Residual Risk**
Chromosome Analysis (karyotype)	Normal male karyotype	No evidence of clinically significant chromosome abnormalities
Hemoglobin evaluation	Normal hemoglobin fractionation and MCV/MCH results	Reduced risk to be a carrier for sickle cell anemia, beta thalassemia, alpha thalassemia trait (aa/-- and a-/a-) and other hemoglobinopathies
Cystic Fibrosis (CF) carrier screening	Negative by gene sequencing in the CFTR gene	1/1250
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 of the SMN1 gene	1/632
Additional standard testing attached- 22 diseases by gene sequencing	Non-carrier for genes sequenced	
Special Testing		
Chromosome Microarray as a follow-up to an offspring pregnancy report	Deletion of 7P22.1 Detected (See attached)	Offspring at 50% risk of inheriting this deletion. Genetic counseling indicated.
Polycystic Kidney Disease, Autosomal Recessive (PKHD1)	Carrier	Testing of the egg source is indicated before using this donor.
Globoid Cell Leukodystrophy (GALC)	Negative by gene sequencing in the GALC gene	<1/204
Nemaline Myopathy 2 (NEB)	Negative by gene sequencing in the NEB gene	1/1175
Wilson Disease (ATP7B)	Negative by gene sequencing in the ATP7B gene	1/248
Glycogen Storage Disease Type II (GAA)	Negative by gene sequencing in the GAA gene	1/310

Nephrotic Syndrome NPHS2 Related	Negative by gene sequencing in the NPHS2 gene	1/1881
Smith-Lemli-Opitz Syndrome (DHCR7)	Negative by gene sequencing in the DHCR7 gene	1/248
Galactosemia (GALT)	Negative by gene sequencing in the GALT gene	1/1679
Congenital Adrenal Hyperplasia due to 21 Hydroxylase Deficiency (CYP21A2)	Negative by gene sequencing in the CYP21A2 gene	1/200-non classic variant 1/1300-classic variant
Carnitine Palmitoyltransferase II Deficiency (CPT2)	Negative by gene sequencing in the CPT2 gene	1/670

*No single test can screen for all genetic disorders. A negative screening result significantly reduces, but cannot eliminate, the risk for these conditions in a pregnancy.

**Donor residual risk is the chance the donor is still a carrier after testing negative.

Client/Sending Facility:
Sema4

333 Ludlow Street / South Tower 3rd
Stamford, CT 06902
Ph: (800)298-6470
Fax: (646) 859-6871 CTB-10

LCLS Specimen Number: 306-225-1207-0

Patient Name: **5163, Donor**

Date of Birth: [REDACTED]

Gender: M

Patient ID: PM-1698709

Lab Number: YU21-96313 QC

Indications: FOLLOW-UP [REDACTED]

Account Number: 06007680

Ordering Physician: **1518415991**

Specimen Type: **DNA_TUBE**

Client Reference: K692

Date Collected: 11/02/2021

Date Received: 11/03/2021

Test: Follow-up Prenatal CMA qPCR

Genomic Targets: 1

Assay Type: QPCR

qPCR Result: DELETION OF 7P22.1 DETECTED

INTERPRETATION: DONOR CARRIER OF DELETION FOUND IN THE PRENATAL ANALYSIS [REDACTED]

rsa[hg19] 7p22.1(6,038,803-6,038,892)x1

Donor follow-up variant targeted qPCR analysis revealed the same copy number change as found in the **prenatal** analysis. Pathogenic variants including deletions in *PMS2* are associated with Lynch syndrome, which is characterized by an increased risk for colorectal cancer and other tumors including the GI, urological, female reproductive tract, and skin (see references). It is important to recognize that members of the same family who carry a *PMS2* mutation may or may not be affected (incomplete penetrance), and may have different types of cancer (variable expressivity).

Genetic counseling is recommended to discuss this deletion and evaluate the family history for cancer.

The FWD and REV qPCR primers were localized to the PMS2 gene.

References:

Kohlmann W, Gruber SB. Lynch Syndrome. 2004 Feb 5 [Updated 2018 Apr 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1211/>

Brea-Fernández et al. High incidence of large deletions in the *PMS2* gene in Spanish Lynch syndrome families. Clin Genet. 2014 Jun;85(6):583-8. PMID: 23837913.

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.



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Hiba Risheg, PhD., FACMG

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Medical Director

Stuart Schwartz, PhD

National Director of Cytogenetics

Technical component performed by Laboratory Corporation of America Holdings,

1904 TW Alexander Drive , RTP , NC , 27709-0153 (800) 345-4363

Professional Component performed by LabCorp CLIA 50D0630157, 550 17th Ave. Suite 200, Seattle WA 98122-5789. Medical Director, Daniel Towell, MD

Integrated Genetics is a brand used by Esoterix Genetic Laboratories, LLC, a wholly-owned subsidiary of Laboratory Corporation of America Holdings.

This document contains private and confidential health information **protected by state and federal law.**

Patient Information

Name: Donor 5163
Date of Birth: [REDACTED]
Sema4 ID: [REDACTED]
Client ID: [REDACTED]
Indication: Carrier Screening

Specimen Information

Specimen Type: Blood
Date Collected: 05/11/2018
Date Received: 12/07/2020
Final Report: 10/06/2021

Referring Provider

[REDACTED]
Fairfax Cryobank, Inc.

Unmask Additional Gene(s)

Number of genes tested: 1

SUMMARY OF RESULTS AND RECOMMENDATIONS

Positive

Carrier of Polycystic Kidney Disease, Autosomal Recessive (AR)

Associated gene(s): *PKHD1*

Variant(s) Detected: c.107C>T, p.T36M, Pathogenic, Heterozygous (one copy)

AR=Autosomal recessive; XL=X-linked

Recommendations

- Testing the partner for the above positive disorder(s) and genetic counseling are recommended.

Interpretation of positive results

Polycystic Kidney Disease, Autosomal Recessive (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic missense variant, c.107C>T, p.T36M, was detected in the *PKHD1* gene (NM_138694.3). When this variant is present in trans with a pathogenic variant, it is considered to be causative for autosomal recessive polycystic kidney disease. Therefore, this individual is expected to be at least a carrier for autosomal recessive polycystic kidney disease. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Polycystic Kidney Disease, Autosomal Recessive?

Polycystic kidney disease is an autosomal recessive, pan-ethnic disorder caused by pathogenic variants in the gene *PKHD1*. It is most prevalent in Afrikaners from South Africa, individuals of Ashkenazi Jewish descent, and Caucasians. Typically, the disease presents in the newborn period with enlarged kidneys causing renal disease and hypertension; at least half of these children will progress to end-stage renal disease by age 10. In severe cases, a deficiency of amniotic fluid, which is caused by the fetus' defective kidneys, results in lung underdevelopment and respiratory insufficiency, which may cause death in the first year of life. Hepatobiliary disease is present in more than half of affected infants and results in significant morbidity. With modern treatments, including kidney transplants, most patients survive childhood. Severity of disease cannot be predicted based on the genotype.

Test description

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested, and go.sema4.com/residualrisk for specific detection rates and residual risk by ethnicity. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.



