Germline Mutation Testing for Hereditary Cancers
Alarming scenario of Cancer in India*

- An estimated **14.5 lakh** people are living with cancer in India
- Over **7 lakh** new cases being registered every year
- Over **8.8 lakh** deaths will be due to cancer by 2020
- Cancers of Breast, Lung and Cervix will top the list

*National Cancer Registry Program - ICMR

MedGenome’s comprehensive offering of the most advanced Genetic and Molecular Tests for Cancer Management

Advanced testing techniques in Prima

- Next Generation Sequencing (NGS)
- Sanger Sequencing
- Microarray
- Immunohistochemistry IHC
- Cytogenetics
- Multiplex Ligation-dependent Probe Amplification (MLPA)
- Fluorescence In-Situ Hybridization (FISH)
- Flow Cytometry
- Droplet Digital PCR (DD-PCR)
- Fragment Analysis
- Real Time PCR
- Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)

How Molecular and Genetic Testing Helps?

- Ability to sub-classify the type of cancer
- Disease prognostication (assessment of survival and response to treatment)
- Theranostic chemotherapy Value and (Finding radiation) the best fit targeted drugs – alleviating unnecessary
- Hereditary Cancer risk assessment
Clinical Background of Hereditary Cancers

- About 5% of cancer patients have genetic preponderance which would be passed on to next generation.
- People who have inherited a mutation (pathogenic variant) in a cancer-susceptibility gene are at significantly greater risk of developing certain types of cancer compared with those without the mutation.
- For example, a woman with a BRCA1 mutation has a 65% lifetime risk of developing breast cancer, whereas a woman without a mutation has a lifetime risk of only 12%.

The Genetic Mutations impacting occurrence of Hereditary Cancers

- Numerous cancer-susceptibility genes have been identified
- Many of these genes are associated with multiple cancer types
- Conversely, a single cancer type can be linked to mutations in several genes

GERMLINE Mutation testing is empowering the Oncologist to change the trend of Cancer care for the First time in History

Positive BRCA Mutation
- Upto 87% increased risk of Ca Breast
- Upto 44% increased risk of Ca Ovarian
- Upto 10% increased risk of other Cancers (Pancreas, Prostate)

Positive FAP/MAP/AFAP
- Upto 99% increased risk of Colorectal Cancer

Diagram:
- Identify at risk unaffected relatives of a cancer patient
- Incorporate stringent screening practices for the at risk individual
- Detect malignancy at early stages or pre-malignant stage
- Cancers detected early are treated better!!
- Long term disease free survival
GERMLINE Mutation tests for Hereditary Cancers

A simple blood sample to answer the most complex questions of Cancer Inheritance

The decision between single gene and panel testing?
Next Generation Sequencing (NGS) is the answer

• NGS based test panels analyse multiple genes simultaneously
• Advantage - Genes and Molecular Pathways that were not anticipated to be involved may be detected
• It is done at a much lower cost than traditional sequencing methods
• Has a higher likelihood of identifying a causative mutation
• Reduces the need for multiple follow-ups and additional testing

Why Panel testing?
Many solution’s to Multigene Panel testing

<table>
<thead>
<tr>
<th>High Penetrant Cancer Susceptibility Genes in Common Cancers²,8,9</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>High Penetrant Cancer Susceptibility Genes</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>BRCA1, BRCA2, p53, PTEN, COH1</td>
</tr>
<tr>
<td>Colon &amp; Colorectal Cancer</td>
<td>MLH1, MSH2, MSH6, PMS2, MYH, APC, STK11, MSI</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>MLH1, MSH2, MSH6, PMS2, PTEN</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, p53</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>BRCA2, RNASEL ELAC2, MSR1</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>BRCA2, STK11/LKB1, PALB2, PRSS1, SPINK1, COKN2A</td>
</tr>
</tbody>
</table>


Lu, Karen H MD. Value of Family History in Common Cancers. Epidemiology: From Genetics to Practice Presentation, Health Services Research and Quality of Care Track. ASCO 2015.
Who should be tested for Hereditary Cancers?

