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Apollo GENOMICS

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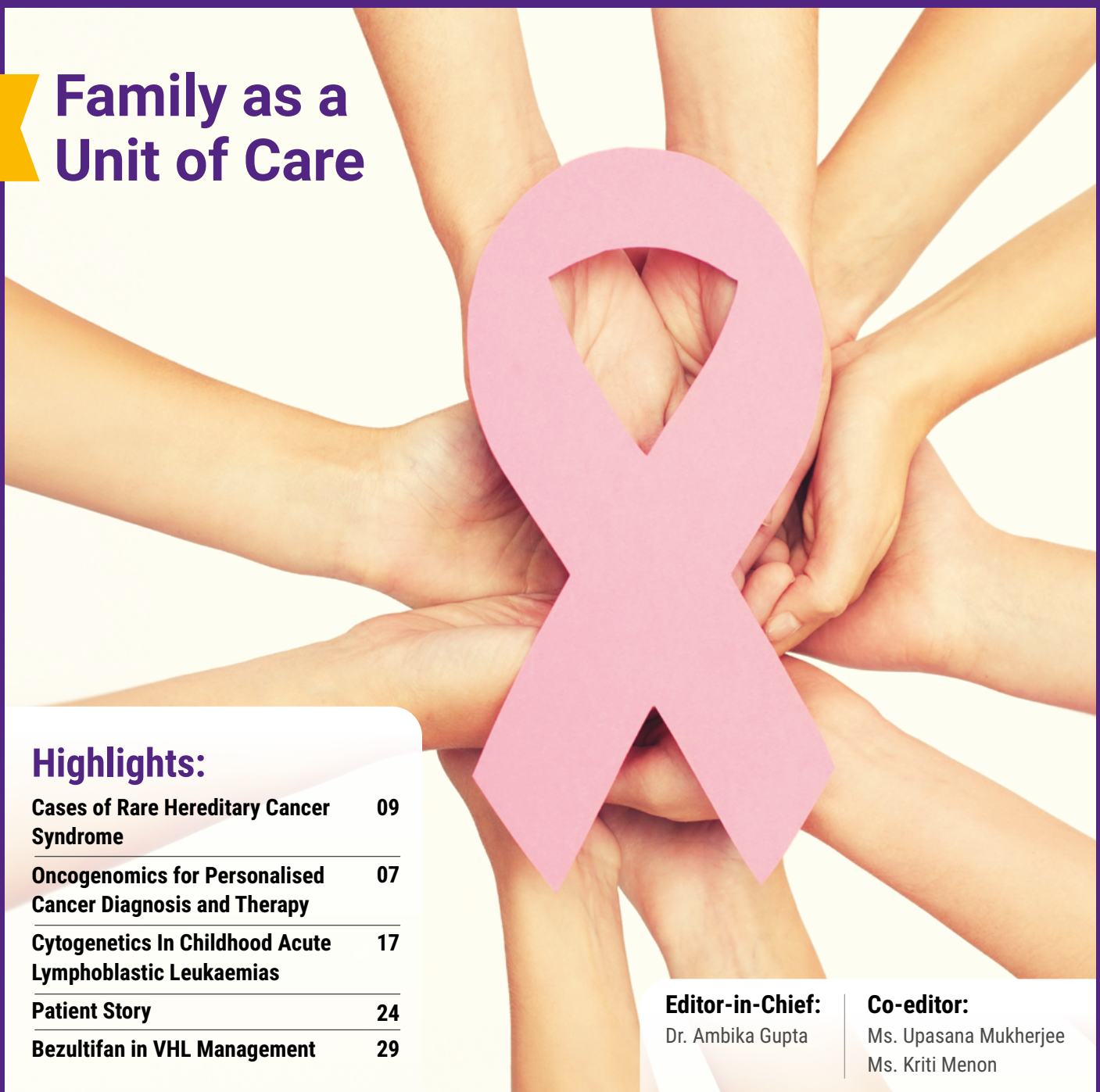
Weaving Precision Cancer Care with the Thread of Genetics

Family as a Unit of Care



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Issue 6; October–December 2024

Foreword

Dr. T Raja

Director of Medical Oncology
Apollo Cancer Centre, Chennai

Genomics has emerged as a revolutionary science, paving the way for precision medicine and personalised treatments for numerous diseases. Among its most significant achievements is its application in cancer care, where genomic information is harnessed to improve patient outcomes. The field of precision oncology has entered a transformative era, bolstered by advancements in diagnostic tools and increased accessibility to genomic technologies. This integration has redefined our understanding of cancer, offering new strategies for its prevention, diagnosis, treatment, and long-term management.