Anastasia Larmore, Ph.D., Associate Laboratory Director

Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D



Genes and diseases tested

For specific detection rates and residual risk by ethnicity, please visit go.sema4.com/residualrisk

Table 1: List of genes and diseases tested with detailed results

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
⊕ Positive				
Polycystic Kidney Disease, Autosomal Recessive	PKHD1	AR	Carrier	c.107C>T, p.T36M, Pathogenic, Heterozygous (one copy)

AR=Autosomal recessive; XL=X-linked

Test methods and comments

Genomic DNA isolated from this patient was analyzed by one or more of the following methodologies, as applicable:

Fragile X CGG Repeat Analysis

PCR amplification using Asuragen, Inc. AmpliX® *FMR1* PCR reagents followed by capillary electrophoresis for allele sizing was performed. Samples positive for *FMR1* CGG repeats in the premutation and full mutation size range are further analyzed by Southern blot analysis to assess the size and methylation status of the *FMR1* CGG repeat.

Genotyping

Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY® System or Luminex® xMAP® technology were used to identify variants that are complex in nature or are present in low copy repeat regions and are, therefore, not amenable to Next Generation Sequencing technologies. Rare sequence variants may interfere with assay performance.

Multiplex Ligation-Dependent Probe Amplification (MLPA)

MLPA® probe sets and reagents, MRC-Holland, were used for the analysis of copy number of specific targets versus known control samples. Each target region was assayed with two adjacent oligonucleotide probes which following hybridization were ligated and used as template for subsequent rounds of amplification. Each complete probe within the assay has a unique length and amplicons are separated and identified by capillary electrophoresis. False positive or negative results may also occur due to rare sequence variants in target regions detected by MLPA probes. Analytical sensitivity and specificity of the MLPA method are both 99%.

For Alpha Thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation are assessed. However, it does not detect all known alpha-thalassemia mutations such as point mutations. In addition, carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, will not be detected. This test detects most alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation using Multiplex Ligation-Dependent Probe Amplification (MLPA). It is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. Therefore, this result reduces, but does not eliminate, the chance that this patient is a carrier of alpha-thalassemia. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported.

For Duchenne Muscular Dystrophy, the copy numbers of all *DMD* exons were analyzed. Please note that single-exon deletions and duplications will not be reported unless they are confirmed by NGS data (for example, if breakpoints occurring in an exon can be visualized).

For Spinal Muscular Atrophy (SMA), the copy numbers of the *SMN1* and *SMN2* genes were analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* and *SMN2* were assessed. Copy number gains and losses can be detected with this assay.

Depending on ethnicity 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *SMN1* gene on one chromosome and loss of *SMN1* (deletion) on the other chromosome (silent 20 carrier) or individuals that carry an intragenic mutation in *SMN1*. Please also note that 2% of individuals with SMA have an *SMN1* mutation that occurred *de novo*. Typically in these cases, only one parent is an SMA carrier.

The presence of the g.27134T>G variant allele in an individual with Ashkenazi Jewish or Asian ancestry is indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, g.27134T>G is likely indicative of a silent (20) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of g.27134T>G significantly increases or decreases, respectively, the likelihood of being a silent 20 carrier.

Next Generation Sequencing (NGS)

NGS was performed on a panel of genes for the purpose of identifying pathogenic or likely pathogenic variants.

Agilent SureSelect™ QXT technology was used with custom capture library to target the guaranteed list of mutations and exonic regions of the relevant genes. These targeted regions were sequenced using the Illumina HiSeq2500 system with 100 bp paired-end reads. The DNA sequences were mapped to and analyzed in comparison with the published human genome build UCSC hg19 reference sequence. The targeted coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage and data quality threshold values. This technology may not detect all small insertion/deletions and is not diagnostic for large duplications/deletions, repeat expansions, and structural genomic variation. This test will detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions will either not be detected or are not guaranteed to be detected. These regions include, but are not limited to, UTRs, promoters, and deep intronic areas or regions that fall within low copy repeat segments. In addition, a mutation(s) in a gene not included on the panel could be present in this patient. All potentially pathogenic variants may be confirmed by either a specific genotyping assay or Sanger sequencing, if indicated. Any benign variants, likely benign variants or variants of uncertain significance identified during this analysis were not reported.

Sanger Sequencing

Sanger sequencing, as indicated, was performed in both directions using BigDye Terminator chemistry with the ABI 3730 DNA analyzer with target specific amplicons. It also may be used to supplement specific guaranteed target regions that fail NGS sequencing due to poor quality or low depth of coverage <20 reads or as a confirmatory method for NGS positive results. False negative results may occur if rare variants interfere with amplification or annealing.

Tay-Sachs Disease (TSD) Enzyme Analysis

Hexosaminidase activity and Hex A % activity were measured by a standard heat-inactivation, fluorometric method using artificial 4-MU- β -N-acetyl glucosaminide (4-MUG) substrate. This assay is highly sensitive and accurate in detecting Tay-Sachs carriers and individuals affected with TSD. It is estimated that less than 0.5% of Tay-Sachs carriers have non-carrier levels of percent Hex A activity, and therefore may not be identified by this assay. In addition, this assay may detect individuals that are carriers of or are affected with Sandhoff Disease. False positive results, such as pseudodeficiency alleles, may occur if benign variants interfere with the enzymatic assay. False negative results may occur if both *HEXA* and *HEXB* pathogenic variants are present in the same individual.

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

SELECTED REFERENCES

Carrier Screening

Grody W et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med*. 2013 15:482-3.

Umbarger MA. Next-generation carrier screening. *Genet Med*. 2014 16:132-40.

Alpha-thalassemia:

Galanello R et al. Gene test review: Alpha-thalassemia. *Genet Med*. 2011 13:83-8.

Waye JS et al. Diagnostic testing for α -globin gene disorders in a heterogeneous North American population. *Int J Lab Hematol*. 2013 35:306-13.

Cystic Fibrosis:

ACOG Committee Opinion. Number 325, Update on carrier screening for cystic fibrosis. 2005.

Fragile X syndrome:

Chen L et al. An information-rich CGG repeat primed PCR that detects the full range of Fragile X expanded alleles and minimizes the need for Southern blot analysis. *J Mol Diag* 2010 12:589-600.

Spinal Muscular Atrophy:

Hendrickson BC et al. Differences in SMN1 allele frequencies among ethnic groups within North America. *J Med Genet*. 2009 46:641-4.

Ogino S et al. Genetic risk assessment in carrier testing for spinal muscular atrophy. *Am J Med Genet*. 2002 110:301-7.

Luo M et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. *Genet Med*. 2014 16:149-56.

Ashkenazi Jewish Disorders:

Scott SA et al. Experience with carrier screening and prenatal diagnosis for sixteen Ashkenazi Jewish Genetic Diseases. *Hum. Mutat*. 2010 31:1-11.

Duchenne Muscular Dystrophy:

Aartsma-Rus A et al. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve*. 2006b 34:135-44.

Flanigan KM et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. *Hum Mutat*. 2009 30:1657-66.

Beta Globin-related Disorders:

Cao A et al. Beta-Thalassemia. GeneReviews (<http://www.ncbi.nlm.nih.gov/books/BK1426/>)

Modell B et al. Epidemiology of haemoglobin disorders in Europe: an overview. *Scand J Clin Lab Invest*. 2007 67:39-69.

For further reading:

Orphanet: <http://www.orpha.net/consor/cgi-bin/index.php>

GeneReviews:



For Disease Specific Standards and Guidelines:

<https://www.acmg.net/>

Additional disease-specific references available upon request.

