Patient Information

Patient Name:	William Naylor
Date of Birth:	01/04/1961
Gender:	Male
Ethnicity:	Not Provided
Collection Kit:	14269021-2-C
Reference ID:	15543158-2-C
Case File ID:	4939041

Test Information

Ordering Physician:	Najmabadi, MD
Clinic Information:	Center for Reproductive Health and Gynecology
Phone:	310 360-7584
Report Date:	08/12/2021
Sample Collected:	08/05/2021
Sample Received:	08/06/2021
Sample Type:	Blood

horizon™ natera carrier screen

CARRIER SCREENING REPORT

ABOUT THIS SCREEN: Horizon™ is a carrier screen for specific autosomal recessive and X-linked diseases. This information can help patients learn their risk of having a child with specific genetic conditions.

ORDER SELECTED: The Horizon **274** panel and **Tay-Sachs Enzyme** were ordered for this patient. Males are not screened for X-linked diseases.

FINAL RESULTS SUMMARY:

CARRIER for Cystic Fibrosis

Positive for the pathogenic variant c.1521_1523delCTT (p.F508del) in the CFTR gene. A small number of Cystic Fibrosis (CF) carriers may have mild respiratory or other CF-related symptoms. If this individual's partner is a carrier for Cystic Fibrosis, their chance to have a child with this condition is 1 in 4 (25%). Carrier screening for this individual's partner is suggested.

Negative for 253 out of 254 diseases

No other pathogenic variants were detected in the genes that were screened. The patient's remaining carrier risk after negative screening results is listed for each disease/gene on the Horizon website at http://www.natera.com/hrzn274/b. Please see the following pages of this report for a comprehensive list of all conditions included on this individual's screen.

Carrier screening is not diagnostic and may not detect all possible pathogenic variants in a given gene.

RECOMMENDATIONS

Individuals who would like to review their Horizon report with a Natera Laboratory Genetic Counselor may schedule a telephone genetic information session by calling 650-249-9090 or visiting naterasession.com. Clinicians with questions may contact Natera at 650-249-9090, 855-866-6478 (toll free) or email support@natera.com. Individuals with positive results may wish to discuss these results with family members to allow them the option to be screened. Comprehensive genetic counseling to discuss the implications of these test results and possible associated reproductive risk is recommended.

Reviewed by: Li Liang, Ph.D., FACMG, Laboratory Director
CLIA Laboratory Director: J. Dianne Keen-Kim, Ph.D., FACMG

natera™ Conceive. Deliver.

CYSTIC FIBROSIS AND CFTR-RELATED DISORDERS

Understanding Your Horizon™ Carrier Screen Results: Cystic Fibrosis and CFTR-Related Disorders

What are Cystic Fibrosis and CFTR-Related Disorders?

Cystic Fibrosis (CF) and CFTR-Related Disorders are inherited disorders that affect many different areas of the body including the lungs, digestive system, and fertility. CF and CFTR-Related Disorders do not affect intelligence. Signs and symptoms of CF start in early childhood and include delayed growth caused by problems in digestion and repeated lung infections that lead to permanent lung damage. Children and adults with CF usually have frequent hospitalizations because of lung infections. Over time, complications of CF can lead to lung transplants and early death. CFTR-Related Disorders cause less severe symptoms, and some only affect male fertility. There are treatments for CF that can lessen the severity of the symptoms; however, there is currently no cure. Clinical trials involving potential new treatments for this condition may be available (see www.clinicaltrials.gov).

What causes CF and CFTR-Related Disorders?

CF and CFTR-Related Disorders are caused by a change, or mutation, in both copies of the *CFTR* gene pair. These mutations cause the genes to not work properly or not work at all. When both copies of this gene do not work correctly, mucus and other body fluids become thick and sticky. This causes problems with how the lungs, digestive system, and other body systems function and leads to the symptoms described above.

CF and CFTR-Related Disorders are inherited in an autosomal recessive manner. This means that, in most cases, both parents must be carriers of a mutation in one copy of the *CFTR* gene to have a child with CF or CFTR-Related Disorders. People who are CF or CFTR-Related Disorders carriers do not have CF or CFTR-Related Disorders themselves. Usually a child inherits two copies of each gene, one copy from the mother and one copy from the father. If the mother and father are both carriers for CF and CFTR-Related Disorders, there is a 1 in 4, or 25%, chance in each pregnancy for both partners to pass on their *CFTR* gene mutations to the child, who will then have CF or CFTR-Related Disorders.

