**Patient Information**

| | |
|---|---|
| Patient Name: | Jane Doe |
| Date of Birth: | 02/02/1975 |
| Gender: | Female |
| Ethnicity: | Hispanic |
| Patient ID: | P99457 |
| Medical Record #: | M84555 |
| Collection Kit: | 254233-2-N |
| Accession ID: | 40192731 |
| Case File ID: | 123456 |

**Test Information**

| | |
|---|---|
| Ordering Physician: | Dr. Goodbirth, M.D. (G123456) |
| Clinic Information: | Natera, Inc. |
| Phone: | 650 555-1212 |
| Report Date: | 02/01/2013 |
| Sample Collected: | 01/31/2013 |
| Sample Received: | 02/01/2013 |
| 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.

## FINAL RESULTS SUMMARY:

### NEGATIVE FOR 274 OUT OF 274 DISEASES

No 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/hrzn274s. 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 or email support@natera.com.

**APPROVED BY:** J. Dianne Keen-Kim, Ph.D., FACMGG, Senior Laboratory Director

**APPROVED BY:** Irina Rakova, M.D., CGMBS, Associate Laboratory Director

CLIA ID #05D1082992; Rev DEV_BUILD
201 Industrial Road, Suite 410 | San Carlos, CA 94070 | www.natera.com | 650-249-9090 | Fax 1-650-730-2272


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# 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*) **negative**
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: [number of SMN1 copies] 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. Plasma: [add HEX activity plasma nmol/hr/ml]; WBC: [add HEX activity WBC nmol/hr/mg]; Hex A %. Plasma [add HEX A % plasma]; WBC [add HEX A % WBC].**
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**

## X-Linked

**A**
Adrenoleukodystrophy, X-Linked (*ABCD1*) **negative**
Alpha-Thalassemia Intellectual Disability Syndrome (*ATRX*) **negative**
Alport Syndrome, X-Linked (*COL4A5*) **negative**

**C**
Charcot-Marie-Tooth Disease with Deafness, X-Linked (*GJB1*) **negative**
Choroideremia (*CHM*) **negative**
Chronic Granulomatous Disease, X-Linked (*CYBB*) **negative**
Creatine Transporter Defect (Cerebral Creatine Deficiency Syndrome 1, X-Linked) (*SLC6A8*) **negative**

**D**
Duchenne/Becker Muscular Dystrophy (*DMD*) **negative**

**E**
Emery-Dreifuss Muscular Dystrophy 1, X-Linked (*EMD*) **negative**

**F**
Fabry Disease (*GLA*) **negative**
Factor IX Deficiency (*F9*) **negative**
Fragile X Syndrome (*FMR1*)
**Negative: [normal repeat size 1] and [normal repeat size 2] CGG repeats were detected in the FMR1 genes.**

**H**
Hypohidrotic Ectodermal Dysplasia, X-Linked (*EDA*) **negative**

**J**
Juvenile Retinoschisis, X-Linked (*RS1*) **negative**

**M**
Menkes Syndrome (*ATP7A*) **negative**
Mucopolysaccharidosis, Type II (Hunter Syndrome) (*IDS*) **negative**
Myotubular Myopathy, X-Linked (*MTM1*) **negative**

**O**
Ornithine Transcarbamylase Deficiency (*OTC*) **negative**

**P**
Pyruvate Dehydrogenase Deficiency, X-Linked (*PDHA1*) **negative**

**S**
Severe Combined Immunodeficiency, X-Linked (*IL2RG*) **negative**

## Testing Methodology, Limitations, and Comments:

Genomic DNA isolated from this patient was analyzed using one or more of the following methodologies.

## Copy Number Analysis

MLPA® (Multiplex Ligation-dependent Probe Amplification) probe sets and reagents, MRC-Holland, are used to determine the copy number of specific targets versus known control samples. Each target region is analyzed with two adjacent oligonucleotide probes which, following hybridization, are 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 occur due to rare sequence variants in target regions detected by MLPA probes.

## Genotyping

Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY® System or Luminex® xMAP® technology are used to identify variants that are complex in nature or that 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.