Ordering Practice:

Practice Code: [REDACTED]
Fairfax Cryobank - [REDACTED]
[REDACTED]
Physician: Suzanne Seitz
Report Generated: 2017-05-02

5163

DOB: [REDACTED]
Gender: Male
Ethnicity: Latin American and European
Procedure ID: 90320
Kit Barcode: [REDACTED]
Specimen: Blood, #91524
Specimen Received: 2017-04-17
Specimen Analyzed: 2017-05-01

Partner Not Tested

TEST INFORMATION


Test: CarrierMap^{SEQ} (Genotyping & Sequencing)
Panel: Fairfax Cryobank Panel V2- Sequencing
Diseases Tested: 22
Genes Tested: 22
Genes Sequenced: 18

SUMMARY OF RESULTS: NO MUTATIONS IDENTIFIED

5163 was not identified to carry any pathogenic mutations in the gene(s) tested.

No pathogenic mutations were identified in the genes tested, reducing but not eliminating the chance to be a carrier for the associated genetic diseases. CarrierMap assesses carrier status for genetic disease via molecular methods including targeted mutation analysis and/ or next-generation sequencing; other methodologies such as CBC and hemoglobin electrophoresis for hemoglobinopathies and enzyme analysis for Tay-Sachs disease may further refine risks for these conditions. Results should be interpreted in the context of clinical findings, family history, and/or other testing. A list of all the diseases and mutations screened for is included at the end of the report. This test does not screen for every possible genetic disease.

For additional disease information, please visit recombine.com/diseases. To speak with a Genetic Counselor, call 855.OUR.GENES.

Assay performed by 
Reprogenetics

CLIA ID: 31D1054821
3 Regent Street, Livingston, NJ 07039
Lab Technician: Bo Chu

Recombine CLIA # 31D2100763
Reviewed by Pere Colls, PhD, HCLD, Lab Director

ADDITIONAL RESULTS: NO INCREASED REPRODUCTIVE RISK

The following results are not associated with an increased reproductive risk.

Disease (Gene)	5163	Partner Not Tested
Spinal Muscular Atrophy: SMN1 Linked (SMN1) *	SMN1 Copy Number: 2 or more copies Method: dPCR & Genotyping	

* SMA Risk Information for Individuals with No Family History of SMA

	Detection Rate	Pre-Test Carrier Risk	Post-Test Carrier Risk (2 SMN1 copies)	Post-Test Carrier Risk (3 SMN1 copies)
European	95%	1/35	1/632	1/3,500
Ashkenazi Jewish	90%	1/41	1/350	1/4,000
Asian	93%	1/53	1/628	1/5,000
African American	71%	1/66	1/121	1/3,000
Hispanic	91%	1/117	1/1,061	1/11,000

For other unspecified ethnicities, post-test carrier risk is assumed to be <1%. For individuals with multiple ethnicities, it is recommended to use the most conservative risk estimate.

Methods and Limitations

Genotyping: Genotyping is performed using the Illumina Infinium Custom HD Genotyping assay to identify mutations in the genes tested. The assay is not validated for homozygous mutations, and it is possible that individuals affected with disease may not be accurately genotyped.

Sequencing: Sequencing is performed using a custom next-generation sequencing (NGS) platform. Only the described exons for each gene listed are sequenced. Variants outside of these regions may not be identified. Some splicing mutations may not be identified. Triplet repeat expansions, intronic mutations, and large insertions and deletions may not be detected. All identified variants are curated, and determination of the likelihood of their pathogenicity is made based on examining allele frequency, segregation studies, predicted effect, functional studies, case/control studies, and other analyses. All variants identified via sequencing that are reported to cause disease in the primary scientific literature will be reported. Variants considered to be benign and variants of unknown significance (VUS) are NOT reported. In the sequencing process, interval drop-out may occur, leading to intervals of insufficient coverage. Intervals of insufficient coverage will be reported if they occur.

Spinal Muscular Atrophy: Carrier status for SMA is assessed via copy number analysis by dPCR and via genotyping. Some individuals with a normal number of SMN1 copies (2 copies) may carry both copies of the gene on the same allele/chromosome; this analysis is not able to detect these individuals. Thus, a normal SMN1 result significantly reduces but does not eliminate the risk of being a carrier. Additionally, SMA may be caused by non-deletion mutations in the SMN1 gene; CarrierMap tests for some, but not all, of these mutations. Some SMA cases arise as the result of de novo mutation events which will not be detected by carrier testing.

Limitations: In some cases, genetic variations other than that which is being assayed may interfere with mutation detection, resulting in false-negative or false-positive results. Additional sources of error include, but are not limited to: sample contamination, sample mix-up, bone marrow transplantation, blood transfusions, and technical errors. The test does not test for all forms of genetic disease, birth defects, and intellectual disability. All results should be interpreted in the context of family history; additional evaluation may be indicated based on a history of these conditions. Additional testing may be necessary to determine mutation phase in individuals identified to carry more than one mutation in the same gene. All mutations included within the genes assayed may not be detected, and additional testing may be appropriate for some individuals.

This test was developed and its performance determined by Recombine, Inc., and it has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

Diseases & Mutations Assayed

Alpha Thalassemia (HBA1, HBA2): Mutations (9): ♂ Genotyping | SEA deletion, c.207C>A (p.N69K), c.223G>C (p.D75H), c.2T>C (p.M1T), c.207C>G (p.N69K), c.340_351delCTCCCGCCGAG (p.L114_E117del), c.377T>C (p.L126P), c.427T>C (p.X143Qext32), c.*+94A>G

Beta Thalassemia (HBB): Mutations (81): ♂ Genotyping | c.124_127delTTCT (p.F42Lfs), c.17_18delCT, c.20delA (p.E7Gfs), c.217insA (p.S73Kfs), c.223+702_444+342del620insAAGTAGA, c.230delC, c.25_26delAA, c.315+1G>A, c.315+2T>C, c.316-197C>T, c.316-146T>G, c.315+745C>G, c.316-1G>A, c.316-1G>C, c.316-2A>G, c.316-3C>A, c.316-3C>G, c.4delG (p.V2Cfs), c.51delC (p.K18Rfs), c.93-21G>A, c.92+1G>A, c.92+5G>A, c.92+5G>C, c.92+5G>T, c.92+6T>C, c.93-1G>A, c.93-1G>T, c.-50A>C, c.-78a>g, c.-79A>G, c.-81A>G, c.52A>T (p.K18X), c.-137c>g, c.-138c>t, c.-151C>T, c.118C>T (p.Q40X), c.169G>C (p.G57R), c.295G>A (p.V99M), c.415G>C (p.A139P), c.47G>A (p.W16X), c.48G>A (p.W16X), c.-80T>a, c.2T>C (p.M1T), c.75T>A (p.G25G), c.444+111A>G, c.-29g>a, c.68_74delAAGTTGG, c.92G>C (p.R31T), c.92+1G>T, c.93-15T>G, c.93-1G>C, c.112delT, c.113G>A (p.W38X), c.114G>A (p.W38X), c.126delC, c.444+113A>G, c.250delG, c.225delC, c.383_385delAGG (p.Q128_A129delQAinsP), c.321_322insG (p.N109fs), c.316-1G>T, c.316-2A>C, c.287_288insA (p.L97fs), c.271G>T (p.E91X), c.203_204delTG (p.V68Afs), c.154delC (p.P52fs), c.135delC (p.F46fs), c.92+2T>A, c.92+2T>C, c.90C>T (p.G30G), c.84_85insC (p.L29fs), c.59A>G (p.N20S), c.46delT (p.W16Gfs), c.45_46insG (p.L16fs), c.36delT (p.T13fs), c.2T>G (p.M1R), c.1A>G (p.M1V), c.-137c>t, c.-136c>g, c.-142c>t, c.-140c>t Sequencing | NM_000518:1-3

