MEDGENOME

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GeKNOWme

Internal Quarterly Newsletter

Cover Story

Riding through Genomic turmoil:

Double strand DNA repair mechanisms to rescue Genomic scaring a novel phenotype in Cancer

WORDS FROM THE **FRONTLINE**

Madhavi Latha, PhD
Principal Genetic Counsellor

Dear MedGenome Family, Warm Greetings!!!

It gives me immense pleasure to write about the journey of genetic counselling at MedGenome. It's my 8th year here, and it has not only been a beautifully challenging journey, but also very gratifying. I cannot but start this article with a profound sense of gratitude to Sam Sir, Dr. Ram, Dr. Ravi, Dr. Venkat, Dr. Sakthi, Dr. Priya and Dr. Prasanna for their unwavering support all these years.

As Dr. Priya rightly mentioned in the previous issue of GeKNOWme, Genetic Counselling is the backbone of any genetic testing. The first genetic counsellors hired by MedGenome were part of the customer support and the scientific affairs. Genetic Counselling was offered initially by Dr. Govindasamy Kumarmanikavel who was part of the MedGenome advisory board. Dr. Kumar also happens to be my first teacher in genetic counselling; the initial handholding and the confidence he instilled in me, is still a priceless blessing.

Genetic counselling as a service was first offered and advertised by MedGenome for NIPT, when the test was initially launched. A toll-free number for patients and family members was created. We were a team of two people addressing patient queries. Today, we have a team of more than 9 counsellors who offer counselling in all domains of genetic testing.

Genetic counselling requires a sense of both self-awareness and social awareness, and the ability to manage emotions and connect with others. Genetic counsellors are trained to present complex and difficult-to-comprehend information about genetic risks, testing, and diagnosis to patients and their families. Today counsellors not only offer counselling, but also handle sensitive issues and situations.
At MedGenome, we have a team of proficient genetic counsellors, who are skilled to engage empathically with patients and their family members, aiming to provide unbiased, ethical and accurate information in a simple and precise manner. Our team is equipped to assist patients with the medical, familial and emotional aspects of a genetic diagnosis, acting as a liaison between clinicians and patients. We also aid clinicians in choosing genetic tests relevant to the patient's condition.

The GC team has experience in multiple speciality areas of counselling, from pre-marital, preconception and prenatal, to neonatal, paediatric and adult-onset conditions along with precision medicine and pharmacogenetics. Genetic Counselling is offered across all domains of medicine including neurology, cardiology, nephrology, ophthalmology, ENT, reproductive medicine, and oncology. Both pre-test and post-test genetic counselling is offered to patients and/or their family members. Treatment and management options are not discussed in the counselling session, and patients are referred back to the referring clinician. Counselling is offered in different Indian languages other than Hindi and English by the team.

All counsellors are certified by the Board of Genetic Counselling, India (BGC-I), and counselling is offered by telephone, video and in person (in selected cities only.) Here, I would like to comment that Dr. Kumar was probably the first one in our country to offer video counselling in 2015 itself. Actually, there have been many firsts in genetic counselling at MedGenome. We are the first to offer telephonic and video counselling successfully. We also are the first to understand and offer counselling in different Indian languages, and hire counsellors accordingly. We are also the first to provide genetic counselling support to hospitals.

The GC team gets counselling leads and cases through the sales team, marketing team, techsupport team or the customer support, or directly from the patients/doctors though the tolls free number or email. The genetic counsellor makes a call within 24-48 hrs, and sessions are scheduled anywhere between from 9.00am to 9.00pm as per the convenience of the patient and the family, and the available slot that day. As per our policy prenatal cases are a priority and all efforts are made to address these cases immediately, and efficiently.

Dr. Govindasamy Kumarmanikavel and Dr. Madhavilatha

From handling ~200 cases/year, the team now handles more than 200 cases/month. For each case, the counsellor makes at least 5 calls, and schedules a minimum of two sessions, irrespective of whether the request was for both pre and post, or only for pre/post-test counselling. At this juncture, I would like to mention that no other genetic testing company in our country handles so many cases/sessions. MedGenome's genetic counselling support is unparalleled currently. Also, more than 75% cases are post-test counselling, and more than 50% of them have a VUS reported or no variant reported. So there is a good amount of homework to be done by the counsellor before talking to the patient/family. Here I would like to say my thanks to the GA team, tech support team, sales team, and the clinical geneticists for their support, so that we can offer our best to the patients and their families.