At its core, cancer is a genomic disease. The ability to sequence and analyse cancer genomes has unveiled the genetic and molecular mechanisms driving this complex illness. Through genomic profiling, researchers have identified a vast array of mutations, epigenetic modifications, and gene expression changes that contribute to cancer development and resistance to treatment. These discoveries have fuelled the rise of precision medicine, where therapies are customised to target the specific genetic characteristics of an individual's tumour, maximising effectiveness while minimising adverse effects.

Genomics in cancer care extends well beyond treatment. In the areas of early detection and prevention, genomic tools such as genetic testing and liquid biopsies are being utilised to identify individuals at high risk, enabling timely interventions. Additionally, population genomics is generating valuable insights into cancer risk across various demographics, helping to design equitable and effective screening programs.

The rapid expansion of research in this field is driving significant advancements in cancer genomics. From discovering new biomarkers to developing next-generation sequencing technologies and sophisticated computational methods for analysing large genomic datasets, the synergy between research and clinical practice is evident.

However, the rapid adoption of genomics in oncology also brings challenges and ethical dilemmas. Key concerns include data privacy, equitable access to genomic testing, and the fair distribution of genomic-based therapies. As we stand at the forefront of genomic medicine, the articles in this issue showcase the incredible progress being made in the field of genomics. They not only highlight current advancements but also point to the immense potential for future breakthroughs that could further revolutionise precision medicine.

Best wishes,
Dr. T Raja

From the Editor's Desk

Dr. Ambika Gupta

Editor, Consultant Medical Genetics
Apollo Hospitals Ahmedabad,
Apollo Health & Lifestyle Limited (AHLL)

The Vital Role of Oncogenetics in Modern Cancer Care

Dear Readers,

As cancer care evolves, oncogenomics—the study of cancer-related genes—has become essential in transforming diagnosis, prognosis, and treatment. This issue of the **Apollo Genomics Newsletter** highlights the crucial role medical geneticists play in advancing oncology, and why oncologists should collaborate with geneticists to improve patient outcomes.

Historically, cancer treatment followed a uniform approach, but we now understand that **no two tumours are genetically identical**. The identification of oncogenes, tumour suppressor genes, and mutations, such as BRCA1/BRCA2 in breast cancer or EGFR in lung cancer, has led to the rise of **precision oncology**. Genetic profiling provides invaluable insights into how cancers behave, which helps in diagnosing, predicting prognosis, and choosing tailored treatments.

Collaboration with medical geneticists ensures that oncologists can fully utilise these insights. Genetic tests can identify hereditary cancer syndromes, personalise treatments with **targeted therapies**, and predict responses to immunotherapies. Moreover, genomics can **minimise over-treatment** by distinguishing between aggressive and indolent cancers, sparing patients from unnecessary side effects. The expertise of medical geneticists can also help **identify patients for clinical trials** based on their genetic profiles.

Despite the progress in oncogenomics, integrating it into routine oncology practice remains a challenge—often due to limited interdisciplinary communication. **Interesting cases of familial cancer syndromes like breast and ovarian cancer, VHL, hepatocellular carcinoma, prostate cancer, and leukaemia**, depict how medical geneticists can bridge the gap between complex genomic data and practical clinical application. They can help oncologists stay updated with the latest advancements and provide guidance on appropriate genetic testing.

This special issue calls on oncologists and medical geneticists to work together, ensuring that the promise of precision medicine becomes a reality for every cancer patient. By fostering collaboration, we can make cancer care more personalised, effective, and hopeful.