Bloom Syndrome (BLM): Mutations (25): ♂ Genotyping | c.2207_2212delATCTGainsTAGATTC (p.Y736Lfs), c.2407insT, c.557_559delCAA (p.S186X), c.1284G>A (p.W428X), c.1701G>A (p.W567X), c.1933C>T (p.Q645X), c.2528C>T (p.T843I), c.2695C>T (p.R899X), c.3107G>T (p.C1036F), c.2923delC (p.Q975K), c.3558+1G>T, c.3875-2A>G, c.2074+2T>A, c.2343_2344dupGA (p.781EfsX), c.318_319insT (p.L107fs), c.380delC (p.127Tfs), c.3564delC (p.1188Dfs), c.4008delG (p.1336Rfs), c.947C>G (p.S316X), c.2193+1_2193+9del9, c.1642C>T (p.Q548X), c.3143delA (p.1048NfsX), c.356_357delTA (p.C120Hfs), c.4076+1delG, c.3281C>A (p.S1094X) Sequencing | NM_000057:2-22

Canavan Disease (ASPA): Mutations (8): ♂ Genotyping | c.433-2A>G, c.854A>C (p.E285A), c.693C>A (p.Y231X), c.914C>A (p.A305E), c.71A>G (p.E24G), c.654C>A (p.C218X), c.2T>C (p.M1T), c.79G>A (p.G27R) Sequencing | NM_000049:1-6

Cystic Fibrosis (CFTR): Mutations (150): ♂ Genotyping | c.1029delC, 1153_1154insAT, c.1477delCA, c.1519_1521delATC (p.507del), c.1521_1523delCTT (p.508delF), c.1545_1546delTA (p.Y515Xfs), c.1585-1G>A, c.164+12T>C, c.1680-886A>G, c.1680-1G>A, c.1766+1G>A, c.1766+1G>T, c.1766+5G>T, c.1818del84, c.1911delG, c.1923delCTCAAACTinsA, c.1973delGAAATCAATCTinsAGAAA, c.2052delA (p.K684fs), c.2052insA (p.Q685fs), c.2051_2052delAAinsG (p.K6845fsX38), c.2174insA, c.261delIT, c.2657+5G>A, c.273+1G>A, c.273+3A>C, c.274-1G>A, c.2988+1G>A, c.3039delC, c.3140-26A>G, c.325delTAinsG, c.3527delC, c.3535delACCA, c.3691delT, c.3717+12191C>T, c.3744delG, c.3773_3774insT (p.L1258fs), c.442delA, c.489+1G>T, c.531delT, c.579+1G>T, c.579+5G>A (IVS4+5G>A), c.803delA (p.N268fs), c.805_806delAT (p.1269fs), c.933_935delCTT (p.311delF), c.946delT, c.1645A>C (p.S549R), c.2128A>T (p.K710X), c.1000C>T (p.R334W), c.1013C>T (p.T338I), c.1364C>A (p.A455E), c.1477C>T (p.Q493X), c.1572C>A (p.C524X), c.1654C>T (p.Q552X), c.1657C>T (p.R553X), c.1721C>A (p.P574H), c.2125C>T (p.R709X), c.223C>T (p.R75X), c.2668C>T (p.Q890X), c.3196C>T (p.R1066C), c.3276C>G (p.Y1092X), c.3472C>T (p.R1158X), c.3484C>T (p.R1162X), c.349C>T (p.R117C), c.3587C>G (p.S1196X), c.3712C>T (p.Q1238X), c.3764C>A (p.S1255X), c.3909C>G (p.N1303K), c.1040G>A (p.R347H), c.1040G>C (p.R347P), c.1438G>T (p.G480C), c.1558G>T (p.V520F), c.1624G>T (p.G542X), c.1646G>C (p.S549N), c.1646G>T (p.S549I), c.1652G>A (p.G551D), c.1675G>A (p.A559T), c.1679G>C (p.R560T), c.178G>T (p.E60X), c.1865G>A (p.G622D), c.254G>A (p.G85E), c.271G>A (p.G91R), c.274G>T (p.E92X), c.3209G>A (p.R1070Q), c.3266G>A (p.W1089X), c.3454G>C (p.D1152H), c.350G>A (p.R117H), c.3611G>A (p.W1204X), c.3752G>A (p.S1251N), c.3846G>A (p.W1282X), c.3848G>T (p.R1283M), c.532G>A (p.G178R), c.988G>T (p.G330X), c.1090T>C (p.S364P), c.3302T>A (p.M1101K), c.617T>G (p.L206W), c.14C>T (p.P51), c.19G>T (p.E7X), c.171G>A (p.W57X), c.313delA (p.I105fs), c.328G>C (p.D110H), c.580-1G>T, c.1055G>A (p.R352Q), c.1075C>A (p.Q359K), c.1079C>A (p.T360K), c.1647T>G (p.S549R), c.1976delA (p.N659fs), c.2290C>T (p.R764X), c.2737_2738insG (p.Y913X), c.3067_3072delATAGTG (p.I1023_V1024delT), c.3536_3539delCCAA (p.T1179fs), c.3659delC (p.T1220fs), c.54-5940_273+10250del21080bp (p.S18fs), c.4364C>G (p.S1455X), c.4003C>T (p.L1335F), c.2538G>A (p.W846X), c.200C>T (p.P67L), c.4426C>T (p.Q1476X), c.1116+1G>A, c.1986_1989delAACT (p.T663R), c.2089_2090insA (p.R697Kfs), c.2215delG (p.V739Y), c.263T>G (p.L196X), c.3022delG (p.V1008S), c.3908dupA (p.N1303Kfs), c.658C>T (p.Q220X), c.868C>T (p.Q290X), c.1526delG (p.G509fs), c.2908+1085-3367+260del7201, c.11C>A (p.S4X), c.3878_3881delTAAT (p.V1293fs), c.3700A>G (p.L1234V), c.416A>T (p.H139L), c.366T>A (p.Y122X), c.3767_3768insC (p.A1256fs), c.613C>T (p.P205S), c.293A>G (p.Q98R), c.3731G>A (p.G1244E), c.535C>A (p.Q179K), c.3368-2A>G, c.455T>G (p.M152R), c.1610_1611delAC (p.D537fs), c.3254A>G (p.H1085R), c.496A>G (p.K166E), c.1408_1417delGTGATTATGG (p.V470fs), c.1585-8G>A, c.2909G>A (p.G970D), c.653T>A (p.L218X), c.1175T>G (p.V392G), c.3139_3139+1delGG, c.3717+4A>G (IVS22+4A>G) Sequencing | NM_000492:1-27

Familial Dysautonomia (IKBKAP): Mutations (4): ♂ Genotyping | c.2204+6T>C, c.2741C>T (p.P914L), c.2087G>C (p.R696P), c.2128C>T (p.Q710X) Sequencing | NM_003640:2-37