Although most *CFTR* gene mutations cause classic CF, there are some specific *CFTR* mutations that cause less severe symptoms, and some only affect male fertility. It is sometimes, but not always, possible to determine whether a specific *CFTR* mutation causes classic CF or a milder form of the condition.

A small number of CF carriers may have mild respiratory or other symptoms. If you have concerns about your own health or symptoms, we encourage you to discuss your results and health history with your health care provider.

Individuals found to carry more than one mutation in the *CFTR* genes should discuss their risk for having an affected child, and any potential effects to their own health, with their health care provider.

What can I do next?

You may wish to speak with a local genetic counselor about your CF and CFTR-Related Disorders carrier test results. A genetic counselor in your region can be located on the National Society of Genetic Counselors website (www.nsgc.org).

Your siblings and other relatives are at increased risk to also have this mutation. You are encouraged to inform your family members of your test results as they may wish to consider being tested themselves.

If you are pregnant, your partner can have carrier screening for CF and CFTR-Related Disorders ordered by a health care professional. If your partner is not found to be a carrier of CF and CFTR-Related Disorders, your risk of having a child with CF and CFTR-Related Disorders is greatly reduced. Couples at risk of having a baby with CF and CFTR-Related Disorders can opt to have prenatal diagnosis done through chorionic villus sampling (CVS) or amniocentesis during pregnancy or can choose to have the baby tested after birth for CF and CFTR-Related Disorders. Although CF is screened for as part of the Newborn Screening program in some US states, babies at 25% for this condition may need diagnostic testing in addition to newborn screening.

If you are not yet pregnant, your partner can have CF and CFTR-Related Disorders carrier testing ordered by a health care professional. If your partner is found to be a carrier for CF and CFTR-Related Disorders, you have several reproductive options to consider:

- Natural pregnancy with or without prenatal diagnostic testing of the fetus or testing the baby after birth for CF
- Preimplantation genetic diagnosis (PGD) with in vitro fertilization (IVF) to test embryos for CF and CFTR-Related Disorders
- Adoption or use of a sperm or egg donor who is not a carrier for CF and CFTR-Related Disorders

What resources are available?

- Cystic Fibrosis Foundation: www.cff.org
- GeneReviews: Cystic Fibrosis: https://www.ncbi.nlm.nih.gov/books/NBK1250/
- Prenatal diagnosis done through CVS: http://www.marchofdimes.org/chorionic-villus-sampling.aspx
- Prenatal diagnosis done through Amniocentesis: http://www.marchofdimes.org/amniocentesis.aspx
- PGD with IVF: http://www.natera.com/spectrum

DISEASES SCREENED

Below is a list of all diseases screened and the result. Certain conditions have unique patient-specific numerical values, therefore, results for those conditions are formatted differently.

Autosomal Recessive

3
3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency (*HSD3B2*) **negative**
3-Hydroxy-3-Methylglutaryl-Coenzyme A Lyase Deficiency (*HMGCL*) **negative**
3-Methylcrotonyl-CoA Carboxylase 1 Deficiency (*MCCC1*) **negative**
3-Methylcrotonyl-CoA Carboxylase 2 Deficiency (*MCCC2*) **negative**
3-Phosphoglycerate Dehydrogenase Deficiency (*PHGDH*) **negative**

6
6-Pyruvoyl-Tetrahydropterin Synthase (PTPS) Deficiency (*PTS*) **negative**

A
Abetalipoproteinemia (*MTTP*) **negative**
Achondrogenesis, Type 1B (*SLC26A2*) **negative**
Achromatopsia, CNGB3-Related (*CNGB3*) **negative**
Acrodermatitis Enteropathica (*SLC39A4*) **negative**
Acute Infantile Liver Failure, TRMU-Related (*TRMU*) **negative**
Acyl-CoA Oxidase I Deficiency (*ACOX1*) **negative**
Aicardi-Goutières Syndrome (*SAMHD1*) **negative**
Alpha-Mannosidosis (*MAN2B1*) **negative**
Alpha-Thalassemia (*HBA1/HBA2*) **negative**
Alport Syndrome, COL4A3-Related (*COL4A3*) **negative**
Alport Syndrome, COL4A4-Related (*COL4A4*) **negative**
Alstrom Syndrome (*ALMS1*) **negative**
Andermann Syndrome (*SLC12A6*) **negative**
Argininosuccinate Lyase Deficiency (*ASL*) **negative**
Aromatase Deficiency (*CYP19A1*) **negative**
Asparagine Synthetase Deficiency (*ASNS*) **negative**
Aspartylglycosaminuria (*AGA*) **negative**
Ataxia with Vitamin E Deficiency (*TTPA*) **negative**
Ataxia-Telangiectasia (*ATM*) **negative**
Autism Spectrum, Epilepsy and Arthrogryposis (*SLC35A3*) **negative**
Autoimmune Polyglandular Syndrome, Type 1 (*AIRE*) **negative**
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (*SACS*) **negative**