Many issues faced by the counsellors during counselling are primarily due to nonavailability of pre-test counselling, and lack of awareness about genetic testing and the different testing techniques. People perceive genetic testing to be like any other medical test, and do not understand the need for proper personal/family/medical history. The ideal scenario of course would be to offer pre-test genetic counselling to every case that comes for germline testing. But there are not enough genetic counsellors in our country, or for that matter in any country. Thus, to be able to provide genetic counselling to all cases with pathogenic/likely pathogenic variants is one of our goals, so that the recurrence of a condition in a family can be avoided wherever possible. Otherwise, the whole effort taken for genetic testing becomes meaningless for the family. So, one of the responsibilities of a genetic counsellor is also to create awareness about genetic testing, genetic counselling and its importance, both in the medical community and in society.

There is so much more that is going to happen in the field of genetics, genomics, and genetic testing. And genetic counsellors are always going to be the bridge between technology, the clinician and patient. MedGenome being a leader, opportunities are plenty, and as genetic counsellors there is so much more we can offer to our company, our society and our country.

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Home > Projects > MedGenome Labs offers clonoSEQ Assay to assess MRD in patients

PROJECTS

MedGenome Labs offers clonoSEQ Assay to assess MRD in patients

clonoSEQ is the 1st U. S. Food and Drug Administration (FDA) cleared MRD test for Multiple Myeloma, Chronic Lymphoblastic Leukaemia (CLL), and B-Acute Lymphoblastic Leukaemia (B-ALL).

Nitin Sood, Chief Commercial Officer, MRD, Adaptive Biotechnologies

MedGenome announced it is offering Adaptive Biotechnologies' next-generation sequencing (NGS)-based clonoSEQ Assay to assess minimal residual disease (MRD) in patients with multiple myeloma (MM), chronic lymphocytic Leukaemia (CLL), and B-cell acute lymphoblastic leukaemia (B-ALL).

MRD is described as the number of very small cancer cells that remain in the body during or after treatment. The number of remaining cells can be so small that they do not show any physical signs or symptoms and often can go undetected through traditional methods. The clonoSEQ test may effectively detect and monitor MRD in

THE TIMES OF INDIA

Doctors use genome sequencing to treat drug-resistant tuberculosis patients

PUNE: Twenty-six-year-old medical student Anita, a patient of hip-joint tuberculosis (TB), was bed-ridden for almost three months as the anti-TB drugs she was taking failed to relieve her symptoms. Seeing no improvement in her condition, doctors from Deenanath Mangeshkar Hospital (DMH) used next generation sequencing (NGS) technique to figure out the right treatment plan.

'We did NGS and found that the TB bacterium responsible for affecting her hip-joint had certain mutations that can potentially be associated with isoniazid and pyrazinamide drug resistance. She was taking both these medicines. We changed these drugs and she started showing improvement," said DMH's infectious diseases expert Dr Parikshit Prayag.

Dr Prayag has treated four carefully selected drug resistant TB patients using the NGS technique to determine the right line of treatment in the last six months.

While the existing GeneXpert (Xpert XDR), a more widely used molecular test for

For press articles, please click https://diagnostics.medgenome.com/press/

MedGenome Connect

Claria
Reproductive Genetics

In the last quarter for Claria, many engaging activities were focussed on. We participated in a multiple face-to-face conferences and our aim was to plan and conduct more CMEs, RTMs with our KOLs. We also executed the world DNA day campaign which was highly appreciated by our KOLs.

micra
Infectious Disease Genetics

The last quarter has been a very active one for Micra with a focus to engage more clinicians with CME, conference participation, etc. The team is also working on a comprehensive Micra catalogue which contains in depth information about the new tests launched in Micra.