Familial Hyperinsulinism: Type 1: ABCC8 Related (ABCC8): Mutations (11): ♂ Genotyping | c.3989-9G>A, c.4159_4161delITTC (p.1387delF), c.4258C>T (p.R1420C), c.4477C>T (p.R1493W), c.2147G>T (p.G716V), c.4055G>C (p.R1352P), c.560T>A (p.V187D), c.4516G>A (p.E1506K), c.2506C>T (p.Q836X), c.579+2T>A, c.1333-1013A>G (IVS8-1013A>G) Sequencing | NM_000352:1-39

Fanconi Anemia: Type C (FANCC): Mutations (8): ♂ Genotyping | c.456+4A>T, c.67delG, c.37C>T (p.Q13X), c.553C>T (p.R185X), c.1661T>C (p.L554P), c.1642C>T (p.R548X), c.66G>A (p.W22X), c.65G>A (p.W22X) Sequencing | NM_000136:2-15

Gaucher Disease (GBA): Mutations (6): ♂ Genotyping | c.84_85insG, c.1226A>G (p.N409S), c.1343A>T (p.D448V), c.1504C>T (p.R502C), c.1297G>T (p.V433L), c.1604G>A (p.R535H)

Glycogen Storage Disease: Type IA (G6PC): Mutations (13): ♂ Genotyping | c.376_377insTA, c.79delC, c.979_981delITTC (p.327delF), c.1039C>T (p.Q347X), c.247C>T (p.R83C), c.724C>T (p.Q242X), c.248G>A (p.R83H), c.562G>C (p.G188R), c.648G>T, c.809G>T (p.G270V), c.113A>T (p.D38V), c.975delG (p.L326fs), c.724delC Sequencing | NM_000151:1-5

Joubert Syndrome (TMEM216): Mutations (2): ♂ Genotyping | c.218G>T (p.R73L), c.218G>A (p.R73H) Sequencing | NM_001173991:1-5

Maple Syrup Urine Disease: Type 1B (BCKDHB): Mutations (6): ♂ Genotyping | c.1114G>T (p.E372X), c.548G>C (p.R183P), c.832G>A (p.G278S), c.970C>T (p.R324X), c.487G>T (p.E163X), c.853C>T (p.R285X) Sequencing | NM_183050:1-10

Maple Syrup Urine Disease: Type 3 (DLD): Mutations (8): ♂ Genotyping | c.104_105insA, c.685G>T (p.G229C), c.214A>G (p.K72E), c.1081A>G (p.M361V), c.1123G>A (p.E375K), c.1178T>C (p.I393T), c.1463C>T (p.P488L), c.1483A>G (p.R495G) Sequencing | NM_000108:1-14

Mucopolidosis: Type IV (MCOLN1): Mutations (5): ♂ Genotyping | c.-1015_788del6433, c.406-2A>G, c.1084G>T (p.D362Y), c.304C>T (p.R102X), c.244delC (p.L82fsX) Sequencing | NM_020533:1-14

Nemaline Myopathy: NEB Related (NEB): Mutations (2): ♂ Genotyping | c.7434_7536del2502bp, c.8890-2A>G (IVS63-2A>G) Sequencing | NM_001164508:63-66,86,95-96,103,105,143,168-172, NM_004543:3-149

Niemann-Pick Disease: Type A (SMPD1): Mutations (6): ♂ Genotyping | c.996delC, c.1493G>T (p.R498L), c.911T>C (p.L304P), c.1267C>T (p.H423Y), c.1734G>C (p.K578N), c.1493G>A (p.R498H) Sequencing | NM_000543:1-6

Sickle-Cell Anemia (HBB): Mutations (1): ♂ Genotyping | c.20A>T (p.E7V) Sequencing | NM_000518:1-3

Spinal Muscular Atrophy: SMN1 Linked (SMN1): Mutations (19): ♂ Genotyping | DEL EXON 7, c.22_23insA, c.43C>T (p.Q15X), c.91_92insT, c.305G>A (p.W102X), c.400G>A (p.E134K), c.439_443delGAAGT, c.558delA, c.585_586insT, c.683T>A (p.L228X), c.734C>T (p.P245L), c.768_778dupTGCTGATGCTT, c.815A>G (p.Y272C), c.821C>T (p.T274I), c.823G>A (p.G275S), c.834+2T>G, c.835-18_835-12delCCTTTAT, c.835G>T, c.836G>T dPCR | DEL EXON 7

Tay-Sachs Disease (HEXA): Mutations (78): ♂ Genotyping | c.1073+1G>A, c.1277_1278insATC, c.1421+1G>C, c.805+1G>A, c.532C>T (p.R178C), c.533G>A (p.R178H), c.805G>A (p.G269S), c.1510C>T (p.R504C), c.1496G>A (p.R499H), c.509G>A (p.R170Q), c.1003A>T (p.I335F), c.910_912delITTC (p.305delF), c.749G>A (p.G250D), c.632T>C (p.F211S), c.629C>T (p.S210F), c.613delC, c.611A>G (p.H204R), c.598G>A (p.V200M), c.590A>C (p.L39R), c.78G>A (p.W26X), c.1A>G>T (p.M1V), c.1495C>T (p.R499C), c.459+5G>A (IVS4+5G>A), c.1422-2A>G, c.535C>T (p.H179Y), c.1141delG (p.V381fs), c.796T>G (p.W266G), c.155C>A (p.S52X), c.426delT (p.F142fs), c.413-2A>G, c.570+3A>G, c.536A>G (p.H179R), c.1146+1G>A, c.736G>A (p.A246T), c.1302C>G (p.F434L), c.778C>T (p.P260S), c.1008G>T (p.Q336H), c.1385A>T (p.E462V), c.964G>A (p.D322N), c.340G>A (p.E114K), c.1432G>A (p.G478R), c.1178G>C (p.R393P), c.805+1G>C, c.1426A>T (p.R476X), c.623A>T (p.D208V), c.1537C>T (p.Q513X), c.1511G>T (p.R504L), c.1307_1308delITA (p.L436fs), c.571-8A>G, c.624_627delTCTCT (p.D208fs), c.1211_1212delITG (p.L404fs), c.621T>G (p.D207E), c.1511G>A (p.R504H), c.1177C>T (p.R393X), c.2T>C (p.M1T), c.1292G>A (p.W431X), c.947_948insA (p.Y316fs), c.607T>G (p.W203G), c.1061_1063delITCT (p.F354_Y355delinsX), c.615delG (p.L205fs), c.805+2T>C, c.1123delG (p.E375fs), c.1121A>G (p.Q374R), c.1043_1046delITCAA (p.F348fs), c.1510delC (p.R504fs), c.1451T>C (p.L484P), c.964G>T (p.D322V), c.1351C>G (p.L451V), c.571-2A>G (IVS5-2A>G) Sequencing | NM_000520:1-14

Usher Syndrome: Type 1F (PCDH15): Mutations (7): ♂ Genotyping | c.733C>T (p.R245X), c.2067C>A (p.Y684X), c.7C>T (p.R3X), c.1942C>T (p.R648X), c.1101delT (p.A367fsX), c.2800C>T (p.R934X), c.4272delA (p.L1425fs) Sequencing | NM_001142763:2-35

Usher Syndrome: Type 3 (CLRN1): Mutations (5): ♂ Genotyping | c.144T>G (p.N48K), c.131T>A (p.M120K), c.567T>G (p.Y189X), c.634C>T (p.Q212X), c.221T>C (p.L74P) Sequencing | NM_001195794:1-4

Walker-Warburg Syndrome (FKN): Mutations (5): ♂ Genotyping | c.1167insA (p.F390fs), c.139C>T (p.R47X), c.748T>G (p.C250G), c.648-1243G>T (IVS5-1243G>T), c.515A>G (p.H172R) Sequencing | NM_006731:2-10

Residual Risk Information

Detection rates are calculated from the primary literature and may not be available for all ethnic populations. The values listed below are for genotyping. Sequencing provides higher detection rates and lower residual risks for each disease. More precise values for sequencing may become available in the future.