B
Bardet-Biedl Syndrome, BBS1-Related (*BBS1*) **negative**
Bardet-Biedl Syndrome, BBS10-Related (*BBS10*) **negative**
Bardet-Biedl Syndrome, BBS12-Related (*BBS12*) **negative**
Bardet-Biedl Syndrome, BBS2-Related (*BBS2*) **negative**
Bare Lymphocyte Syndrome, CIITA-Related (*CIITA*) **negative**
Bartter Syndrome, BSND-Related (*BSND*) **negative**
Batten Disease, CLN3-Related (*CLN3*) **negative**
Beta-Hemoglobinopathies (*HBB*) **negative**
Beta-Ketothiolase Deficiency (*ACAT1*) **negative**
Bilateral Frontoparietal Polymicrogyria (*GPR56*) **negative**
Biotinidase Deficiency (*BTD*) **negative**
Bloom Syndrome (*BLM*) **negative**

C
CRB1-Related Retinal Dystrophies (*CRB1*) **negative**
Canavan Disease (*ASPA*) **negative**
Carbamoyl Phosphate Synthetase I Deficiency (*CPS1*) **negative**
Carnitine Deficiency (*SLC22A5*) **negative**
Carnitine Palmitoyltransferase IA Deficiency (*CPT1A*) **negative**
Carnitine Palmitoyltransferase II Deficiency (*CPT2*) **negative**
Carpenter Syndrome (*RAB23*) **negative**
Cartilage-Hair Hypoplasia (*RMRP*) **negative**
Cerebrotendinous Xanthomatosis (*CYP27A1*) **negative**
Charcot-Marie-Tooth Disease, Type 4D (*NDRG1*) **negative**
Choreoacanthocytosis (*VPS13A*) **negative**
Chronic Granulomatous Disease, CYBA-Related (*CYBA*) **negative**
Ciliopathies, RPGRIP1L-Related (*RPGRIP1L*) **negative**
Citrin Deficiency (*SLC25A13*) **negative**
Citrullinemia, Type 1 (*ASS1*) **negative**
Cohen Syndrome (*VPS13B*) **negative**
Combined Malonic and Methylmalonic Aciduria (*ACSF3*) **negative**
Combined Oxidative Phosphorylation Deficiency 1 (*GFM1*) **negative**
Combined Oxidative Phosphorylation Deficiency 3 (*TSFM*) **negative**
Combined Pituitary Hormone Deficiency-2 (*PROP1*) **negative**
Congenital Adrenal Hyperplasia, 17-Alpha-Hydroxylase Deficiency (*CYP17A1*) **negative**
Congenital Amegakaryocytic Thrombocytopenia (*MPL*) **negative**
Congenital Disorder of Glycosylation, Type 1A, PMM2-Related (*PMM2*) **negative**
Congenital Disorder of Glycosylation, Type 1B (*MPI*) **negative**
Congenital Disorder of Glycosylation, Type 1C (*ALG6*) **negative**
Congenital Finnish Nephrosis (*NPHS1*) **negative**
Congenital Hyperinsulinism, KCNJ11-Related (*KCNJ11*) **negative**
Congenital Insensitivity to Pain with Anhidrosis (CIPA) (*NTRK1*) **negative**
Congenital Myasthenic Syndrome, CHRNE-Related (*CHRNE*) **negative**
Congenital Myasthenic Syndrome, RAPSN-Related (*RAPSN*) **negative**
Congenital Neutropenia, HAX1-Related (*HAX1*) **negative**
Congenital Neutropenia, VPS45-Related (*VPS45*) **negative**
Corneal Dystrophy and Perceptive Deafness (*SLC4A11*) **negative**
Corticosterone Methyloxidase Deficiency (*CYP11B2*) **negative**
Costeff Syndrome (3-Methylglutaconic Aciduria, Type 3) (*OPA3*) **negative**
Cystic Fibrosis (*CFTR*) **see first page**
Cystinosis (*CTNS*) **negative**

D
D-Bifunctional Protein Deficiency (*HSD17B4*) **negative**
Deafness, Autosomal Recessive 77 (*LOXHD1*) **negative**
Dyskeratosis Congenita, RTEL1-Related (*RTEL1*) **negative**
Dystrophic Epidermolysis Bullosa, COL7A1-Related (*COL7A1*) **negative**

