

Northwest Clinical Genomics Laboratory

University of Washington
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Name:
Gender:
DOB:

ID(s):
Date Received:
Report date:

Cancer Health Assessment Reaching Many (CHARM) Study

Clinical Exome Sequencing Results

This individual has enrolled in the CHARM research study providing clinical exome sequencing to individuals with an increased risk of breast and/or colorectal cancer. *****Include the following according to participant's category selection***** [A subset of non-cancer related genes related to [other conditions of medical significance] and/or [carrier risk] were also tested]. *****Any positive finding***** [**Genetic counseling is recommended and was offered through the CHARM study.**] *****Negative report***** [**Genetic counseling was offered through the CHARM study.**]

Sequencing technology is continually evolving, and the interpretation of genetic findings may change over time. If you believe your patient has a genetic condition, evaluation by a genetic specialist to determine the need for additional genetic testing may be warranted. This test does not detect all types of variants (see limitations).

A guide to interpreting genomic test reports can be found here: <http://www.ashg.org/education/csertoolkit/index.html>

**Indication: Personal history of [breast cancer and/or ovarian cancer and/or colorectal cancer]
Family history of [breast cancer and/or ovarian cancer and/or colorectal cancer]**

Results related to the indication for testing (diagnostic): NORMAL RESULT.

NO REPORTABLE VARIANTS IDENTIFIED

Reportable variants (pathogenic variants, likely pathogenic variants and variants of uncertain significance) were not identified in the following genes associated with inherited cancer risk: [list genes]. Variants of uncertain significance are not reported unless they are in genes associated with [cancer type].

OR

Results related to the indication for testing (diagnostic):

This participant with a [personal and/or family history of XXX] has a [**PATHOGENIC VARIANT or LIKELY PATHOGENIC VARIANT or VARIANT OF UNCERTAIN SIGNIFICANCE**] in the [gene] gene which is associated with [description]. *****If VUS***** [The vast majority of Variants of Uncertain Significance will eventually be reclassified as benign].

Gene	Variant	Clinical Significance	Recommendation
			Genetic counseling was offered through the CHARM study. Clinical genetic

			counseling recommended if not performed as part of the study.
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Reportable variants (pathogenic variants, likely pathogenic variants and variants of uncertain significance) were not identified in the following genes associated with inherited cancer risk: XXX, XXX, etc. Variants of uncertain significance are not reported unless they are in genes associated with [cancer type].

****This section only included for participant's who selected receiving other results that may require medical attention****

Results related to other genetic conditions of medical significance (incidental findings): NORMAL RESULT.

NO PATHOGENIC VARIANTS IDENTIFIED

Pathogenic variants were not identified in the following genes associated with medically actionable, adult onset conditions: [list genes].

OR

Results related to other genetic conditions of medical significance (additional findings):

This participant has a **PATHOGENIC VARIANT** in the [gene] gene, which is associated with [description].

Gene	Variant	Clinical Significance	Recommendation
			Genetic counseling was offered through the CHARM study. Clinical genetic counseling recommended if not performed as part of the study.

Pathogenic variants were not identified in the following genes associated with medically actionable, adult onset conditions: [list genes].

****This section only included for participant's who selected receiving results for carrier conditions that my shorten a child's life and/or carrier conditions that cause serious health problems and/or carrier conditions that have unpredictable health problems.****

Results that are not expected to impact participant health but may be relevant to family members or children (carrier results for reproductive risk): NORMAL RESULT.

NO PATHOGENIC VARIANTS IDENTIFIED

Pathogenic variants were not identified in the following genes associated with reproductive risk: [list genes]. This participant has not had comprehensive carrier screening. Discussion of clinical preconception carrier screening, which considers participant ethnicity and family history, may be indicated for participants of reproductive age.

OR

Results that are not expected to impact participant health, but may be relevant to family members or children (carrier results for reproductive risk):

Gene and Chromosome	Variant Position (hg19)	Nucleotide variant (1 = the A of the initiator methionine codon)	Protein variant (1 = the initiator methionine, the first translated amino acid of the precursor protein)

This participant has a **PATHOGENIC VARIANT** in the [gene] gene, which is associated with [type of inheritance pattern].