Sincerely,
Dr. Ambika Gupta, Editor

Together, Let's Spread Awareness

Ms. Kriti Menon

Co-Editor, Genetic Counsellor
Indraprastha Apollo Hospitals

Dear Readers,

As we enter October, a month dedicated to breast cancer awareness—let's take a pause and remember the significant role genetics play in our overall health. This month not only highlights breast cancer awareness but also coincides with Hereditary Cancer Awareness Week. Breast cancer continues to be the most common cancer worldwide, with approximately 2.3 million new cases occurring annually. Additionally, breast cancer is one of the most common hereditary cancers. Gaps in healthcare systems, coupled with limited patient awareness and understanding, contribute to the low use of early detection services. This results in delayed diagnoses and poorer outcomes.

At the heart of our mission is a simple yet profound belief: **family is the cornerstone of care**. By equipping families with knowledge about hereditary cancer risks, we can spark meaningful conversations and **informed decisions** that enhance prevention and promote early detection. In this issue of the Apollo Genomics Newsletter, we're excited to share the **latest insights, inspiring patient stories, and interesting case reports**, while highlighting the critical importance of genetics in family health.

Warm regards,
Kriti Menon, Co-Editor

Genetic Counselling: A Crucial Resource

Ms. Upasana Mukherjee

Co-editor, Consultant Genetic Counsellor
Apollo Multispeciality Hospitals, Kolkata

Dear Readers,

October serves as a poignant reminder of the importance of spreading awareness surrounding hereditary cancers, particularly during Breast Cancer Awareness Month and Hereditary Cancer Awareness Week. Genetic counselling emerges as a vital service for individuals at risk, equipping them with essential information and support.

Hereditary cancers, particularly breast and ovarian cancers, account for about 5–10% of cases, with BRCA1 and BRCA2 mutations being the most common. Women with these mutations have a 55–75% risk of developing breast cancer by age 70, compared to approximately 12% in the general population. This stark contrast underscores the urgency of conducting genetic counselling for at-risk individuals.
Awareness campaigns aim to educate both patients and healthcare professionals about the importance of family history and genetic predisposition. Many individuals are unaware of their increased risk, as hereditary cancers can skip generations. Genetic counselling offers risk assessments and guidance on genetic testing, helping patients make informed decisions about their health.

We, genetic counsellors, provide crucial risk assessments, helping patients understand their family history and the implications of genetic testing. At Apollo, we offer guidance on surveillance options and preventive strategies, such as lifestyle modifications or prophylactic surgeries, which can significantly reduce cancer risk. As we acknowledge Breast Cancer Awareness Month and Hereditary Cancer Awareness Week, let us champion the importance of genetic counselling. By enhancing awareness and encouraging open discussions about genetic risks, we can empower individuals to take control of their health and well-being. Together, we can foster a more informed and proactive approach to hereditary cancer prevention and management.

Warm regards,
Upasana Mukherjee, Co-editor

Editorial Commentary

Prof. Dhavendra Kumar

Senior Consultant Advisor to
Apollo Genomics Institutes

The current newsletter of the Apollo Genomics Academy is exclusively about cancer genetics and genomics in clinical practice. The role of clinical geneticists and genetic counsellors has evolved rapidly — moving ahead dealing with challenges associated with disorders from the preconception stage to the late advanced age. Some of the systemic diseases are life-threatening and lead to sudden death, shortened life spans, or debilitated lives. Amongst these disorders, different types of familial cancers, appropriately described as 'family cancer syndromes', pose a huge challenge for early detection, precision molecular diagnosis, personalised targeted therapy, risk assessment and genetic counselling, and lifetime management (including clinical surveillance of healthy unaffected close family members). Medical oncologists and radiation oncologists are now increasingly using precise molecular information for selecting and instituting the best possible personalised cancer treatment. Novel modalities, such as immunotherapy, stem cell therapy, gene editing, and even gene therapy, are now available. The field of cancer pharmacogenetics and pharmacogenomics offers the opportunity to select cancer drugs based on a patient's genotype to achieve the highest possible efficacy and effectiveness.