E
Ehlers-Danlos Syndrome, Type VIIC (*ADAMTS2*) **negative**
Ellis-van Creveld Syndrome, EVC-Related (*EVC*) **negative**
Enhanced S-Cone Syndrome (*NR2E3*) **negative**
Ethylmalonic Encephalopathy (*ETHE1*) **negative**

F
Factor XI Deficiency (*F11*) **negative**
Familial Dysautonomia (*IKBKAP*) **negative**
Familial Hypercholesterolemia, LDLR-Related (*LDLR*) **negative**
Familial Hypercholesterolemia, LDLRAP1-Related (*LDLRAP1*) **negative**
Familial Hyperinsulinism, ABCC8-Related (*ABCC8*) **negative**
Familial Mediterranean Fever (*MEFV*) **negative**
Familial Nephrogenic Diabetes Insipidus, AQP2-Related (*AQP2*) **negative**
Fanconi Anemia, Group A (*FANCA*) **negative**
Fanconi Anemia, Group C (*FANCC*) **negative**
Fanconi Anemia, Group G (*FANCG*) **negative**
Fumarase Deficiency (*FH*) **negative**

G
GRACILE Syndrome (*BCS1L*) **negative**
Galactokinase Deficiency (Galactosemia, Type II) (*GALK1*) **negative**
Galactosemia (*GALT*) **negative**
Gaucher Disease (*GBA*) **negative**
Gitelman Syndrome (*SLC12A3*) **negative**
Glutaric Acidemia, Type 1 (*GCDH*) **negative**
Glutaric Acidemia, Type 2A (*ETFA*) **negative**

Glutaric Acidemia, Type 2C (*ETFDH*) **negative**
Glycine Encephalopathy, AMT-Related (*AMT*) **negative**
Glycine Encephalopathy, GLDC-Related (*GLDC*) **negative**
Glycogen Storage Disease, Type 1a (*G6PC*) **negative**
Glycogen Storage Disease, Type 1b (*SLC37A4*) **negative**
Glycogen Storage Disease, Type 2 (Pompe Disease) (*GAA*) **negative**
Glycogen Storage Disease, Type 3 (*AGL*) **negative**
Glycogen Storage Disease, Type 4 (*GBE1*) **negative**
Glycogen Storage Disease, Type 5 (McArdle Disease) (*PYGM*) **negative**
Glycogen Storage Disease, Type 7 (*PFKM*) **negative**
Guanidinoacetate Methyltransferase Deficiency (*GAMT*) **negative**

H
Hemochromatosis, Type 2A (*HFE2*) **negative**
Hemochromatosis, Type 3, TFR2-Related (*TFR2*) **negative**
Hepatocerebral Mitochondrial DNA Depletion Syndrome, MPV17-Related (*MPV17*) **negative**
Hereditary Fructose Intolerance (*ALDOB*) **negative**
Hereditary Spastic Paraparesis, Type 49 (*TECPR2*) **negative**
Hermansky-Pudlak Syndrome, HPS1-Related (*HPS1*) **negative**
Hermansky-Pudlak Syndrome, HPS3-Related (*HPS3*) **negative**
Holocarboxylase Synthetase Deficiency (*HLCS*) **negative**
Homocystinuria due to Deficiency of MTHFR (*MTHFR*) **negative**
Homocystinuria, CBS-Related (*CBS*) **negative**
Homocystinuria, Type cblE (*MTRR*) **negative**
Hydrolethalus Syndrome (*HYLS1*) **negative**
Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH Syndrome) (*SLC25A15*) **negative**
Hypophosphatasia, ALPL-Related (*ALPL*) **negative**

I
Inclusion Body Myopathy 2 (*GNE*) **negative**
Infantile Cerebral and Cerebellar Atrophy (*MED17*) **negative**
Isovaleric Acidemia (*IVD*) **negative**