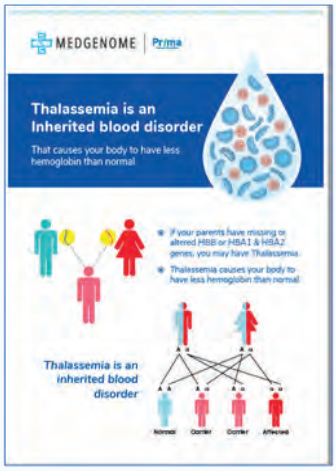
ACTIA
Inherited Genetics

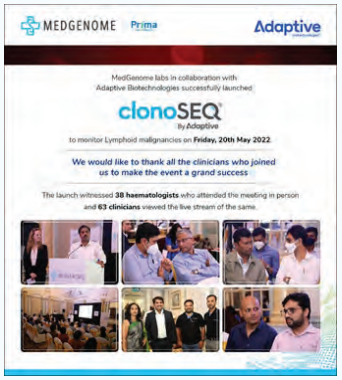
In this quarter, we focussed on participating in multiple events across the length & breadth of the country, both at the regional & national levels. There were also a few online webinars where the role of MedGenome's Actia portfolio was discussed. A variety of collaterals were created for showcasing MedGenome's USPs to the customers to help them understand our expertise and excellence in molecular diagnostics solutions.

MedGenome Connect

Prima Cancer Genetics

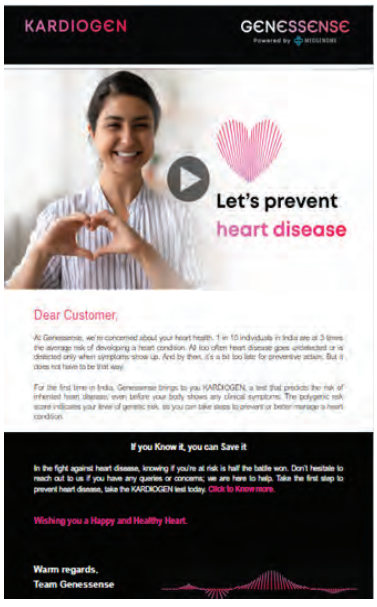
The last quarter was a very busy one for Prima as the team engaged the clinicians in multiple physical as well as digital activities. We have launched the **ClonoSEQ** Assay in collaboration with Adaptive Biotechnologies and the launch event was hosted at ITC Windsor among our esteemed clinicians. We have also conducted many face to face meetings with KOLs at our NN office and organised an engaging talk by **Dr. Alka Chaubey, Chief Medical Officer at Binano Genomics on Optical Genome Mapping: High Resolution Detection of Structural Variations in Hematological Malignancies and Rare Undiagnosed Diseases** which was conducted in-person as well as streamed online.





GENESSENSE

We continued to evolve the various tests being offered under the Genessense portfolio in this quarter. We focussed on forging partnership with a few aggregators & conversations were initiated with some of the major players in this space. To ensure awareness about this brand, we also sent out emailers to our databases. The version 1 of the BMI Gen test report was created, and the test was made available for internal testing with a prospective partner organisation.



What's new

Research Publications

1. *Chorea-acanthocytosis: 3 New Families with Novel Genetic and Metabolic Findings*
   Journal : Annals of Indian Academy of Neurology
   PMID: 34447025 | Click here for more

2. *Clinical, radiological and molecular studies in 24 individuals with Dyggve-Melchior-Clausen dysplasia and Smith-McCort dysplasia from India*
   Journal : Journal of Medical Genetics
   PMID: 35477554 | Click here for more

3. *Clinical, genetic profile and disease progression of sarcoglycanopathies in a large cohort from India: high prevalence of SGCB c.544A > C*
   Journal : Neurogenetics
   PMID: 35416532 | Click here for more

4. *Genome-Wide Polygenic Score Predicts Large Number of High-Risk Individuals in Monogenic Undiagnosed Young Onset Parkinson's Disease Patients from India*
   Journal : Advanced Biology
   PMID: 35810474 | Click here for more

5. *Metabolic and Genetic Evaluation in Children with Nephrolithiasis*
   Journal : Indian Journal of Pediatrics
   PMID: 35819704 | Click here for more

Tests launched

1. HRR Liquid Biopsy
2. Thyroid Prognostication Next Gen Sequencing panel test (Thyro Track)

From Our US Office

We are happy to share with you that our Blog has been featured recently as one among the widely read Top Genomics Blogs. We wish to enrich our content with more insightful and deep connects with the latest trends in Genomics Research.

Please visit our blog at https://research.medgenome.com/blog/ to see the archives. You can share your viewpoints and articles at mgus-blog@medgenome.com

Some of the recent articles we have published are as below:

1.How TCR and BCR sequencing is changing the immune research landscape

2.Single Cell RNA Sequencing (scRNA-seq) – it's role in understanding immunity and vaccine development

3.Immune profiling and genome sequencing solutions by MedGenome for cancer immunotherapy

MedGenome US conducts regular internal trainings for Commercial and NGS lab members on assays offered. One of them on '10x TCR, BCR, Cite Seq' is available in the link below.

https://youtu.be/8eWp6QjtYoY

The recordings are archived in LIMS for all the team members to review at any time.

