CŌRE DIAGNOSTICS™

geneCŌRE

Homologous Recombination Repair Gene Panel (Germline) Extended

Specimen Type	
EDTA peripheral blood	
Specimen Collection Date & Time	Date & Time of Accessioning
15/07/2024	17/07/2024 13:08 Hrs

Case Number:	24010010576
Patient Name:	R. A. D. G. FRANCIS
Age/Sex:	72 Yrs/Male
Patient Location:	Colombo
Hospital Name:	Aegle Omics (Private) Limited
Physician Name:	Dr. Mahendra Perera
Date & Time of Reporting:	09/08/2024 10:00 Hrs

TEST INFORMATION

The ***gene*CŌRE Homologous Recombination Repair Gene Panel (Germline) Extended test** is a targeted **next-generation sequencing (NGS)** assay that enables the detection of clinically relevant genomic alterations: **single nucleotide variants (SNVs)** and **small Insertion/ Deletions (Indels)** from **DNA**, within the **28** unique **Homologous Recombination Repair (HRR)** pathway genes, from peripheral blood sample. This assay is designed to facilitate successful selection and identification of samples most likely to derive responses from PARP inhibitors.

CLINICAL HISTORY

?Ca. Colon.

RESULTS

- **Negative**

RECOMMENDATIONS

1. Genetic counseling is recommended for the accurate interpretation of test results.
2. Clinical correlation of the identified variant is mandatory and If the identified variant do not correlate completely with the patient's phenotype, then the additional testing needs to be considered based on referring clinician's discretion.
3. The observed variant (s) has been identified by NGS, therefore, Sanger confirmation is recommended.
4. BRCA1 & BRCA2 MLPA study is recommended to analyze deletion/duplications in the sample.
5. The results should be interpreted in the context of the patient's medical evaluation. Correlation of the genetic findings with the clinical condition of the patient is required to arrive at accurate diagnosis, prognosis or for therapeutic decisions.

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COLLEGE of AMERICAN PATHOLOGISTS
AU-ID-2010258

Aditi Aggarwal, Molecular Scientist

Dr. Shivani Sharma
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Dr. Rahul Katara, Ph.D.

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Case Number: **24010010576** Patient Name: **R. A. D. G. FRANCIS** Ordering Physician Name: **Dr. Mahendra Perera**

QC METRICS - DNA

MEAN_TARGET_COVERAGE	**1151.35**
PCT_TARGET_BASES_100X	**100.00%**
AFTER FILTERING Q30_RATE	**93.27%**

VARIANT ANNOTATION

Variant classification (based on ACMG recommendations)

Class 1 – Pathogenic

Class 2 – Likely pathogenic

Class 3 – Variant of uncertain significance (VUS)

Class 4 – Likely benign

Class 5 – Benign

HRD DESCRIPTION

- Homologous recombination deficiency (HRD) is a phenotype that is characterized by the inability of a cell to effectively repair DNA double-strand breaks using the homologous recombination repair (HRR) pathway. A deficiency in the HRR pathway has been associated with several tumor types including breast, ovarian, prostate, and pancreatic cancers and has been termed homologous recombination deficiency (HRD), whereas tumors that are not HRD are termed homologous recombination proficient (HRP).
- Loss-of-function genes involved in this pathway can sensitize tumors to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors and platinum-based chemotherapy, which target the destruction of cancer cells by working in concert with HRD through synthetic lethality.
- [PMID: 35274707].

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THERAPY RECOMMENDATIONS—PARP INHIBITORS

FDA APPROVED DRUGS	
DRUGS	**INDICATION**
Rucaparib Camsylate	• Ovarian epithelial, fallopian tube, or primary peritoneal cancer. • Prostate cancer (Castration-Resistant) that is metastatic, has a germline or somatic mutation in the BRCA1 or BRCA2 gene
Olaparib*	• Breast cancer that is HER2 negative and has certain germline mutations in the BRCA1 or BRCA2 gene. • Ovarian epithelial, fallopian tube, or primary peritoneal cancer. • Pancreatic cancer that has certain germline mutations in the BRCA1 or BRCA2 gene. • Prostate cancer (Castration-Resistant) that is metastatic, has a germline or somatic mutation in the BRCA1 or BRCA2 gene
Talazoparib Tosylate	• Breast cancer that is HER2 negative and has certain germline mutations in the BRCA1 or BRCA2 gene. • Prostate cancer (Castration-Resistant) that has certain mutations in genes involved in the HRR pathway.
Niraparib* Tosylate Monohydrate and Abiraterone Acetate	• Prostate cancer (Castration-Resistant) that is metastatic, has a germline or somatic mutation in the BRCA1 or BRCA2 gene

*On 23 October 2019, the US Food and Drug Administration (FDA) approved **niraparib** for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status.

*on May 8, 2020, expanded the indication of **olaparib** to include its use in combination with bevacizumab for first -line maintenance treatment of homologous recombination deficient (HRD)–positive advanced ovarian cancer.