J
Joubert Syndrome 2 / Meckel Syndrome 2 (*TMEM216*) **negative**

K
Krabbe Disease (*GALC*) **negative**

L
Lamellar Ichthyosis, Type 1 (*TGM1*) **negative**
Leber Congenital Amaurosis 2 (*RPE65*) **negative**
Leber Congenital Amaurosis, Type CEP290 (*CEP290*) **negative**
Leber Congenital Amaurosis, Type LCA5 (*LCA5*) **negative**
Leber Congenital Amaurosis, Type RDH12 (*RDH12*) **negative**
Leigh Syndrome, French-Canadian Type (*LRPPRC*) **negative**
Lethal Congenital Contracture Syndrome 1 (*GLE1*) **negative**
Leukoencephalopathy with Vanishing White Matter (*EIF2B5*) **negative**
Limb-Girdle Muscular Dystrophy, Type 2A (*CAPN3*) **negative**
Limb-Girdle Muscular Dystrophy, Type 2B (*DYSF*) **negative**
Limb-Girdle Muscular Dystrophy, Type 2C (*SGCG*) **negative**
Limb-Girdle Muscular Dystrophy, Type 2D (*SGCA*) **negative**
Limb-Girdle Muscular Dystrophy, Type 2E (*SGCB*) **negative**
Limb-Girdle Muscular Dystrophy, Type 2I (*FKRP*) **negative**
Lipoamide Dehydrogenase Deficiency (Dihydrolipoamide Dehydrogenase Deficiency) (*DLD*) **negative**
Lipoid Adrenal Hyperplasia (*STAR*) **negative**
Lipoprotein Lipase Deficiency (*LPL*) **negative**
Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (*HADHA*) **negative**
Lysinuric Protein Intolerance (*SLC7A7*) **negative**

M
Maple Syrup Urine Disease, Type 1A (*BCKDHA*) **negative**
Maple Syrup Urine Disease, Type 1B (*BCKDHB*) **negative**
Meckel-Gruber Syndrome, Type 1 (*MKS1*) **negative**
Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) **negative**
Megalencephalic Leukoencephalopathy with Subcortical Cysts (*MLC1*) **negative**
Metachromatic Leukodystrophy, ARSA-Related (*ARSA*) **negative**
Metachromatic Leukodystrophy, PSAP-Related (*PSAP*) **negative**
Methylmalonic Aciduria and Homocystinuria, Type cblC (*MMACHC*) **negative**
Methylmalonic Aciduria and Homocystinuria, Type cblD (*MMADHC*) **negative**
Methylmalonic Aciduria, MMAA-Related (*MMAA*) **negative**
Methylmalonic Aciduria, MMAB-Related (*MMAB*) **negative**
Methylmalonic Aciduria, Type mut(0) (*MUT*) **negative**
Microphthalmia/Anophthalmia, VSX2-Related (*VSX2*) **negative**
Mitochondrial Complex 1 Deficiency, ACAD9-Related (*ACAD9*) **negative**
Mitochondrial Complex 1 Deficiency, NDUFAF5-Related (*NDUFAF5*) **negative**
Mitochondrial Complex 1 Deficiency, NDUFS6-Related (*NDUFS6*) **negative**
Mitochondrial Myopathy and Sideroblastic Anemia (MLASA1) (*PUS1*) **negative**
Mucolipidosis II/IIIA (*GNPTAB*) **negative**
Mucolipidosis III gamma (*GNPTG*) **negative**
Mucolipidosis, Type IV (*MCOLN1*) **negative**
Mucopolysaccharidosis, Type I (Hurler Syndrome) (*IDUA*) **negative**
Mucopolysaccharidosis, Type IIIA (Sanfilippo A) (*SGSH*) **negative**
Mucopolysaccharidosis, Type IIIB (Sanfilippo B) (*NAGLU*) **negative**
Mucopolysaccharidosis, Type IIIC (Sanfilippo C) (*HGSNAT*) **negative**
Mucopolysaccharidosis, Type IIID (Sanfilippo D) (*GNS*) **negative**
Mucopolysaccharidosis, Type IVB / GM1 Gangliosidosis (*GLB1*) **negative**
Mucopolysaccharidosis, Type IX (*HYAL1*) **negative**
Mucopolysaccharidosis, Type VI (Maroteaux-Lamy) (*ARSB*) **negative**
Multiple Sulfatase Deficiency (*SUMF1*) **negative**
Muscle-Eye-Brain Disease, POMGNT1-Related (*POMGNT1*) **negative**
Myoneurogastrointestinal Encephalopathy (MNGIE) (*TYMP*) **negative**

N
N-acetylglutamate Synthase Deficiency (*NAGS*) **negative**
Nemaline Myopathy, NEB-Related (*NEB*) **negative**
Neuronal Ceroid Lipofuscinosis, CLN5-Related (*CLN5*) **negative**
Neuronal Ceroid Lipofuscinosis, CLN6-Related (*CLN6*) **negative**
Neuronal Ceroid Lipofuscinosis, CLN8-Related (*CLN8*) **negative**
Neuronal Ceroid Lipofuscinosis, MFSD8-Related (*MFSD8*) **negative**
Neuronal Ceroid Lipofuscinosis, PPT1-Related (*PPT1*) **negative**
Neuronal Ceroid Lipofuscinosis, TPP1-Related (*TPP1*) **negative**
Niemann-Pick Disease, Type C1/D (*NPC1*) **negative**
Niemann-Pick Disease, Type C2 (*NPC2*) **negative**
Niemann-Pick Disease, Types A/B (*SMPD1*) **negative**
Nijmegen Breakage Syndrome (*NBN*) **negative**
Non-Syndromic Hearing Loss, GJB2-Related (*GJB2*) **negative**