Disease	Carrier Rate	Detection Rate	Residual Risk
Alpha Thalassemia	♂ General: 1/48	50.67%	1/97
Beta Thalassemia	♂ African American: 1/75	84.21%	1/475
	♂ Indian: 1/24	74.12%	1/93
	♂ Sardinians: 1/23	97.14%	1/804
	♂ Spaniard: 1/51	93.10%	1/739
Bloom Syndrome	♂ Ashkenazi Jewish: 1/134	96.67%	1/4,020
	♂ European: Unknown	66.22%	Unknown
	♂ Japanese: Unknown	50.00%	Unknown
Canavan Disease	♂ Ashkenazi Jewish: 1/55	98.86%	1/4,840
	♂ European: Unknown	53.23%	Unknown
Cystic Fibrosis	♂ African American: 1/62	69.99%	1/207
	♂ Ashkenazi Jewish: 1/23	96.81%	1/721
	♂ Asian: 1/94	65.81%	1/275
	♂ European: 1/25	94.96%	1/496
	♂ Hispanic American: 1/48	77.32%	1/212
	♂ Native American: 1/53	84.34%	1/338
Familial Dysautonomia	♂ Ashkenazi Jewish: 1/31	>99%	<1/3,100
Familial Hyperinsulinism: Type 1: ABCC8 Related	♂ Ashkenazi Jewish: 1/52	98.75%	1/4,160
	♂ Finnish: 1/101	45.16%	1/184
Fanconi Anemia: Type C	♂ Ashkenazi Jewish: 1/101	>99%	<1/10,100
	♂ General: Unknown	30.00%	Unknown
Gaucher Disease	♂ Ashkenazi Jewish: 1/15	87.16%	1/117
	♂ General: 1/112	31.60%	1/164
	♂ Spaniard: Unknown	44.29%	Unknown
	♂ Turkish: 1/236	59.38%	1/581
Glycogen Storage Disease: Type IA	♂ Ashkenazi Jewish: 1/71	>99%	<1/7,100
	♂ Chinese: 1/159	80.00%	1/795
	♂ European: 1/177	76.88%	1/765
	♂ Hispanic American: 1/177	27.78%	1/245
	♂ Japanese: 1/177	89.22%	1/1,641
Joubert Syndrome	♂ Ashkenazi Jewish: 1/92	>99%	<1/9,200
Maple Syrup Urine Disease: Type 1B	♂ Ashkenazi Jewish: 1/97	>99%	<1/9,700
Maple Syrup Urine Disease: Type 3	♂ Ashkenazi Jewish: 1/94	>99%	<1/9,400
	♂ General: Unknown	68.75%	Unknown
Mucopolipidosis: Type IV	♂ Ashkenazi Jewish: 1/97	96.15%	1/2,522
Nemaline Myopathy: NEB Related	♂ Ashkenazi Jewish: 1/108	>99%	<1/10,800

Disease	Carrier Rate	Detection Rate	Residual Risk
Niemann-Pick Disease: Type A	♂ Ashkenazi Jewish: 1/101	95.00%	1/2,020
Sickle-Cell Anemia	♂ African American: 1/10	>99%	<1/1,000
	♂ Hispanic American: 1/95	>99%	<1/9,500
Tay-Sachs Disease	♂ Argentinian: 1/280	82.35%	1/1,587
	♂ Ashkenazi Jewish: 1/29	99.53%	1/6,177
	♂ Cajun: 1/30	>99%	<1/3,000
	♂ European: 1/280	25.35%	1/375
	♂ General: 1/280	32.09%	1/412
	♂ Indian: Unknown	85.71%	Unknown
	♂ Iraqi Jewish: 1/140	56.25%	1/320
	♂ Japanese: 1/127	82.81%	1/739
	♂ Moroccan Jewish: 1/110	22.22%	1/141
	♂ Portuguese: 1/280	92.31%	1/3,640
	♂ Spaniard: 1/280	67.65%	1/865
	♂ United Kingdom: 1/161	71.43%	1/564
Usher Syndrome: Type 1F	♂ Ashkenazi Jewish: 1/126	93.75%	1/2,016
Usher Syndrome: Type 3	♂ Ashkenazi Jewish: 1/120	>99%	<1/12,000
	♂ Finnish: 1/134	>99%	<1/13,400
Walker-Warburg Syndrome	♂ Ashkenazi Jewish: 1/150	>99%	<1/15,000

Ordering Practice

Practice Code: [REDACTED]
Fairfax Cryobank [REDACTED]
[REDACTED]
Physician: [REDACTED]
Report Generated: 2018-04-20

Donor 5163

DOB: [REDACTED]
Gender: Male
Ethnicity: European, Latin American
Procedure ID: 90,320
Kit Barcode: [REDACTED]
Specimen: Blood, #91,524
Specimen Collection: 2017-04-14
Specimen Received: 2017-04-17
Specimen Analyzed: 2018-04-13

Partner Not Tested

TEST INFORMATION

Test: Carriermap^{SEO} (Genotyping & Sequencing)
Panel: Custom Panel
Diseases Tested: 1
Genes Tested: 1
Genes Sequenced: 1

SUMMARY OF RESULTS: NO MUTATIONS IDENTIFIED

Donor 5163 was not identified to carry any pathogenic mutations in the gene(s) tested

No pathogenic mutations were identified in the genes tested, reducing but not eliminating the chance to be a carrier for the associated genetic diseases. CarrierMap assesses carrier status for genetic disease via molecular methods including targeted mutation analysis and/ or next-generation sequencing; other methodologies such as CBC and hemoglobin electrophoresis for hemoglobinopathies and enzyme analysis for Tay-Sachs disease may further refine risks for these conditions. Results should be interpreted in the context of clinical findings, family history, and/or other testing. A list of all the diseases and mutations screened for is included at the end of the report. This test does not screen for every possible genetic disease.

For additional disease information, please visit www.coopergenomics.com/diseases . To speak with a genetic counselor, call 855.687.4363 .

Methods and Limitations

Genotyping : Genotyping is performed using the Illumina Infinium Custom HD Genotyping assay to identify mutations in the genes tested. The assay is not validated for homozygous mutations, and it is possible that individuals affected with disease may not be accurately genotyped.

Sequencing : Sequencing is performed using a custom next-generation sequencing (NGS) platform. Only the described exons for each gene listed are sequenced. Variants outside of these regions may not be identified. Some splicing mutations may not be identified. Triplet repeat expansions, intronic mutations, and large insertions and deletions may not be detected. All identified variants are curated, and determination of the likelihood of their pathogenicity is made based on examining allele frequency, segregation studies, predicted effect, functional studies, case/control studies, and other analyses. All variants identified via sequencing that are reported to cause disease in the primary scientific literature will be reported. Variants considered to be benign and variants of unknown significance (VUS) are NOT reported. VUS reporting can be requested and will be assessed on a case-by-case basis. Variants may be re-curated over time due to emerging literature or other information. In the sequencing process, interval drop-out may occur, leading to intervals of insufficient coverage. Intervals of insufficient coverage will be reported if they occur.