This new issue, wholly conceptualised, designed, and written by the Apollo Genomics team, is commendable. Ours is a young team with only three years of existence. We have established ourselves as reputable specialised professionals who help patients, families, and our clinical or healthcare colleagues within the Apollo networks as well as outside. In this issue, the reader will find informative examples and discussions on individual genetic cancer, familial cancer (like Von Hippel Lindau Syndrome), cancer affecting closely related family members (like breast and ovarian cancer), molecular genetic cancer diagnosis, risk assessment and communication through the process of cancer genetic counselling. It also deals with the role of the cancer genetics team (clinical geneticist, genetic counsellor, genetic/genomic scientist) in the multidisciplinary tumour board-based personalised cancer management and in assisting the clinical oncology team (medical oncology, radiation oncology, cancer pharmacology, and others) for the best possible personalised cancer therapy and management. The field is rapidly evolving with new explorations of novel cancer drugs, immunotherapy, and harnessing the uncharted gains of artificial intelligence. The reader will find stimulating examples of selected cases, personal anecdotes, book reviews, and outcomes of specialist or targeted workshops and conferences.

It gives me immense satisfaction to present this issue on 'Oncogenomics' on behalf of the Apollo Genomics Academy.

—**Dhavendra Kumar**

Personal Perspectives

'Oncogenomics for personalised cancer diagnosis and therapy'

Professor Dhavendra Kumar, MD MMedSci FRCP FRCPE FRCPI FRCPCH FACMG DSc (Hon.)
William Harvey Research Institute, Faculty of Medicine and Dentistry, Queen Mary University of London, England, UK; Faculty of Medicine, Swansea University Medical School, Wales, UK; Senior Consultant Adviser, Apollo Genomics Institutes, Apollo Group of Hospitals, India.

Keywords

Oncogenes; tumour suppressor genes; cancer genetics; familial cancer; oncogenomics; cancer epigenetics (onco-epigenomics); personalised chemotherapy; cancer genome database.

The current concepts and approaches in oncogenomics have evolved from the basic understanding of cancer as a genetic disease at the cellular level, involving a multitude of single molecules and interacting molecular clusters.[1] Vogelstein's seminal 'two-hit' theory in oncogenesis was the landmark concept that is now applied in many other non-cancer conditions. While the cancer is essentially a genetic change, only a small proportion of cancer is heritable due to highly penetrant and deleterious germline mutations. The majority of genetic or genomic aberrations are somatic and confined to a single organ or tissue. In addition to specific genes and genomic loci, environmental and epigenetic factors play a key role in oncogenesis. Fundamentally, cancer development is either triggered by point mutations or pathogenic sequence variants in specific oncogenes. In contrast, loss of function in tumour suppressor genes is through either structural locus change (deletion, inversion, insertion, recombination, etc.) or loss of heterozygosity.[2]

Oncogenomics is now established in the practice of clinical oncology managing both solid and non-solid tumours. Next-generation genomic diagnosis (single gene, gene panel, whole exome sequencing, RNA sequencing, etc.) is now employed in precision diagnosis to facilitate personalised cancer therapy.[3] The liquid biopsy, a spin-off from non-invasive prenatal testing (NIPT), is by far the most powerful application that may allow early detection of peripheral circulating pathogenic nucleic acid sequence variants associated with extremely small cancerous lesions, such as the glioblastoma multiforme and other CNS tumours.[4]

Many leading clinical and advanced cancer centres have organised multi-specialist tumour boards for interpreting and making joint decisions on precision diagnosis and therapeutic considerations.[5] Perhaps, the major impact is in relation to Mendelian familial cancer where, apart from the precision diagnosis, the 'at-risk' close family members are offered cancer surveillance and options for minimising the impact of cancer development and progression. It is now common knowledge that long-term surveillance and prevention of cancer is best achieved through precision and predictive confirmation of the potential cancer-associated sequence variants or deleterious mutation. Examples include BRCA and other related breast or ovarian genes, mismatch repair genes associated with colorectal cancer (Lynch Syndrome), and many other genes for rare cancer family syndromes (von Hippel-Lindau Disease, Type 2 Neurofibromatosis, Tuberous Sclerosis Complex, etc.) There are now clearly validated and evidence-based protocols for long-term surveillance, medical prophylaxis (tamoxifen and aromatase inhibitors for breast cancer), and the option for risk-reducing surgery (mastectomy, oophorectomy, colectomy, thyroidectomy, etc.). Personalised cancer therapy is by far the major development from systematic and applied oncogenomics research.[6] Current research efforts are targeted at searching all genomic processes and pathways that could reveal actionable treatment indicators utilising multi-drug chemotherapeutic modalities. Unfortunately, as a sequel to various chemotherapies, patients develop resistance to chemotherapy drugs and therapies. Additionally, other cancer theories and therapies continue to be proposed.[7] Major cancer research projects are predominantly focused on the following issues:

i. What are the agents (e.g. viruses) and genetic changes (e.g. mutations) that cause or facilitate oncogenesis?
ii. What is the precise molecular nature of the genetic damage in cancer development?
iii. What are the consequences of those genetic changes on the biology of the cell that lead to further progression of the cancer?

There are several novel cancer therapy models under development, either directly or indirectly

related to oncogenomic research.[8] The major recent developments in cancer treatment include immunotherapy (innate and systemic), PD-1 inhibitors (for example Pembrolizumab in mismatch repair genes associated cancer), Chimeric antigen receptor T-cells (T-cells related cancers), DNA Origami/Trojan (for example, daunorubicin in acute myeloid leukaemia), anti-inflammatory agents (for example, interleukin IL-1ß in chronic inflammation leading to cancer), and physical approaches like electrochemotherapy and nano-chemotherapy. Details on this research are beyond the scope of this brief commentary. An interested reader or researcher may browse through listed references or literature for further information.

In summary, oncogenomics or cancer genomics is the basis for precision, personalised and preventive clinical oncology. It involves scanning the genome of an individual patient for actionable genomic indicators. This information is used for precision cancer diagnosis and for designing personalised cancer treatment. [9] In addition to specific genes or clusters of genes in a molecular pathway, recent progress has made it possible to employ the copy number variants to enable clinical decisions in managing cancer. Other measures include using multi-OMIC information derived from transcriptomics, including reverse transcriptome, and proteomics [10]. Future successes would largely depend on intellectual and technical resources including artificial intelligence (AI)[11]. Meanwhile, the clinical cancer genetic professionals (clinical oncologists, clinical geneticists, genome scientists, cancer pharmacologists, cancer radiologists, cancer nurses, and cancer genetic counsellors) will need to continue working together and develop more effective and efficient evidence-based protocols and pathways for precision cancer management and prevention. [12, 13] The era of multi-OMICS would be a major milestone for oncogenomics research and applications [14]

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Case 1

Mitochondrial DNA Depletion Syndrome and Hepatocellular Carcinoma—A Rare Adult Phenotype

Dr. Snehal Mallakmir[1], Dr. Aabha Nagral[2], Ms. Shilpa Kamble[1]

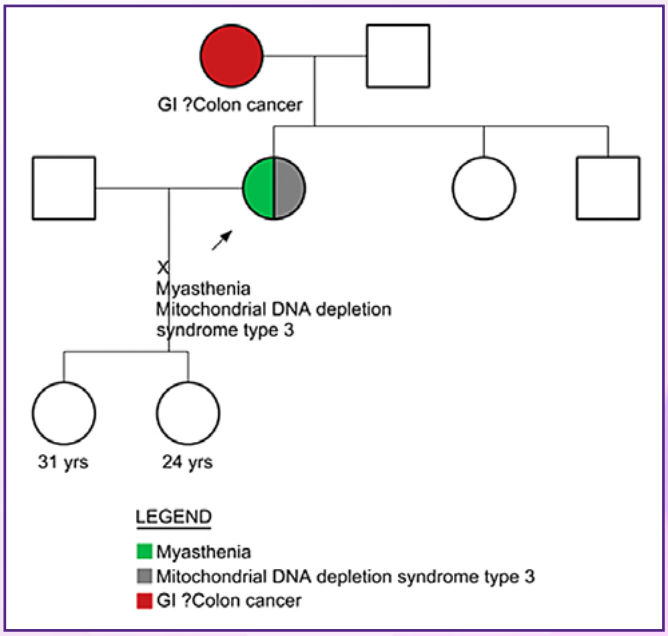
Apollo Genomics Institutes, Navi Mumbai[1]
Dept. of Gastroenterology and Hepatology, Jaslok Hospital and Research Centre, Mumbai[2]