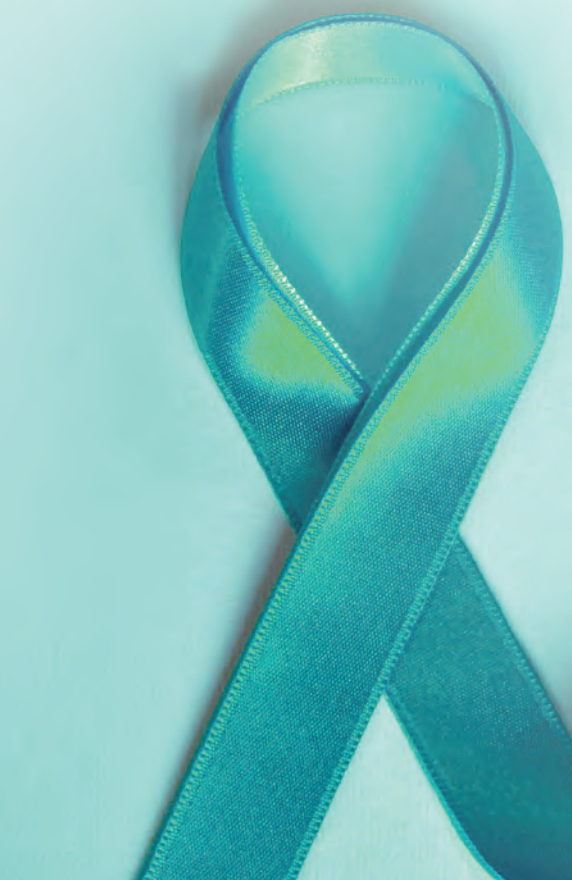
Riding through Genomic turmoil:

Double strand DNA repair mechanisms to rescue Genomic scaring a novel phenotype in Cancer

By: Vijay Nagampalli, PhD
Senior Scientist I, Bioinformatics Dept.

Cancer arises from genetic alterations that drive and accompany tumor growth, the very same can also play a role in genomic turmoil. Alterations occur in genes that preserve genomic integrity increase genomic instability that can contribute to selection of cancer clones with fitness advantage for proliferation. Tracing this genomic instability early on can be direct therapies to target these origins.

Several studies discovered that *BRCA1/2* genes play a significant role in hereditary breast and ovarian cancer (HBOC), and early individual risk assessment was done using tedious sequencing of these genes. Interestingly approximately 30% of the mutations have remained negative after testing *BRCA1/2*, even in families with a Mendelian inheritance pattern for breast cancer. This indicates that an additional non-*BRCA* genes has been identified as predisposing to breast cancer. These genes encode products that are involved in Homologous Recombination. Two decades after the BRCA genes were identified, technical advances in next-generation sequencing allowed for the development of multi-gene cancer predisposition panels. This also helped in extending from personal or family risk assessment to personalized treatment strategies like for example, women with *BRCA1* or *BRCA2* mutations may benefit from improved response to platinum agents and poly(ADP-ribose) polymerase (PARP) inhibitors



Homologous Recombination Deficiency (HRD) an Ovarian cancer Biomarker

DNA continuously undergoes damage and repair processes in our bodies. Though we have various DNA repair processes which faithfully guard our DNA, any deviations in them may lead to genomic instability which in turn would modulate different disease states of tumorigenesis. One of the DNA repair processes is HRR - homologous recombination repair pathway. Mutations in *BRCA1* and *BRCA2* genes account for 5-15% of ovarian cancer cases. These mutations along with other genetic abnormalities would prevent production of DNA repair proteins contributing to the halt of the DNA repair pathway, ultimately accumulating genetic aberrations and causing multiple cases of ovarian cancer every year.

What is HRD?