O
Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome (*WNT10A*) **negative**
Omenn Syndrome, RAG2-Related (*RAG2*) **negative**
Ornithine Aminotransferase Deficiency (*OAT*) **negative**
Osteopetrosis, Infantile Malignant, TCIRG1-Related (*TCIRG1*) **negative**

P
Pendred Syndrome (*SLC26A4*) **negative**
Phenylketonuria (*PAH*) **negative**
Pituitary Hormone Deficiency, Combined 3 (*LHX3*) **negative**
Polycystic Kidney Disease, Autosomal Recessive (*PKHD1*) **negative**
Pontocerebellar Hypoplasia, RARS2-Related (*RARS2*) **negative**
Pontocerebellar Hypoplasia, Type 1A (*VRK1*) **negative**
Pontocerebellar Hypoplasia, Type 2D (*SEPSECS*) **negative**
Primary Ciliary Dyskinesia, DNAH5-Related (*DNAH5*) **negative**
Primary Ciliary Dyskinesia, DNAI1-Related (*DNAI1*) **negative**
Primary Ciliary Dyskinesia, DNAI2-Related (*DNAI2*) **negative**
Primary Hyperoxaluria, Type 1 (*AGXT*) **negative**
Primary Hyperoxaluria, Type 2 (*GRHPR*) **negative**

Primary Hyperoxaluria, Type 3 (*HOGA1*) **negative**
Progressive Familial Intrahepatic Cholestasis, Type 2 (*ABCB11*) **negative**
Propionic Acidemia, PCCA-Related (*PCCA*) **negative**
Propionic Acidemia, PCCB-Related (*PCCB*) **negative**
Pycnodysostosis (*CTSK*) **negative**
Pyruvate Dehydrogenase Deficiency, PDHB-Related (*PDHB*) **negative**

R
Renal Tubular Acidosis and Deafness, ATP6V1B1-Related (*ATP6V1B1*) **negative**
Retinitis Pigmentosa 25 (*EYS*) **negative**
Retinitis Pigmentosa 26 (*CERKL*) **negative**
Retinitis Pigmentosa 28 (*FAM161A*) **negative**
Retinitis Pigmentosa 59 (*DHDDS*) **negative**
Rhizomelic Chondrodysplasia Punctata, Type 1 (*PEX7*) **negative**
Rhizomelic Chondrodysplasia Punctata, Type 3 (*AGPS*) **negative**
Roberts Syndrome (*ESCO2*) **negative**

S
Salla Disease (*SLC17A5*) **negative**
Sandhoff Disease (*HEXB*) **negative**
Schimke Immunoosseous Dysplasia (*SMARCAL1*) **negative**
Segawa Syndrome, TH-Related (*TH*) **negative**
Severe Combined Immunodeficiency, ADA-Related (*ADA*) **negative**
Severe Combined Immunodeficiency, Type Athabaskan (*DCLRE1C*) **negative**
Sjögren-Larsson Syndrome (*ALDH3A2*) **negative**
Smith-Lemli-Opitz Syndrome (*DHCR7*) **negative**
Spinal Muscular Atrophy (*SMN1*)
Negative: SMN1: Two copies; g.27134T>G: absent; the absence of the g.27134T>G variant decreases the chance to be a silent (2+0) carrier.
Spondylothoracic Dysostosis, MESP2-Related (*MESP2*) **negative**
Steroid-Resistant Nephrotic Syndrome (*NPHS2*) **negative**
Stuve-Wiedemann Syndrome (*LIFR*) **negative**

T
Tay-Sachs Disease (DNA and enzyme) (*HEXA*)
Negative: No pathogenic variants detected. Normal Hexosaminidase Activity. WBC: 1768.00 nmol/hr/mg; Hex A %. WBC 59.00.
Tyrosinemia, Type 1 (*FAH*) **negative**