INTRODUCTION

Mitochondrial DNA Depletion Syndrome (MDS) is a group of genetically and clinically heterogeneous disorders with autosomal recessive inheritance affecting various tissues[1]. MDS-3, caused by biallelic pathogenic variants in the **DGUOK**, is characterised by the onset of **progressive liver disease and neurologic abnormalities** in infancy. Few cases of **hepatocellular carcinoma (HCC)** have been reported in the **paediatric age group** and were treated with **liver transplants**. Our report is on an adult female with MDS and HCC and discusses clinical decision-making issues as well as genetic counselling.

Case report

A 55-year-old female, with a history of accidental detection of **abnormal liver enzymes** during the workup of her **neuromuscular complaints**, was presented. She had a long history of muscular weakness, in the form of difficulty in climbing, noted at around 30 years of age. Weakness was slowly progressive followed by mild ptosis and ophthalmoplegia. In early adulthood, she had a history of jaundice which was of unusually long duration but had complete recovery and no confirmed diagnosis. Her mother died of suspected colon cancer. With signs like **horizontal supranuclear gaze palsy, hypothyroidism, proximal muscle weakness in upper and lower limbs and ptosis**, the index case was worked up (investigation results shown in **Table 1**).



For raised liver enzymes, USG and MRI abdomen were done, which showed **liver parenchymal disease**, but she did not have symptoms of liver disease or positive examination findings at the time of presentation. Aetiology workup for cirrhosis, including viral, autoimmune and Wilson's Disease, was negative. **Exome sequencing showed compound heterozygous, likely pathogenic variations, in the DGUOK gene (c.598_610del & c.736C>G). A liver biopsy confirmed HCC**. Liver transplantation was planned with her elder daughter being the donor. The elder daughter was asymptomatic and showed mildly raised liver enzymes and a fatty liver. After nutritional management and weight loss, liver enzymes returned to normal. She was negative for the genetic variants found in the index case. The successful liver transplant was done in the patient and a regular follow-up was advised to monitor the neuromuscular symptoms.

DISCUSSION

MDS can have different phenotypes like myopathic, encephalomyopathic, hepatocerebral, or neurogastrointestinal. Hepatocerebral type is caused by biallelic mutations in **DGUOK, MPV17, POLG, or C10orf genes**, and presents in early childhood with liver dysfunction and neurological involvement [1]. **DGUOK gene mutations may have phenotypes like MDS Type 3 (OMIM #251880), non-cirrhotic portal hypertension-1(OMIM# 617068) or progressive external ophthalmoplegia with MDS 4 (OMIM# 617070)**.

Our patient had proximal muscle weakness along with ophthalmoplegia. She had unexplained liver disease in early adulthood with complete recovery, which has not been reported. HCC has been reported in early childhood [2], but adult cases have not been reported with this phenotype. Other aetiologies of HCC in adulthood were excluded in this patient but the exact genotype-phenotype correlation remains incomplete as there was a history of gastrointestinal cancer in immediate family members. There is a need for correlation with liver biopsy, muscle biopsy, and mitochondrial studies with enzyme assay as well as electron microscopic examination. The initial workup of the donor daughter showing fatty liver and abnormal enzymes led to anxiety and queries from the family about genetic inheritance and the risk of recurrence in the daughter. Sanger sequencing did not show a variant in her, as was observed in the mother's DGUOK gene. Nutritional management led to weight reduction and return of the liver to normal status.

More reports of adult-onset MDS Type 3 and HCC are needed for further correlation and may explain variable phenotypes. Genetic counselling involves dealing with issues like risk to family members, impact on prognosis, and therapeutic options, especially liver transplant and its impact on the prognosis of neuromuscular symptoms.