The homologous repair (HRR) pathway repairs double-strand breaks in DNA and interstrand cross-links by using a second copy of the gene as a template to restore the genomic integrity of DNA. *BRCA1* and *BRCA2*, proteins of the MNR complex *(MRE11/RAD50/NBS1)*, *H2AX*, *MRE11*, *CtIP*, *RAD51*, *ATM*, *PALB2*, *RAD52*, *RPA*,) and proteins of the Fanconi anemia pathway are just a few of the proteins that Homologous Recombination (HR) depends on to function during the S and G2 phases of the cell cycle. HRD is the phenotype that occurs due to cells' inability to repair DNA double-strand breaks using the HRR pathway and overly dependence of the repair pathway on less precise and more error-prone alternate repair systems like NHEJ. Over time, the accumulation of unrepaired and inaccurately repaired mutations like insertions and deletions would lead to malignant transformation of cells. (Figure 1)

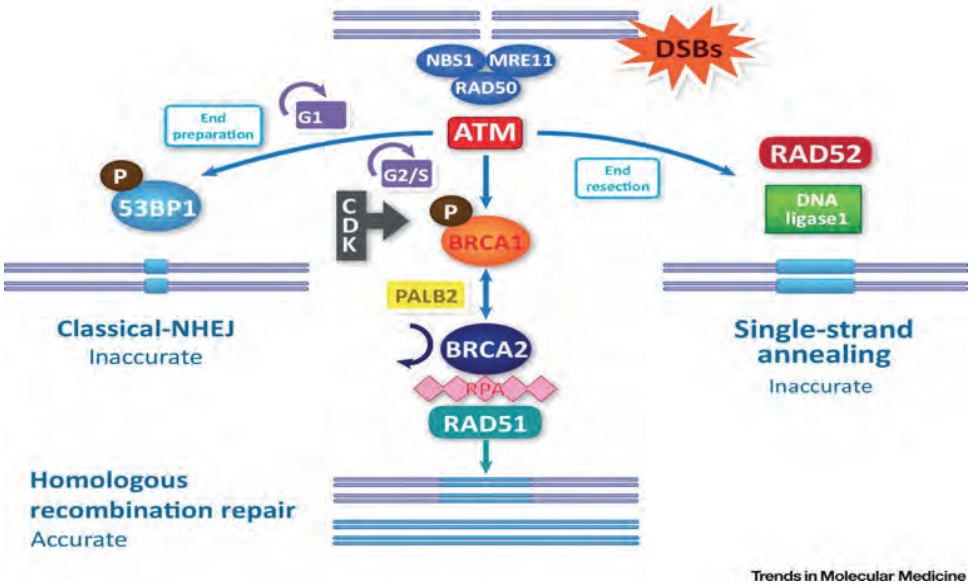


Figure 1: Overview of Double strand DNA repair Mechanisms (Adapted from Grainne M. O'Kane et.al. 2017)

What is HRD testing?

HRD testing helps in diagnosis of ovarian cancer by guiding health professionals into thorough analysis of the changes to the genome and its molecules in patients and aids in personalizing medicines.

Testing for the consequences of an impaired HRR pathway is performed by probing the genome for evidence of genomic abnormalities. Several studies in breast and ovarian cancer have identified genomic patterns or signatures of instability associated with an HRD phenotype. Germline and somatic mutations, as well as epigenetic modifications in *BRCA1* and *BRCA2*, have been consistently associated with an HRD phenotype in breast, ovarian, pancreatic, and prostate cancer. A patient's tumor HRD status is assessed by calculating HRD score based on the following three independent measures of genomic instability: Loss of heterozygosity (LOH): Permanent loss of one parent's contributed allele copy of a gene at a specific part of a chromosome (regions of intermediate size (>15 MB and < whole chromosome). Telomeric allelic imbalance (TAI): Copy choice or chromosomal cross-over events caused by error-prone repair processes or genomic rearrangement can lead to Allelic Imbalance or copy number changes that can spread from the site of DNA damage to the telomere (The number of regions with allelic imbalance which extend to the sub-telomere but not cross the centromere). Large scale transitions (LST): genome breaks (translocations, inversions, or deletions generating higher than or equivalent to 10 Mb in chromosomal gains or losses. LOH, TAI and LST metrics are significantly associated with *BRCA1/BRCA2* status at both individual and combination levels (Figure 2). The testing process evaluates the presence of HRD-related genomic signatures (often referred to as scars) that are thought to be a consequence of error-prone DNA repair through alternative pathways (eg, non-homologous end joining [NHEJ]