Limitations: In some cases, genetic variations other than that which is being assayed may interfere with mutation detection, resulting in false-negative or false-positive results. Additional sources of error include, but are not limited to: sample contamination, sample mix-up, bone marrow transplantation, blood transfusions, and technical errors. The test does not test for all forms of genetic disease, birth defects, and intellectual disability. All results should be interpreted in the context of family history; additional evaluation may be indicated based on a history of these conditions. Additional testing may be necessary to determine mutation phase in individuals identified to carry more than one mutation in the same gene. All existing mutations within the genes assayed may not be detected, and additional testing may be appropriate for some individuals.

This test was developed and its performance determined by Recombine, Inc., and it has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA does not currently regulate laboratory developed tests (LDTs).

Diseases & Mutations Assayed

Globoid Cell Leukodystrophy (GALC): Mutation(s) (10): ♂ Genotyping | c.1153G>T (p.E385X), c.1161+6555_*9573del31670bp, c.1472delA (p.K491fs), c.1586C>T (p.T529M), c.1700A>C (p.Y567S), c.2002A>C (p.T668P), c.246A>G (p.I82M), c.683_694delATCTCTGGGAGTinsCTC (p.N228_S232del5insTP), c.857G>A (p.G286D), c.913A>G (p.I305V) | Sequencing | NM_000153:2-17

Residual Risk Information

Detection rates are calculated from the primary literature and may not be available for all ethnic populations. The values listed below are for genotyping. Sequencing provides higher detection rates and lower residual risks for each disease. More precise values for sequencing may become available in the future.

Disease	Carrier Rate	Detection Rate	Residual Risk
Globoid Cell	♂ Dutch: 1/137	60.98%	1/351
Leukodystrophy	♂ European: 1/150	26.47%	1/204
	♂ Japanese: 1/150	36.00%	1/234

Patient	Sample	Referring Doctor
Patient Name: Donor 5163 Date of Birth: [REDACTED] Reference #: P0642160 Indication: Carrier Testing Test Type: NGS single gene full sequencing test	Specimen Type: Blood Lab #: [REDACTED] Date Collected: 5/11/2018 Date Received: 5/12/2018 Final Report: 5/26/2018	Fairfax Cryobank [REDACTED] [REDACTED] [REDACTED]

RESULT SUMMARY

NGS single gene full sequencing test

Results: No clinically significant variant(s) detected

Gene(s) analyzed: *NEB* and *ATP7B*

Interpretation: Screening for the presence of pathogenic variants in the *NEB* and *ATP7B* genes which are associated with nemaline myopathy 2 and Wilson disease, respectively, was performed by next generation sequencing and possibly genotyping for select variants on DNA extracted from this patient's sample. No clinically significant variants were detected during this analysis. This negative result does not rule out the possibility that a pathogenic variant in the genes examined is present.

Genetic counseling is recommended.

This technology may not detect all small insertion/deletions and is not diagnostic for large duplications/deletions and structural genomic variation. The coding DNA sequence of the gene plus at least five base pairs flanking splice sites were sequenced and analyzed relative to the hg19 assembly. A mutation(s) deep in intronic sequences or in untranslated regions of the gene except a portion described above or a pathogenic variant(s) in other genes not included in this test could be present in this patient. The analytical sensitivity of this test is estimated at 99% for single base substitutions and 97% overall. All potentially pathogenic variants were subjected to Sanger sequencing or genotyping by allele specific primer extension analysis for confirmation of the result. Any benign variants identified during this analysis were not reported.

Please note that this carrier screening test masks likely benign variants and variants of uncertain significance (VUS) if there are any. Only known pathogenic variants or likely pathogenic variants which are expected to result in deleterious effects on protein function are reported. If reporting of likely benign variants and VUS is desired in this patient, please contact the laboratory (tel. 212-241-2537) to request an amended report.

Comments: This test was developed and its performance characteristics were determined by Mount Sinai Genomics, Inc. It is considered acceptable for patient testing. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary.

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This type of mutation analysis generally provides highly accurate genotype information for point mutations and single nucleotide polymorphisms. Despite this level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, mosaicism or other rare genetic variants that interfere with analysis. In addition, families should understand the limitations of the testing and that rare diagnostic errors may occur for the reasons described.

For Disease Specific Standards and Guidelines:

<https://www.acmg.net/>

Additional disease-specific references available upon request.

This case has been reviewed and electronically signed by Rebekah Zimmerman, Ph.D., FACMG, Laboratory Director

Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D.

Table of Residual Risks by Ethnicity

Please note: This table displays residual risks after a negative result for each of the genes and corresponding disorders. **If a patient is reported to be a carrier of a disease, their residual risk is 1 and this table does not apply for that disease.**

Disease (Inheritance)	Gene	Ethnicity	Carrier Frequency	Detection Rate	Residual Risk	Analytical Detection Rate
Nemaline Myopathy 2 (AR) NM_001271208.1 <i>Exception: Exons 82 - 105</i>	NEB	Ashkenazi Jewish	1 in 168	>95%	1 in 3341	>95%
		Worldwide	1 in 224	81%	1 in 1175	94%
		Finnish	1 in 112	75%	1 in 445	75%
Wilson Disease (AR) NM_000053.3	ATP7B	Caucasian	1 in 90	64%	1 in 248	>95%
		Asian	1 in 50	63%	1 in 133	>95%
		Ashkenazi Jewish	1 in 67	>95%	1 in 1321	>95%
		Worldwide	1 in 90	79%	1 in 425	>95%
		Canary Islands	1 in 25	88%	1 in 201	>95%
		Sardinian	1 in 42	>95%	1 in 821	>95%
		Sephardic Jewish - North African,	1 in 65	>95%	1 in 1281	>95%
		Iraqi, Yemenite, Iranian and Bukharian				

AR: Autosomal Recessive

Patient	Sample	Referring Doctor
Patient Name: Donor 5163 Date of Birth: [REDACTED] Reference #: [REDACTED] Indication: Carrier Testing Test Type: Unmask Additional Gene(s)	Specimen Type: Blood Lab #: [REDACTED] Date Collected: 5/11/2018 Date Received: 2/13/2020 Final Report: 3/3/2020	[REDACTED] Fairfax Cryobank, Inc. [REDACTED] [REDACTED] [REDACTED] [REDACTED]

RESULT SUMMARY

Negative: No clinically significant variant(s) detected

Gene(s) analyzed: *DHCR7*, *GAA*, and *NPHS2*

Recommendations:

Consideration of residual risk by ethnicity after a negative carrier screen is recommended, especially in the case of a positive family history for a specific disorder.

Interpretation:

Screening for the presence of pathogenic variants in the *DHCR7*, *GAA*, and *NPHS2* genes which are associated with Smith-Lemli-Opitz syndrome, glycogen storage disease, type II, and nephrotic syndrome (*NPHS2*-related) / steroid-resistant nephrotic syndrome, respectively, was performed by next generation sequencing and possibly genotyping for select variants on DNA extracted from this patient's sample. No clinically significant variants were detected during this analysis.

Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for the disorder(s) tested. Please see table of residual risks for specific detection rates and residual risk by ethnicity. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.