Gene	Variant	Clinical Significance	Recommendation
		<u>[Include category – lifespan limiting, serious or unpredictable]</u>	Genetic counseling was offered through the CHARM study. Clinical genetic counseling to discuss risks to family members or children is recommended if not performed as part of the study.

Pathogenic variants were not identified in the following genes associated with reproductive risk: [list genes]. This participant has not had comprehensive carrier screening. Discussion of clinical preconception carrier screening, which considers participant ethnicity and family history, may be indicated for participants of reproductive age.

RECOMMENDATIONS: Genetic counseling was offered through the CHARM study. ****Any positive finding**** [Clinical genetic counseling is recommended if not performed as part of the study.]

Further Interpretation

GENE, VARIANT, rsID

[Description of variant]

[Description of evidence supporting interpretation]

****Diagnostic**** Recommendations: Genetic counseling is recommended to discuss the implications of this finding for the patient and their family. *If applicable* [NCCN guidelines for the management of patients with Lynch syndrome are available.]

****Incidental finding**** Recommendations: Genetic counseling is recommended to discuss the implications of this finding for the patient and their family.

****Carrier**** Recommendations: This single variant is not sufficient to cause [condition], but results in risk to family members who have a second pathogenic variant (on the other allele). Genetic counseling is recommended to discuss risks to family members or children.

References: [List references]

Coverage: The mean depth of coverage was ___X (___% at $\geq 20X$). [*X number*] of the analyzed genes was/were covered at less than 95% at 20X: XXX and XXX

Test: Clinical Exome Sequencing (CES)

CES examines the portion of the exome that is clinically meaningful. Currently, this represents 4,503 of the approximately 20,000 genes in the human genome. DNA sequence variants from [one or two or three ****based on ppts category selection*] gene subpanels were evaluated: 1) inherited cancer risk, ****include sections of the following text as applicable**** [2) medically actionable conditions, and 3) carrier status. Medically actionable genes were chosen based on their association with adult onset conditions for which there is recommended screening and/or treatment. Carrier status genes were chosen based on their association with conditions that are common in the general population and/or the specific ethnic populations enrolled in this study.]

Thus, this individual's exome was not comprehensively interrogated. Known pathogenic, likely pathogenic and variants of uncertain significance are reported for genes associated with increased cancer risk. ****include sections of the following text as applicable****[Only known pathogenic variants in medically actionable and carrier status genes are returned.]

This laboratory test was developed and its performance characteristics determined by the Northwest Clinical Genomics Laboratory (CLIA-certified/CAP-accredited). Consistent with laboratory-developed tests, this test has not been cleared or approved by the U.S. Food and Drug Administration.

Procedure:

I. Clinical Exome Sequencing

Genomic DNA was extracted from blood using standard procedures. A library of DNA fragments was constructed and enriched for protein and RNA coding portions of the human genome using the xGEN Inherited Disease Panel (Integrated DNA Technologies). Paired-end sequencing of the enriched library was performed using standard TruSeq chemistry on a HiSeq 2500 (Illumina) sequencer according to the manufacturer's recommended protocol. Resulting sequences were aligned to the human genome reference (hg19) using the Burrows-Wheeler Aligner (BWA) and variants identified with the Genome Analysis Tool Kit (GATK). An in-house tool was used to annotate variants found within the defined set of cancer-related, medically actionable, and carrier status genes.

Limitations:

1. This assay does not detect large deletions or duplications and has limited ability to identify small insertions and deletions. This test is also has limited ability to detect mosaicism.
2. The assay does not detect variants located: 1) outside the captured exome, 2) in regions of insufficient coverage, 3) in regions containing paralogous genes or pseudogenes, or 4) where the reference genome is inaccurate or contains gaps and insertions.
3. Genes not associated with treatable genetic conditions at the time this test was performed were not analyzed.

II. Validation of Sequence Variants

Primers based on the hg19 (February 2009) version of the human genome sequence, were used to amplify targets containing CES identified sequence variants. PCR-amplified fragments were sequenced using standard dye-terminator chemistry.

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