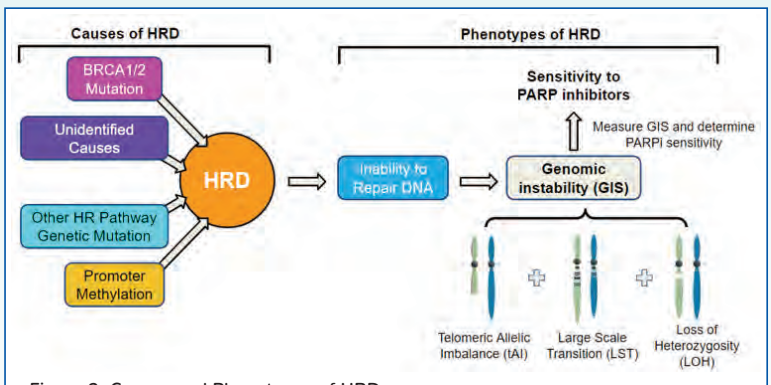


Figure 2: Causes and Phenotypes of HRD

What to expect from HRD?

HRD testing has various strategies based upon the requirement of different HRD mutations in different individuals. Usually health professionals recommend germline and/or somatic testing based upon the prognosis of patients. Somatic testing is always a preferred test to begin with, a tumor sample is taken during surgery and a biopsy is done to examine tumor cells under microscope for identifying HRD mutations in tumor cells and evaluating their genetic composition. Somatic testing won't detect BRCA1/BRCA2 mutations, hence given the need of hour to query about germline cancer status of the patient, germline testing is done. In this case, DNA is taken from healthy cell samples from blood/saliva to check if mutations are inherited.

How HRD testing helps?

HRD testing is used as a biomarker for Ovarian cancer especially at high grade serous stage. It aids oncologists in finding better insights into the following areas:

Prognosis

It helps in getting insights in the course of disease and helps in the identification of variants that may have caused HRD in individuals leading to cancer.

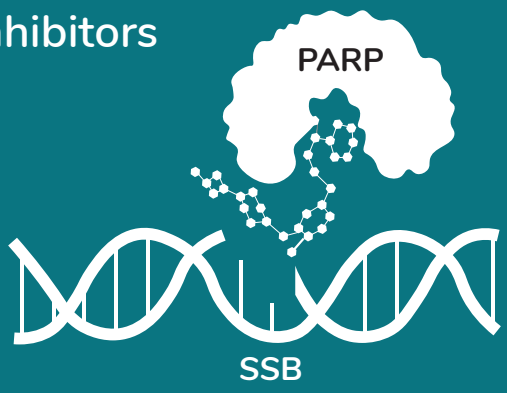
Predisposition

Family history of ovarian cancer to find the patient's susceptibility towards cancer and its progression.

Treatment

It helps to plan a comprehensive treatment

Does HRD patients benefit form PARP inhibitors treatment?



The presence of HRD can make tumors more sensitive to ICL-inducing platinum-based therapies and poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors (PARPi). Adenosine diphosphate-ribose polymerase inhibitors work via synthetic lethality; blocking base excision repair with PARPi results in an accumulation of DNA single-strand breaks and replication fork collapse resulting in DNA double-strand breaks that cannot be repaired by the HRR pathway if HRR is deficient thus leading to cellular apoptosis (Figure 3). PARP inhibitors and platinum-based chemotherapies are administered by using HRD as a biomarker in newly diagnosed individuals as the first line of management rather than being used after unsuccessful therapies. Platinum-based chemotherapy (cisplatin or carboplatin) combined with Taxane is given to patients after removal surgery. HRD testing has been observed to be very promising in providing treatment and guidance for ovarian cancer. People being positive for HRD mutations and BRCA mutations, when treated with PARP inhibitors, have shown 70-80% improvement with 5 years of increased life span.