Comments:

This carrier screening test masks likely benign variants and variants of uncertain significance (VUS) if there are any. Only known pathogenic variants or likely pathogenic variants which are expected to result in deleterious effects on protein function are reported. If reporting of likely benign variants and VUS is desired in this patient, please contact the laboratory (tel. 212-241-2537) to request an amended report.

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

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Table of Residual Risks by Ethnicity

Please note: This table displays residual risks after a negative result for each of the genes and corresponding disorders. **If a patient is reported to be a carrier of a disease, their residual risk is 1 and this table does not apply for that disease.**

Disease (Inheritance)	Gene	Ethnicity	Carrier Frequency	Detection Rate	Residual Risk	Analytical Detection Rate
Glycogen Storage Disease, Type II (AR) NM_000152.3	GAA	Caucasian	1 in 100	68%	1 in 310	89%
		African	1 in 70	83%	1 in 407	>95%
		Asian	1 in 112	64%	1 in 309	>95%
		Ashkenazi Jewish	1 in 58	>95%	1 in 1141	>95%
		Worldwide	1 in 132	73%	1 in 486	>95%
Nephrotic Syndrome (NPHS2-Related) / Steroid-Resistant Nephrotic Syndrome (AR) NM_014625.3	NPHS2	Worldwide	1 in 377	80%	1 in 1881	>95%
Smith-Lemli-Opitz Syndrome (AR) NM_001360.2	DHCR7	Caucasian	1 in 48	81%	1 in 248	>95%
		African	1 in 93	67%	1 in 280	>95%
		Asian	< 1 in 500	84%	1 in 3120	>95%
		Ashkenazi Jewish	1 in 41	>95%	1 in 801	>95%
		Worldwide	1 in 68	80%	1 in 336	>95%

AR: Autosomal Recessive

This case has been reviewed and electronically signed by Anastasia Larmore, PhD, Assistant Director

Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D.

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Test Methods and Comments

Genomic DNA isolated from this patient was analyzed by one or more of the following methodologies, as applicable:

Fragile X CGG Repeat Analysis

PCR amplification using Asuragen, Inc. AmpliX[®] *FMR1* PCR reagents followed by capillary electrophoresis for allele sizing was performed. Samples positive for *FMR1* CGG repeats in the premutation and full mutation size range are further analyzed by Southern blot analysis to assess the size and methylation status of the *FMR1* CGG repeat.

Genotyping

Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY[®] System or Luminex[®] xMAP[®] technology were used to identify variants that are complex in nature or are present in low copy repeat regions and are, therefore, not amenable to Next Generation Sequencing technologies. Rare sequence variants may interfere with assay performance.

Multiplex Ligation-Dependent Probe Amplification (MLPA)

MLPA[®] probe sets and reagents, MRC-Holland, were used for the analysis of copy number of specific targets versus known control samples. Each target region was assayed with two adjacent oligonucleotide probes which following hybridization were ligated and used as template for subsequent rounds of amplification. Each complete probe within the assay has a unique length and amplicons are separated and identified by capillary electrophoresis. False positive or negative results may also occur due to rare sequence variants in target regions detected by MLPA probes. Analytical sensitivity and specificity of the MLPA method are both 99%.

For Alpha Thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation are assessed. However, it does not detect all known alpha-thalassemia mutations such as point mutations. In addition, carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, will not be detected. This test detects most alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation using Multiplex Ligation-Dependent Probe Amplification (MLPA). It is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. Therefore, this result reduces, but does not eliminate, the chance that this patient is a carrier of alpha-thalassemia. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported.

For Duchenne Muscular Dystrophy, the copy numbers of all *DMD* exons were analyzed. Please note that single-exon deletions and duplications will not be reported unless they are confirmed by NGS data (for example, if breakpoints occurring in an exon can be visualized).

For Spinal Muscular Atrophy (SMA), the copy numbers of the *SMN1* and *SMN2* genes were analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* and *SMN2* were assessed. Copy number gains and losses can be detected with this assay.

Depending on ethnicity 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *SMN1* gene on one chromosome and loss of *SMN1* (deletion) on the other chromosome (silent 2+0 carrier) or individuals that carry an intragenic mutation in *SMN1*. Please also note that 2% of individuals with SMA have an *SMN1* mutation that occurred *de novo*. Typically in these cases, only one parent is an SMA carrier.

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The presence of the g.27134T>G variant allele in an individual with Ashkenazi Jewish or Asian ancestry is indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, g.27134T>G is likely indicative of a silent (2+0) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of g.27134T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 silent carrier.

Next Generation Sequencing (NGS)

NGS was performed on a panel of genes for the purpose of identifying pathogenic or likely pathogenic variants.

Agilent SureSelect™QXT technology was used with custom capture library to target the guaranteed list of mutations and exonic regions of the relevant genes. These targeted regions were sequenced using the Illumina HiSeq2500 system with 100 bp paired-end reads. The DNA sequences were mapped to and analyzed in comparison with the published human genome build UCSC hg19 reference sequence. The targeted coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage and data quality threshold values. This technology may not detect all small insertion/deletions and is not diagnostic for large duplications/deletions, repeat expansions, and structural genomic variation. This test will detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions will either not be detected or are not guaranteed to be detected. These regions include, but are not limited to, UTRs, promoters, and deep intronic areas or regions that fall within low copy repeat segments. In addition, a mutation(s) in a gene not included on the panel could be present in this patient. All potentially pathogenic variants may be confirmed by either a specific genotyping assay or Sanger sequencing, if indicated. Any benign variants, likely benign variants or variants of uncertain significance identified during this analysis were not reported.

Sanger Sequencing

Sanger sequencing, as indicated, was performed in both directions using BigDye Terminator chemistry with the ABI 3730 DNA analyzer with target specific amplicons. It also may be used to supplement specific guaranteed target regions that fail NGS sequencing due to poor quality or low depth of coverage <20 reads or as a confirmatory method for NGS positive results. False negative results may occur if rare variants interfere with amplification or annealing.

Tay-Sachs Disease (TSD) Enzyme Analysis

Hexosaminidase activity and Hex A% activity were measured by a standard heat-inactivation, fluorometric method using artificial 4-MU-β-N-acetyl glucosaminide (4-MUG) substrate. This assay is highly sensitive and accurate in detecting Tay-Sachs carriers and individuals affected with TSD. It is estimated that less than 0.5% of Tay-Sachs carriers have non-carrier levels of percent Hex A activity, and therefore may not be identified by this assay. In addition, this assay may detect individuals that are carriers of or are affected with Sandhoff Disease. False positive results, such as pseudodeficiency alleles, may occur if benign variants interfere with the enzymatic assay. False negative results may occur if both *HEXA* and *HEXB* pathogenic variants are present in the same individual.

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

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Carrier Screening

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Aartsma-Rus A et al. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve*. 2006b 34:135-44.

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Beta Globin-related Disorders:

Cao A et al. Beta-Thalassemia. GeneReviews (<http://www.ncbi.nlm.nih.gov/books/NBK1426/>)

Modell B et al. Epidemiology of haemoglobin disorders in Europe: an overview. *Scand J Clin Lab Invest*. 2007 67:39-69.

For further reading:

Orphanet: <http://www.orpha.net/consor/cgi-bin/index.php>

GeneReviews: <http://www.ncbi.nlm.nih.gov/books/NBK1116/>

For Disease Specific Standards and Guidelines:

<https://www.acmg.net/>

Additional disease-specific references available upon request.