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TEST DETAILS

- The ***gene*CŌRE Homologous Recombination Repair Gene Panel (Germline)** is a targeted, next-generation sequencing (NGS) assay that enables the detection of relevant SNVs, and indels from 28 unique genes. The test utilizes in-house validated assay that sequences **28 HRR Genes.**
- The genes that are coved in the assay are: **ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCD2, FANCL, KRAS, MRE11, NBN, PALB2, PIK3CA, POLD1, POLE, PPP2R2A, PTEN, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, TP53 and XRCC2.**

TEST METHODOLOGY

- Genomic DNA is isolated from the peripheral Blood is used for targeted capture-based Library preparation. Targeted capture provides an efficient and sensitive means for sequencing specific genomic regions in a high-throughput manner. The libraries were sequenced to mean >500x coverage on Illumina Novaseq 6000 sequencing platform with Paired End 2x150 chemistry.
- GATK bioinformatics pipeline has been followed for identification of variants in the sample. The output sequences are aligned to the NCBI RefSeq transcripts and human genome build (GRCh37).
- The raw read sequences obtained from NGS are processed to remove adapters and filter poor quality reads.
- Clinically relevant germline mutations were identified and annotated using published variants in literature and a set of diseases databases.
- The canonical transcript has been used for clinical reporting, which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.
- Multiple in-silico predictors, such as SIFT, PolyPhen, MutationTaster, NNSPLICE, and ASSP etc. are used for variant impact on the protein function. Population and literature databases such as 1000Genome, dbSNP, Exome Aggregation Consortium (ExAC), genome Aggregation Database (gnomAD), ClinVar, HGMD and PubMed etc are used for variant summary and classification.
- Variants are labelled based on the American College of Medical Genetics (ACMG) recommendations for 5-tier variant classification system: Pathogenic, Likely Pathogenic, Variant of Uncertain Significance (VUS), Likely Benign and Benign.

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REFERENCES

1. Marilyn M Li, et al. “Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.” J Mol Diagn. 2017 Jan;19(1):4-23.
2. Melinda L Telli, et al. "Homologous recombination deficiency (HRD) status predicts response to standard neoadjuvant chemotherapy in patients with triple-negative or BRCA1/2 mutation-associated breast cancer." Breast Cancer Res Treat. 2018 Apr;168(3):625-630.
3. Tatiana Kekeeva, et al. "HRD Testing of Ovarian Cancer in Routine Practice: What Are We Dealing With?.” Int J Mol Sci. 2023 Jun 22;24(13):10497.
4. David Gonzalez, et al. “Homologous recombination repair deficiency (HRD): From biology to clinical exploitation.” Genes Chromosomes Cancer. 2021 May;60(5):299-302.
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7. Luan Nguyen, et al. “Pan-cancer landscape of homologous recombination deficiency.” Nat Commun. 2020 Nov 4;11(1):5584.
8. Aikaterini Tsantikidi, et al. “The Utility of NGS Analysis in Homologous Recombination Deficiency Tracking.” Diagnostics (Basel) . 2023 Sep 15;13(18):2962.
9. Kenneth D Doig, et al. “Homologous Recombination Repair Deficiency: An Overview for Pathologists.” Mod Pathol . 2023 Mar;36 (3):100049.

LIMITATIONS AND DISCLAIMER

Despite all precautions taken, the error (administrative and technical) associated with these types of molecular diagnostic tests can be as high as 1% to 2%. Rare polymorphisms may be present that could lead to false negative or false positive results. The quality of sequencing and coverage varies between regions; many factors such as homopolymers, GC-rich regions etc. influence the quality of sequencing and coverage. This may result in an occasional error in sequence reads or lack of detection of a particular genetic variant. Furthermore, A negative (wild type) result does not rule out the presence of a mutation or rearrangement resulting in targeted fusion, that may be present but below the limits of detection of this assay. Variants that have not been confirmed by an independent analysis could represent technical artifacts. Not all variants detected may be listed in the report. Inclusion of variants is dependent upon our assessment of their clinical significance. Additionally, the presence of a mutation may not be predictive of response to therapy in all patients. The selection of any potential treatment/course of action based on this report rests solely within the decision and judgment of the treating physician and patient. Decisions on patient care should be based on the independent medical judgment of the treating physician based upon all available clinical information, according to the applicable standard of care and should not be based solely on the tests and information contained in this report. Accurate interpretation of this report is dependent on provided detailed clinical history of the patient. In the event of unavailability of detailed clinical history, the lab cannot guarantee the accuracy of the interpretation. The results and interpretation are based on current knowledge and might change in the future. Some findings listed in this report may be based on pre-clinical studies or studies not in the given patient's tumor type.

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If you have any questions about this report or would like to have a conversation about the test results, please feel free to reach out to us at

+91 88828 99999 or **info@corediagnostics.in**

CONDITIONS OF REPORTING

1. The tests are carried out in the lab with the presumption that the specimen belongs to the patient named or identified in the bill/test request form.
2. The test results relate specifically to the sample received in the lab and are presumed to have been generated and transported per specific instructions given by the physicians/laboratory.
3. The reported results are for information and are subject to confirmation and interpretation by the referring doctor.
4. Some tests are referred to other laboratories to provide a wider test menu to the customer.
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