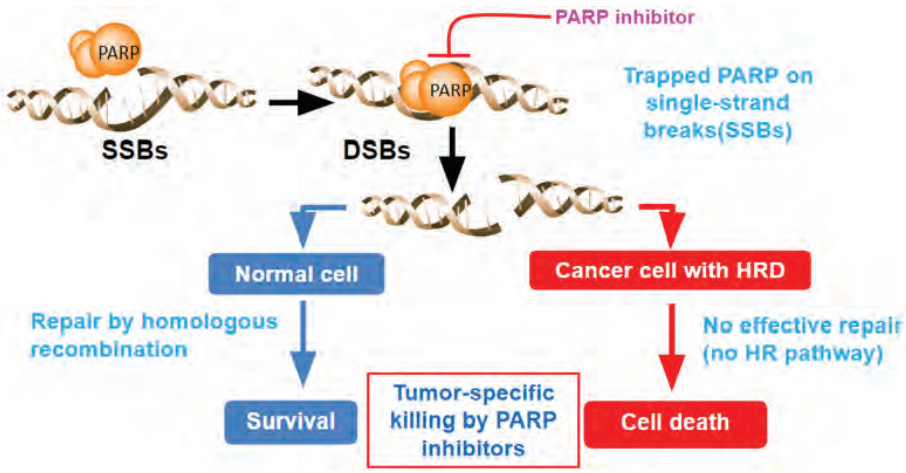


Figure 3 Mechanism and current progress of PARP inhibitors in the treatment

Diagnostic solutions to HRD testing

To date commercial and lab-developed assays utilize Next generation based multi-gene panel that includes BRCA genes and other HRR genes for measuring HRD. These HRD solutions detect SNPs Indels, and Gene amplifications across BRCA and other HRR genes. Several HRD solutions depend on defining HRD by either (1) deleterious or suspected deleterious BRCA/HRR mutations and/or (2) genomic instability. Additionally, many of the commercial HRD solutions incorporate both the causes and consequences of HRR impairment.

MedGenome HRD solutions

Leverages next-generation sequencing-based approaches detecting somatic and germline mutations in BRCA genes. In addition, we also look at the consequence of HRD via machine learning based genomic scar score measurement.

Myriad Mychoice

Myriad myChoice® HRD is used to detect homologous recombination deficiency (HRD) by assessing Genomic Instability Status and Tumor Mutation Status in genomic DNA extracted from tumor specimens. Analytical evaluation done with BRCA genes only.

Qiagen

Qiagen adapts DNA Damage repair as a measure of genomic instability across various cancers including breast, ovarian, prostate and pancreatic. Their NGS based assay looks beyond BRCA genes and includes 15 genes that were part of the study from PROfound study.

Sophia genetics

SOPHiA DDM HRD Solution leverages target capture technology to isolate somatic and germline mutations in 28 HRR genes (including BRCA1 and BRCA2). In addition, they also look at the consequence of HRD via a convolutional neural network-based deep learning algorithm to produce the Genomic Integrity Index that measures genomic scaring

AmbryGenetics TumorNext-HRD solution

A paired tumor and germline analysis of BRCA1 and BRCA2 plus 9 additional genes in the homologous recombination repair pathway.

Conclusion

Biomarkers such as HR status play a critical role in treatment decisions for patients with cancer. A precise and accurate measurement of HRD status can be used as an aid in identifying beneficiary for treatment with the targeted therapies. 30-50% women with advanced ovarian can be HRD positive and avail PARPi benefit.

From our Colleagues

Art meets Science

If what is seen and experienced is portrayed in the language of logic, then it is science. If it is communicated through forms whose connections are not accessible to the conscious mind but are recognized intuitively, then it is art. - Author: Albert Einstein

By: Kirtee Jindal,
Assistant Manager - Legal, Finance dept.

From our Colleagues

Our employee's little Picasso :)

Mother son Duo

By
Suruchi Aggarwal, PhD
Senior Scientist - Oncology

By
Ayan (11 Years)
DNA of Suruchi Aggarwal,
Senior Scientist - Oncology

From our Colleagues

आज है एक नई सुबह,
फिर भी है वही स्वभाव,
हर पल हम रहे छुपा,
रंग से अपनी उखड़ी लज्जा।

आज है एक नया वार,
कहने को असत्य हम तैयार,
ज़ालिम मन को रहे छुपा,
मुख पर रंग कर उज्ज्वल मंदहास।

आज है एक नई रात,
कुस्वप्न में भी सोने को बेक़रार,
कलपती रूह को हम रहे छुपा,
उसपर रंग कर मोहन का प्यार।

आज है एक नया लम्हा,
तोड़ने चले हम चंगुल अपना,
अत्याचार से बना वो फंदा,
नकार रहे थे जो हम हर लम्हा।

आज है एक नया प्रकाश,
मौक़ा लाया जीवन में फिर एक बार,
सहना नहीं है हमको अत्याचार,
छोड़ना है पीछे वो दर्दनाक काल।

आज है एक नया काल,
रंग से नहीं छुपाना अब कोई निशान,
खड़ा होना है हर जुल्म के ख़िलाफ़,
अपनों का ही क्यूँ ना हो इम्तहान।