U
Usher Syndrome, Type 1B (*MYO7A*) **negative**
Usher Syndrome, Type 1C (*USH1C*) **negative**
Usher Syndrome, Type 1D (*CDH23*) **negative**
Usher Syndrome, Type 1F (*PCDH15*) **negative**
Usher Syndrome, Type 2A (*USH2A*) **negative**
Usher Syndrome, Type 3 (*CLRN1*) **negative**

V
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (*ACADVL*) **negative**

W
Walker-Warburg Syndrome, FKTN-Related (*FKTN*) **negative**
Wilson Disease (*ATP7B*) **negative**
Wolman Disease (*LIPA*) **negative**

Z
Zellweger Spectrum Disorders, PEX1-Related (*PEX1*) **negative**
Zellweger Spectrum Disorders, PEX10-Related (*PEX10*) **negative**
Zellweger Spectrum Disorders, PEX2-Related (*PEX2*) **negative**
Zellweger Spectrum Disorders, PEX6-Related (*PEX6*) **negative**

Testing Methodology, Limitations, and Comments:

Genomic DNA is isolated utilizing the Maxwell HT 96 gDNA Blood Isolation System (Promega).

Next Generation Sequencing (NGS)

Sequencing libraries prepared from genomic DNA isolated from patient samples are enriched for targets of interest using standard hybridization capture protocols. NGS is then performed to achieve the standards of quality control metrics, including a minimum depth of 30X. Sequencing data is aligned to human reference sequence, followed by deduplication, metric collection and variant calling. Variants are then classified according to ACMG/AMP standards of interpretation using publicly available databases including but not limited to ENSEMBL, HGMD Pro, ClinGen, ClinVar, 1000G, ESP and gnomAD. Any variants that do not meet internal quality standards are confirmed by orthogonal methods. This test may not provide detection of certain variants or portions of certain genes due to local sequence characteristics, high/low genomic complexity, or the presence of closely related pseudogenes. Analytically difficult features of the genome such as deletions and duplications >20bp may not be detected in this assay. Rarely, novel sequence variants may interfere with NGS read creation, sequence alignment, variant calling and confirmation strategies. Large deletions or duplications, structural variants such as inversions and gene conversions, and mosaic variants may not be detected with this technology.

Sanger Sequencing

Bi-directional Sanger sequencing is performed using target-specific amplicons, BigDye Terminator chemistry, and an ABI 3730 DNA analyzer (Thermo Fisher Scientific). In rare cases where unambiguous bi-directional sequencing is difficult or impossible, unidirectional sequence reads may be used for confirmation. Large deletion or mosaic variants may not be detected with this technology.

Copy Number Analysis

NGS is used to determine the copy number variants in *DMD*, *SMN1* and *HBA* genes, if ordered. For each targeted region, copy number variant (CNV) detection is performed using a bioinformatics pipeline that incorporates both community standard and custom algorithms to identify exon-level CNVs. CNVs are called using internal protocols predicated on evidence-based grading for pathogenicity as recommended by the American College of Medical Genetics and Genomics (ACMG). MLPA® (Multiplex Ligation-dependent Probe Amplification, MRC-Holland) is used to confirm the copy number of specific targets versus known controls. False positive or negative results may occur due to rare sequence variants such as small deletions and insertions, or mismatches within targeted regions detected by MLPA® probes; any mismatch in the probe's target site can affect the probe signal. MLPA® detects the presence of a CNV at the covered regions but will not detect copy number changes outside of the detection region of the individual assay and does not define the exact deletion/duplication boundaries. Single exon deletions or duplications may not be detected or reported using the NGS or MLPA® methodologies.

Alpha Thalassemia (HBA)

Deletions involving the *HBA1* and *HBA2* genes are analyzed using NGS and MLPA®. Pathogenic and likely pathogenic SNVs and in/dels within *HBA1* and *HBA2* variants associated with hemoglobinopathy or thalassemia are detected first by NGS and confirmed by Sanger sequencing due to the repetitive nature of this region. SNVs are detected with concurrent large deletions. In rare cases, Alpha-globin triplications, and polymorphisms may interfere with CNV detection. Alpha-globin triplications and polymorphisms are not reported.

Spinal Muscular Atrophy (SMA)

Copy number analysis for *SMN1* gene is assessed by NGS and MLPA®. Enhanced SMA testing for the presence or absence of a novel SNP within intron 7 (g.27134T>G) and associated with the presence of a *SMN1* duplication allele is performed using NGS (Luo et al. 2014, PMID 23788250). Ethnicity-based carrier risk estimates for individuals who are found to carry two *SMN1* copies are listed below.