Investigations	Normal range
Liver enzymes GGT – 240.9 u/l SGOT – 72.3 u/l SGPT – 36.8 u/l	 <38 <31 <34
USG abdomen – chronic parenchymal disease	
CT liver – parenchymal disease	
MRI – liver cirrhosis most likely hepatocellular carcinoma	
AFP 4565 ng/ml	 <7
Neostigmine test Negative	
Acetylcholine receptor autoantibody 0.34 nmol/l	 <0.45
CPK total 1239 u/l	 39–238

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Case 2

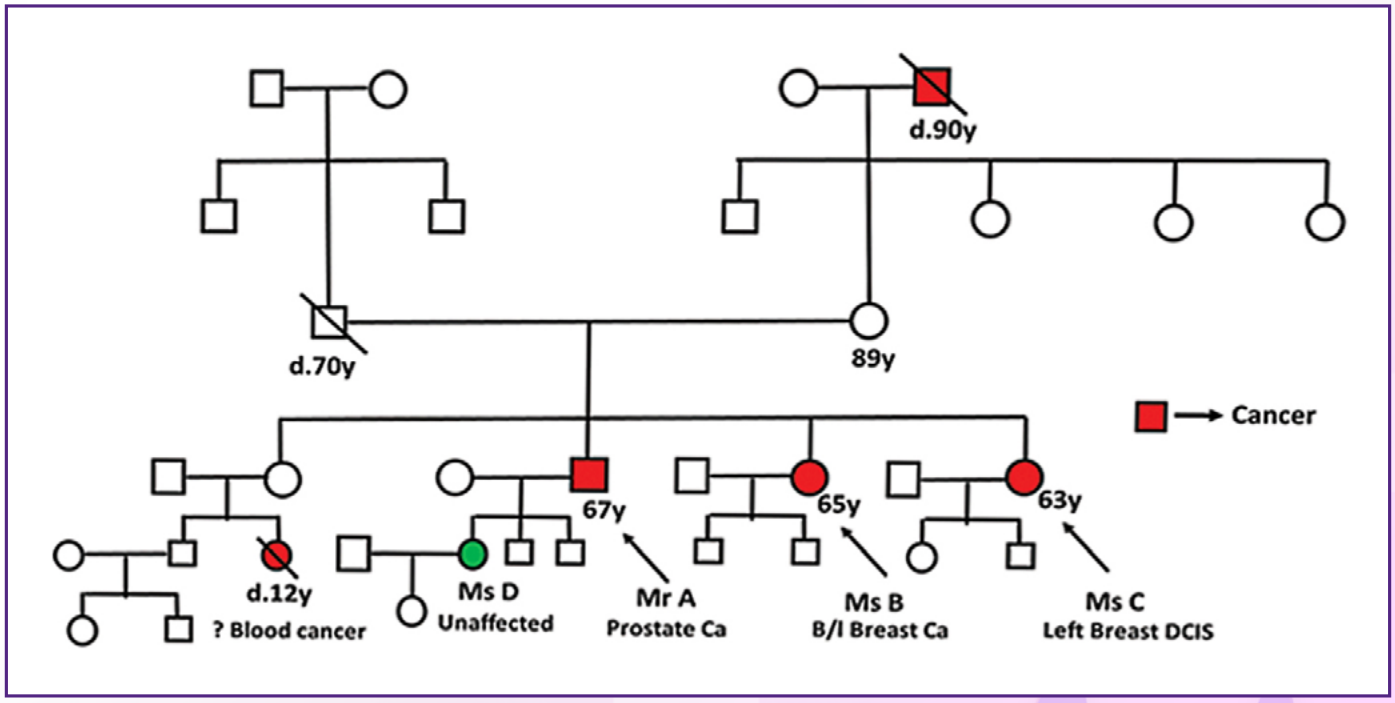
The Whole is Greater than the Sum of its Parts! — A Familial Cancer Odyssey

Dr. Surya Balakrishnan

Apollo Hospitals, Jubilee Hills, Hyderabad

How it began

A 67-year-old well-educated man (Mr A) was referred to the Genetic clinic given a family history of cancers. He was incidentally discovered to have an elevated prostate-specific antigen (12.99ng/mL) during a routine medical check-up in 2019. A string of tests followed, which suggested the possibility of prostate cancer. Three core biopsies on the right side showed a Gleason score of 4+4, suggesting stage T2a. The patient underwent Robotic-assisted radical prostatectomy with extraperitoneal lymph node dissection in March 2020. Histopathology confirmed adenocarcinoma prostate, perineural invasion was absent and lymph node histology was normal.