1. An individual whose first line blood relative has been detected with a pathogenic or likely pathogenic variant in a cancer susceptibility gene

2. An individual with personal history of ≥1 of the following:
   - Cancer diagnosed at age ≤50 years
   - Bilateral or multiple primary cancers
   - Cancer diagnosed at any age and significant family history
   - Rare cancer (e.g., male breast cancer or ovarian cancer)

3. Individuals with family history of cancer with ≥1 of the following:
   - ≥3 Blood relatives on same side of the family with the same or related cancer type
   - ≥2 Blood relatives on same side of the family with the same or related cancer type, at least 1 of whom was diagnosed at age ≤50 years
   - ≥1 Blood relative on same side of the family with the same or related cancer type and Ashkenazi Jewish ancestry

MedGenome offers Broad Multi-Gene NGS panels for evaluation of Hereditary Cancer predisposition

Hereditary Cancer Panel (HCP) - Focussed
- Provides evaluation of 106 genes

Sample Requirement
Blood (3-5ml) EDTA Tubes

Turn Around Time
Time taken for generating a clinical report will be maximum of
- 4 weeks by NGS

In case where the sample quality is poor (sample which fails our QA/QC), the TAT will get prolonged. New batch of sample will need to be submitted for sequencing and analysis.
Free Genetic Counselling

In accordance with the latest global cancer management guidelines (NCCN - National Comprehensive Cancer Network), Prima offers FREE Pre and Post-test Genetic Counselling with our expert and certified Genetic Counsellors to all your patients. Best available support for your patients and families via:

- Latest technologies
- Helpful customer service
- Clear result interpretation
- Counselling sessions with our Genetic Counsellors

Sample Report

**DNA TEST REPORT - MEDGENOME LABORATORIES**

<table>
<thead>
<tr>
<th>Full Name / Ref No:</th>
<th>XXX</th>
<th>Order ID/Sample ID:</th>
<th>XXX / XXX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td>XX</td>
<td>Sample Type:</td>
<td>Blood</td>
</tr>
<tr>
<td>Date of Birth / Age:</td>
<td>XX years</td>
<td>Date of Sample Collection:</td>
<td>XX</td>
</tr>
<tr>
<td>Referring Clinic:</td>
<td>Dr. XXX</td>
<td>Date of Sample Receipt:</td>
<td>XX</td>
</tr>
<tr>
<td>Test Requested:</td>
<td>Hereditary cancer gene panel – focused</td>
<td>Date of Order Booking:</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Date of Report:</td>
<td>XX</td>
</tr>
</tbody>
</table>

**CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY**

XXX is diagnosed with carcinoma right breast. XXX has a family history of breast cancer with mother affected. XXX has been evaluated for pathogenic variations in the genes listed in appendix 1.

**RESULTS**

**PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS IDENTIFIED**

<table>
<thead>
<tr>
<th>Gene (Transcript)</th>
<th>Location</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Disease (OMIM)</th>
<th>Inheritance</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 (ENST00000471181)</td>
<td>Exon 15</td>
<td>c.657C&gt;T (p.Ser152Ter)</td>
<td>Heterozygous</td>
<td>Breast-ovarian cancer, familial, 1</td>
<td>Autosomal Dominant</td>
<td>Pathogenic</td>
</tr>
</tbody>
</table>

**ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED**

No other variant that warrants to be reported was detected. Variations with high minor allele frequencies which are likely to be benign will be given upon request.

**VARIANT INTERPRETATION AND CLINICAL CORRELATION**

Variant description: A heterozygous nonsense variation in exon 15 of the BRCA1 gene (c.657C>T; p.Ser152Ter) that results in a stop codon and premature truncation of the protein at codon 1524 (p.Ser1524Ter; ENST00000471181) was detected (Table). This variation (referred as S1503X) has previously been reported in patients and families with breast and/or ovarian cancer. The Ser1524Ter variant is not reported in the 1000 genomes and our internal database and has a minor allele frequency of 0.00008% in ExAC database. The in-silico predictions of the variant is damaging by Mutation Taster tool. The reference codon is conserved in primates.

OMIM phenotype: Susceptibility to familial breast-ovarian cancer 1 (OMIM #604370) results from heterozygous germline mutations in the BRCA1 gene (OMIM #123705).
Prima by MedGenome offers a wide range of Oncology and Haematology genetic tests, these include:

- Molecular Testing for Hematological Malignancies, Comprehensive Leukemia Panel
- IGHV Gene Mutation Testing for CLL, Comprehensive Leukemia Panel, BCR-ABL1 gene fusion analysis
- Hereditary Cancer Panel, BRCA1 and BRCA2 gene test, Thalassemia Mutation Test
- Comprehensive Tumor Gene Panel, Somatic Mutation Panel, Comprehensive Leukemia Panel, Molecular Testing for Lung Cancer
- OncoTrack, OncoSelect, OncoFocus (Liquid Biopsy Test)
- NGS based IRMA, BCR-ABL1 gene fusion analysis

For more information
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Website: www.medgenome.com