## Next Generation Sequencing (NGS)

NGS is performed on a panel of genes for the purpose of identifying pathogenic or likely pathogenic variants that represent carrier alleles. Agilent SureSelect™ QXT technology is used with custom capture library to target the guaranteed list of mutations and exonic regions of the relevant genes. These targeted regions are sequenced using the Illumina HiSeq2500 system with 100 bp paired-end reads. The DNA sequences are 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 are 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 only detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions 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. A list of these target regions per gene is available upon request. In addition, a mutation(s) in a gene not included on the panel could be present in this patient. All potentially pathogenic variants were confirmed by either a specific genotyping assay or subjected to Sanger sequencing.

## Sanger Sequencing

Sanger sequencing is performed in both directions using BigDye Terminator chemistry with the ABI 3730 DNA analyzer with target specific amplicons. It is 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 amplication.

## Alpha Thalassemia

The copy numbers of the *HBA1* and *HBA2* genes are analyzed. Alpha-globin gene deletions and the Constant Spring (CS) mutation are assessed. Alpha-globin triplications are not reported.

## Duchenne Muscular Dystrophy

The copy number of *DMD* exons are analyzed. NGS of the *DMD* gene is also performed to detect point mutations of promised exons.

## Fragile X

PCR amplification using Asuragen, Inc. AmplideX® *FMR1* PCR reagents followed by capillary electrophoresis for allele sizing is utilized. Samples positive for *FMR1* CGG repeats in the premutation or full mutation size ranges are further evaluated by Southern blot analysis to further determine the size and methylation status of the *FMR1* CGG repeat. Variances of +/- 2 CGG repeats may occur. Reflex testing for number of AGG interruptions is performed for all CGG repeat sizes between 55 and 90. A separate report will be issued with the AGG results. AGG interruption testing is performed by Asuragen, Inc., 2150 Woodward St. Suite 100 Austin, TX 78744 (CLIA ID: 45D1069375).

## Fragile X Repeat Categories

| Categories | CGG Repeat Sizes |
|---|---|
| Normal | <45 |
| Intermediate | 45 – 54 |
| Premutation | 55 - 200 |
| Full | >200 |

## Spinal Muscular Atrophy

For Spinal Muscular Atrophy (SMA), the copy number of the *SMN1* gene is analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* are assessed. Deletions and duplications of *SMN1* are detected. In addition to copy number analysis, Enhanced SMA testing for the presence or absence of a novel single nucleotide polymorphism (g.27134T>G in intron 7 of *SMN1*) associated with the presence of a *SMN1* duplication allele is

performed using primer extension analysis. Ethnicity-based carrier risk estimates for individuals who are found to carry two SMN1 copies are listed in the table 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 (TSD) Enzyme Analysis

Hexosaminidase activity and Hex A% activity are 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.

Tay-Sachs Disease (Hex-A % Carrier Ranges)

| Specimen | Carrier Range (%) | Non-Carrier Range (%) |
|---|---|---|
| Plasma | <54 | 58.0-72.0 |
| White Blood Cells (WBC) | <50 | 55.0-72 |

## Variant Classification

Only pathogenic or likely pathogenic variants are reported. Other variants including benign variants, likely benign variants, variants of uncertain significance, or inconclusive variants identified during this analysis may be reported in certain circumstances. Data interpretation is based on our current understanding of genes and variants at the time of reporting. Natera and its lab partner(s) may reclassify variants at certain intervals but will 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/hrzn274s for a table of carrier rates, detection rates, residual risks and promised variants/exons per gene. 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 mutation in their family is not included on the test, their carrier risk would remain 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.

Horizon carrier screening 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.

## Additional Comments

These tests were developed and their performance characteristics were determined by Mount Sinai Genomics, 1428 Madison Ave, Atran Bldg, Rm-2-25 New York, NY 10029-6574. See Detailed Results and Interpretations section. Data review and reporting were performed by Natera and NSTX, 13011 McCallen Pass, Building A, Suite 110, Austin, TX 78753. These tests have not been cleared or approved by the U.S. Food and Drug Administration (FDA). These analyses 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 and rare diagnostic errors may occur for these reasons.

