Patient Information
Patient Name:
Date of Birth:
Gender:
Ethnicity:
Collection Kit:
Reference ID:
Case File ID:

Test Information
Ordering Physician:
Clinic Information: Prom-Test LLC
Phone:
Report Date:
Sample Collected:
Sample Received:
Sample Type:

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 was ordered for this patient. Males are not screened for X-linked diseases.

FINAL RESULTS SUMMARY:

NEGATIVE FOR 254 OUT OF 254 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/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.

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

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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: 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 only) (*HEXA*) **negative**
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

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.