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 27 panel was ordered for this patient.

FINAL RESULTS SUMMARY:

CARRIER for Polycystic Kidney Disease, Autosomal Recessive

Positive for the pathogenic variant c.10972_10973delAT (p.I3658fs*7) in the PKHD1 gene. If this individual's partner is a carrier for Polycystic Kidney Disease, Autosomal Recessive, 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 26 out of 27 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/hrzn27/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: Yang Wang, Ph.D., FACMGG, Laboratory Director
CLIA Laboratory Director: J. Dianne Keen-Kim, Ph.D., FACMG

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POLYCYSTIC KIDNEY DISEASE, AUTOSOMAL RECESSIVE
Understanding Your Horizon™ Carrier Screen Results

What is Polycystic Kidney Disease, Autosomal Recessive?
Polycystic Kidney Disease, Autosomal Recessive (ARPKD) is an inherited disorder that affects the kidneys and other organs, including the liver. Affected children are typically born with enlarged kidneys with multiple fluid-filled sacs called cysts. The kidneys do not work properly causing serious health problems. In the most severe form, the kidney problems begin in pregnancy and may affect fetal lung development because of low fluid levels in the pregnancy (oligohydramnios) caused by the fetal kidney disease. Infants born with this severe form of ARPKD often have very serious lung disease that may lead to early death. In some cases , the kidney cysts, along with progressive loss of kidney function do not develop until later infancy or childhood. Liver disease (congenital hepatic fibrosis) occurs in about half of all children with ARPKD. Currently there is no cure for this condition, although medical treatment, which may include kidney and/or liver transplantation, is available. Clinical trials involving potential new treatments for this condition may be available (see www.clinicaltrials.gov).

What causes Polycystic Kidney Disease, Autosomal Recessive?
Polycystic Kidney Disease, Autosomal Recessive (ARPKD) is caused by a gene change, or mutation, in both copies of the *PKHD1* 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, the kidneys do not develop properly and liver disease may also occur, leading to the symptoms described above.

ARPKD is 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 *PKHD1* gene to have a child with ARPKD. People who are carriers for ARPKD are usually healthy and do not have symptoms nor do they have ARPKD 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 ARPKD, there is a 1 in 4, or 25%, chance in each pregnancy for both partners to pass on their *PKHD1* gene mutations to the child, who will then have the condition.

Individuals found to carry more than one mutation for ARPKD 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 carrier test results. A genetic counselor in your area 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 ARPKD ordered by a health care professional. If your partner is not found to be a carrier for ARPKD, your risk of having a child with ARPKD is greatly reduced. If your partner is found to be a carrier, you can opt to have prenatal diagnostic testing done through chorionic villus sampling (CVS) or amniocentesis during or can choose to have the baby tested after birth for ARPKD.

If you are not yet pregnant, your partner can have carrier screening for ARPKD ordered by a health care professional. If your partner is found to be a carrier for ARPKD you have several reproductive options to consider:

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

What resources are available?
- ARPKD CHF Alliance: http://www.arpkdchf.org/
- PKD Foundation: http://www.pkdcure.org/
- Prenatal diagnosis done through CVS: http://www.marchofdimes.org/chorionic-villus-sampling.aspx
- Prenatal diagnosis done through Amniocentesis: http://www.marchofdimes.org/amniocentesis.aspx
- Preimplantation genetic diagnosis (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

A
Alpha-Thalassemia (*HBA1/HBA2*) **negative**

B
Batten Disease, CLN3-Related (*CLN3*) **negative**
Beta-Hemoglobinopathies (*HBB*) **negative**
Bloom Syndrome (*BLM*) **negative**

C
Canavan Disease (*ASPA*) **negative**
Citrullinemia, Type 1 (*ASS1*) **negative**
Cystic Fibrosis (*CFTR*) **negative**

F
Familial Dysautonomia (*IKBKAP*) **negative**
Fanconi Anemia, Group C (*FANCC*) **negative**

G
Galactosemia (*GALT*) **negative**
Gaucher Disease (*GBA*) **negative**
Glycogen Storage Disease, Type 1a (*G6PC*) **negative**

I
Isovaleric Acidemia (*IVD*) **negative**

M
Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) **negative**
Methylmalonic Aciduria and Homocystinuria, Type cblC (*MMACHC*) **negative**
Mucolipidosis, Type IV (*MCOLN1*) **negative**
Mucopolysaccharidosis, Type I (Hurler Syndrome) (*IDUA*) **negative**

N
Niemann-Pick Disease, Types A/B (*SMPD1*) **negative**

P
Polycystic Kidney Disease, Autosomal Recessive (*PKHD1*) **see first page**

R
Rhizomelic Chondrodysplasia Punctata, Type 1 (*PEX7*) **negative**

S
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.

T
Tay-Sachs Disease (DNA only) (*HEXA*) **negative**
Tyrosinemia, Type 1 (*FAH*) **negative**

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

X-Linked

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

F
Fragile X Syndrome (*FMR1*)
Negative: 30 and 30 CGG repeats were detected in the FMR1 genes.

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

Duchenne Muscular Dystrophy (DMD)

Targeted NGS and MLPA® are used to determine the copy number of the *DMD* exons. NGS and MLPA® have lower sensitivity for single exon *DMD* deletions or duplications in contrast with multi-exon deletion or duplication. The majority of pathogenic DMD-causing variants are multi-exon CNVs for which this test has a sensitivity of >99%. Natera can only provide limited guidance on the relationship between dystrophin genotypes and expected phenotype.

Fragile X

The CGG repeat region of the *FMR1* 5′-untranslated region is assessed using Asuragen, Inc. AmplideX® FMR1 PCR reagents and capillary electrophoresis. Allele sizes up to 200 repeats are analyzed using a proprietary algorithm. Variances of 1 CGG repeats for repeat ranges <70, +/- 3 CGG repeat ranges of 71 - 120, and +/- 5 CGG repeats for >121 may occur. This analysis does not detect deletions or point mutations, which comprise less than one percent of the *FMR1* pathogenic variants. Reflex testing for the number of AGG interruptions is performed for CGG repeat sizes between 55 and 90. AGG interruption testing is performed by Asuragen, Inc., 2150 Woodward St. Suite 100 Austin, TX 78744 (CLIA ID: 45D1069375), and will be reported separately.

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

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/hrzn27/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.