Ethnicity	Two SMN1 copies carrier risk before g.27134T>G testing	Carrier risk after g.27134T>G testing	
		g.27134T>G ABSENT	g.27134T>G PRESENT
Caucasian	1 in 632	1 in 769	1 in 29
Ashkenazi Jewish	1 in 350	1 in 580	LIKELY CARRIER
Asian	1 in 628	1 in 702	LIKELY CARRIER
African-American	1 in 121	1 in 396	1 in 34
Hispanic	1 in 1061	1 in 1762	1 in 140

Tay-Sachs Disease Enzyme Analysis

The TSE enzyme assay determines total hexosaminidase and hexosaminidase A activities in leukocytes. The hexosaminidase activities are measured before and after heat inactivation using a fluorescence-generating 4-methylumbelliferyl-N-acetyl-β-D-glucosaminide substrate. Thermal fractionation of hexosaminidase is calculated to differentiate Tay-Sachs disease carriers from non-carriers. A small percentage (<0.7 %) of Tay-Sachs disease carriers may be identified as non-carriers by this assay (Triggs-Raine et al. NEJM 1990). In addition, Tay-Sachs disease patients or carriers with certain genetic variants such as AB variant (OMIM 272750) and B1 variant (OMIM 272800) will not be detected by this method. This test was developed and its performance characteristics determined by Baylor Miraca Genetics Laboratories DBA Baylor Genetics (CAP# 2109314/ CLIA# 45D0660090). 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.

Tay-Sachs Disease (Hex A % Carrier Ranges)

Specimen	Carrier Range (%)	Non-Carrier Range (%)
White Blood Cells (WBC)	<49	55.0-75.0

Variant Classification

Variants are classified according to ACMG/AMP variant classification guidelines. Only pathogenic or likely pathogenic variants are reported. Benign, likely benign, and variants of uncertain significance are not reported, but may be reported in certain circumstances. Variant classification is based on our current understanding of genes and variants at the time of reporting. Natera may reclassify variants at certain intervals but may not release updated reports without a specific request made to Natera by the ordering provider. Natera may disclose incidental findings if deemed clinically pertinent to the test performed.

Negative Results

A negative carrier screening result reduces the risk for a patient to be a carrier of a specific disease but does not completely rule out carrier status. Please visit www.natera.com/hrzn274/b for a table of carrier rates, detection rates and residual risks. Carrier rates before and after testing vary by ethnicity and assume a negative family history for each disease screened and the absence of clinical symptoms in the patient. Any patient with a family history for a specific genetic disease will have a higher carrier risk prior to testing and if the disease-causing variant in their family is not included on the test, their carrier risk remains unchanged. Genetic counseling is recommended for patients with a family history of genetic disease so that risk figures based on actual family history can be determined and discussed along with potential implications for reproduction.

Additional Comments

Horizon carrier screening (3.2.1) has been developed to identify the reproductive risks for monogenic inherited conditions. Even when one or both members of a couple screen negative for pathogenic variants in a specific gene, the disease risk for their offspring is not zero. There is still a low risk for the condition in their offspring due to a number of different mechanisms that are not detected by Horizon, including but not limited to, pathogenic variant(s) in the tested gene or in a different gene not included on Horizon, pathogenic variant(s) in an upstream regulator, uniparental disomy, de novo mutation(s), or digenic or polygenic inheritance. Infrequent large genetic deletions or duplications are not detected unless they have been specifically targeted for carrier testing.

These tests were developed and their performance characteristics were determined by Natera (CLIA ID: 05D1082992). A portion of the technical component of these tests may have been performed at NSTX, 13011 McCallen Pass, Building A, Suite 110, Austin, TX 78753 (CLIA ID: 45D2093704). These tests have not been cleared or approved by the U.S. Food and Drug Administration (FDA). These analyses generally provide highly accurate information regarding the patient's carrier status; however, 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.

Patient Information

Patient Name:	William Naylor
Date of Birth:	01/04/1961
Case File ID:	4939041

Test Information

Ordering Physician:	Najmabadi, MD
Clinic Information:	Center for Reproductive Health and Gynecology
Report Date:	08/12/2021

horizon™ natera carrier screen

DETAILED RESULTS AND INTERPRETATIONS

TAY-SACHS ENZYME

Tay Sachs Disease Carrier Testing

Sample	%HexosaminidaseA	Total Activity nmoles/hr/mg protein
Naylor,William	59	1768
Normal Range	55.0-75.0	1023-1961
Carrier Range	34.0-49.0	870-1705

INTERPRETATION: Non-Carrier: Within the limits of this test this patient is NOT a carrier for Tay Sachs Disease.

Results Date: 08/11/2021