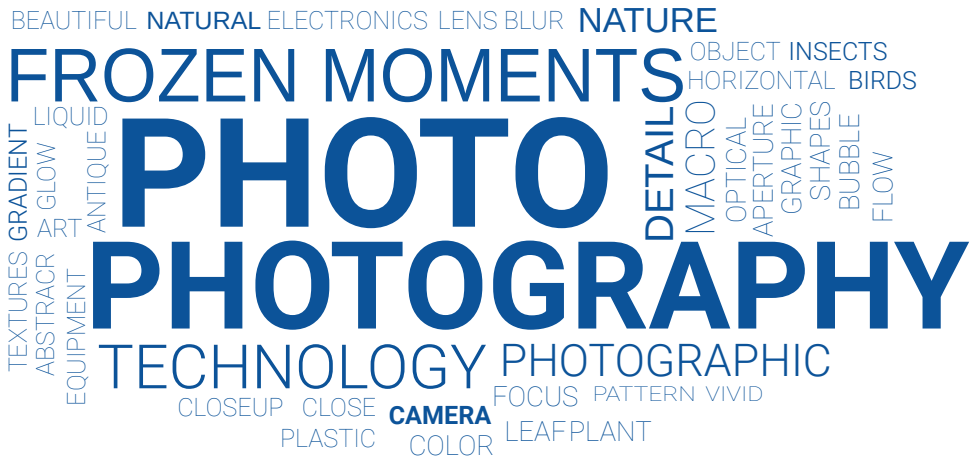
आज है एक नई साँझ,
पराक्रम से होगी अब दोबारा पहचान,
भरने वाला है हर एक घाव,
जिसके लिए उठाई है हमने आवाज़।

आज है एक नया सवेरा,
एक बार फिर कर ले भरोसा,
धैर्य को अपने ना खोना,
नए रंग को जीवन में पिरोना।

~ Kirtee Jindal

By: Kirtee Jindal,
Assistant Manager - Legal, Finance dept.

From our Colleagues



By
Romiya Das
Manager – Public Relations,
Corporate Dept.

Employee Connect

WELCOME

Our New-Joiners


Aarya Senan T S


Aayushi Shakya


Abdul Baseeh P


Abhijeet Das


Abhijit Mhaskuji


Abhishek Soni


Adarsh Kumar


Adhithya K


Ajithkumar


Alice Arati Anthony


Ambadipally Manoj Kumar


Amit Chatterjee


Amita


Anamika Mishra


Anand P S


Ananthan


Anil Kumar Madugundu


Ankit Kumar


Ankita Jagtap


Anushree


Anwesha Paul


Apoorva H R


Arun Mathur


Arun Viswaraj


Arvind Murali Venkatesan


Ashika Sita Jayanthy


Asif Shahbaz Khan


Avesh Khan


Avinash Kumar


Ayon Saha


Ayushi Gupta


Baby M B


Baraneedharan U


Basil Thomas


Bhavanam Srinivasareddy


Bhupendra Mishra


Bipul Mandal


Chaithra L


Chandan Kumar


Chirag Kumawat


Debojyoti Bhattacharya


Debparna Saha


Deecan Sanyo Chillachi


Deepak H L


Deepak Kumar


Deepak Rajagopal


Deepan Chakkravarthi


Dhiraj Kumar Upadhayay


Diksha Singh


Dileep Kumar


Dipesh K B


Dipti Manchanda


Diya


Elsa Joy


Esdanbasha SK


Ganesh Giri


Gaurav Tripathi


Geethu S


Gudi Praveen


Harsh C Gamre


Heera Singh


Hitendra Mahadeo Kadam


Ichchha Jaiswal


Indhushree R


Indra Kamal Medhi


Indumathy Sabarish


Jagan


Jayashree Dey


Jayshree Balasaheb Gare


Jeevana


Jotheeswaran Periannan


Jothi Arjunan


Jubaraj Baral


Jyoti


Kabeer Mahaboob


Kamalakkannan M


Kanuri Pradeep Kumar


Karoline


Kasinathan Anandhan


Katakum Prasad Rao

Keshaw Baindara

Koushik Ponnanna C R

Kranthiraj R

Krishnendu Ghosh

Kritika Passi

Kulkarni

Kumkum Devsharma

Logapriya Rajavel

M. Prabhu

Mahesh Mahalingam

Mahima Nandhini

Malla Divya Jyothi

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