References for disease carrier and detection rates are available upon request.

## DETAILED RESULTS AND INTERPRETATIONS

ALPHA-THALASSEMIA

NEGATIVE for alpha-thalassemia
HBA1 copy number: 2
HBA2 copy number: 2
No pathogenic variants detected (aa/aa)
Reduced risk of being an alpha-thalassemia carrier

Genes analyzed: HBA1 (NM_000558.4) and HBA2 (NM_000517.4)
Inheritance: Autosomal Recessive

Recommendations
Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.

Interpretation
No pathogenic variants were detected in this patient, suggesting that four copies of the alpha-globin gene are present (aa/aa). Typically, individuals have four functional alpha-globin genes: 2 copies of HBA1 and 2 copies of HBA2, whose expression is regulated by a cis-acting regulatory element HS-40. Alpha-thalassemia carriers have three (silent carrier) or two (carrier of the alpha-thalassemia trait) functional alpha-globin genes with or without a mild phenotype. Individuals with only one functional alpha-globin gene have HbH disease with microcytic, hypochromic hemolytic anemia and hepatosplenomegaly. Loss of all four alpha-globin genes results in Hb Barts syndrome with the accumulation of Hb Barts in red blood cells and hydrops fetalis, which is fatal in utero or shortly after birth.

Results Date: 01/01/2018

FRAGILE X

NEGATIVE for Fragile X
FMR1 CGG repeat sizes in the normal range: 31 and 32
No pathogenic or likely pathogenic variants detected by next generation sequencing

Gene analyzed: FMR1 (NM_002024.5)
Inheritance: X-linked

Recommendations
Consideration of residual risk by ethnicity (see below) after a negative carrier screen is recommended, especially in the case of a positive family history of Fragile X syndrome.

Interpretation
Fragile X testing revealed that this patient is heterozygous for alleles having approximately 31 and 32 copies of the trinucleotide repeat, which fall within the NORMAL size range. In addition, next generation sequencing of the FMR1 gene was negative. These results do not rule out the possibility of another uncommon mutation in the FMR1 gene, other causes of intellectual disability, or the presence of a chromosomal defect.

Results Date: 01/01/2018

NEXT GENERATION SEQUENCING

NEGATIVE for all diseases tested

Results Date: 01/01/2018

SPINAL MUSCULAR ATROPHY

NEGATIVE for spinal muscular atrophy
SMN1 Copy Number: >=3
SMN2 Copy Number: 1
g.27134T>G: g.27134T>G negative

Negative copy number result
g.27134T>G status does not modify residual risk (see SMA Table)

Genes analyzed: SMN1 (NM_000344.3) and SMN2 (NM_017411.3)
Inheritance: Autosomal Recessive

Recommendations
Consideration of residual risk by ethnicity after a negative carrier screen is recommended, especially in the case of a positive family history for spinal muscular atrophy.
Interpretation
This patient is negative for loss of SMN1 copy number. Complete loss of SMN1 is causative in spinal muscular atrophy (SMA). Three or more copies of SMN1 were detected in this individual, which is considered a negative copy number result. Parallel testing to assess the presence of an SMN1 duplication allele was also performed to detect a single nucleotide polymorphism (SNP), g.27134T>G, in intron 7 of the SMN1 gene. This individual was found to be negative for this change; however, in individuals with three or more copies of SMN1, the absence or presence of this SNP does not modify residual risk.

Results Date: 01/01/2018

TAY-SACHS ENZYME

| Tests | Total Hexosamindase ActiHex ANormal rang | |
|---|---|---|
| Tay-Sachs WBC | 1112 nmol/hr/mg | 59.8 55.0 - 72. Non-Carrie |
| Tay-Sachs Plasma | 403 nmol/hr/ml | 58.5 58.0 - 72. Non-Carrie |

Interpretation: Expected Carrier Ranges:
Hex A% <54% (Serum/Plasma), Hex A%<50% (WBC)

The test was performed in the patient's plasma and white blood cells (WBC). The Hex A% activities are both within the non-carrier range. These findings are consistent with the patient being a non-carrier for Tay-Sachs disease.

Results Date: 01/01/2017