Unravelling the family history...

Mr A has an unaffected elder sister, however, her daughter expired at the age of 12 years due to a haematological malignancy, details of which are not available. Mr A has two younger sisters, aged 65 years (Ms B) and 63 years (Ms C), both of whom developed breast cancer and were being treated by different oncologists. The patient himself has a daughter and two sons; all were normal.

Patient perspective

The patient also had another interesting revelation. He was concerned if the cancers in himself and the two sisters were the result of **radiation exposure during childhood**. On asking further, he stated that his father was a technician radiographer and his x-ray room shared a common wall with that of the house they had lived in. Although the long-term effects of radiation are known, it is unlikely that a 5-year radiation exposure during childhood would show no interim effects and then manifest more than five decades later in all who were exposed, that too at the same time. Since we couldn't risk missing a genetic defect in this family, we emphasised the need for testing. We checked if any genetic testing had been done previously on other affected members, and the patient said that he would enquire about it.

The results

After appropriate pre-test counselling, a next-generation sequencing-based hereditary cancer panel was ordered. It was negative and we conveyed the news to the patient. This time around, Mr A was able to bring reports of his sisters and daughter, all ordered by their respective clinicians.

Ms B had a lump in both breasts, which was confirmed to be mucinous carcinoma grade 4. On immunohistochemistry, ER/PR was positive and Her2 was negative bilaterally. Exome sequencing suggested the possibility of a **BRCA2 deletion**. [13:g (?_32893195)_(32899335_?) pathogenic del in BRCA2] .

Ms C was diagnosed with an invasive ductal Ca in her left breast, which was grade 2. ER/PR was positive, Her2 was negative and Ki 67 was 30%. Exome sequencing revealed a heterozygous **c.424 G>A variant of uncertain significance in the MLH3 gene**, associated with 'susceptibility to cancer.'

The patient's **daughter** (Ms D), who was a resident of the US, was unaffected but was advised testing because of her strong family history. It showed a heterozygous, pathogenic exon 46 **deletion in the ATM gene**.

So now, in the very same family, we had 4 different genetic results (Negative in Mr A, BRCA2 variant in Ms B, MLH3 variant in Ms C & ATM deletion in Ms D). It was now the onus of the geneticist to put things in perspective!

What we did

We suggested that the exome data be l reanalysed to find a common variant shared by the three affected individuals in this family. ATM gene coverage was specifically asked for, to identify any missed deletions.

On enquiring the lab, **Ms B's BRCA2 variant was found to be false positive, since a reflex MLPA had failed to show this variant. The coverage for exon 46 in the ATM gene was reduced by 50%, confirming the presence of a heterozygous deletion.**

Ms C's exome data did not show the ATM deletion and it was probably **due to the type of capture kit used**. MLPA was advised to definitively confirm this.

The fog lifts

Now, since we had two individuals with heterozygous ATM deletion—the patient's sister and daughter—it was likely that he was also an obligate carrier for the same. We ordered the MLPA on him and voila, the ATM deletion was indeed present. We are yet to confirm this variant in Ms C, who had an MLH3 variant on the initial test.

Although reports from the 90s have debunked the oncogenic potential of **heterozygous ATM variants**, recently published literature has confirmed their association with the **increasing incidence of breast, gastric, and prostate cancers**.

Lessons from the case

- Pathogenic copy number changes involving cancer genes may be missed and must be actively looked for, especially in families with a strong cancer history and a negative sequencing result.
- It's important to include a geneticist early in the patient's genetic evaluation, so that a family can be tested as a unit and important details are not missed.
- An integrated approach will significantly reduce redundant tests, which result in misinterpretations. It will also promote better reporting and aid in appropriate counselling of families.
- Pathogenic heterozygous ATM variants are likely to increase the risk for several cancers and the family must be counselled on appropriate testing, cascade screening of 'at risk' relatives, and institution of surveillance measures.

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Case 3

A Classical Case of Von Hippel-Lindau Syndrome

Ms. Shreya Satheesh, Dr. Alec Correa

Medical Genetics Apollo Proton Cancer Centre, Kolkata

INTRODUCTION

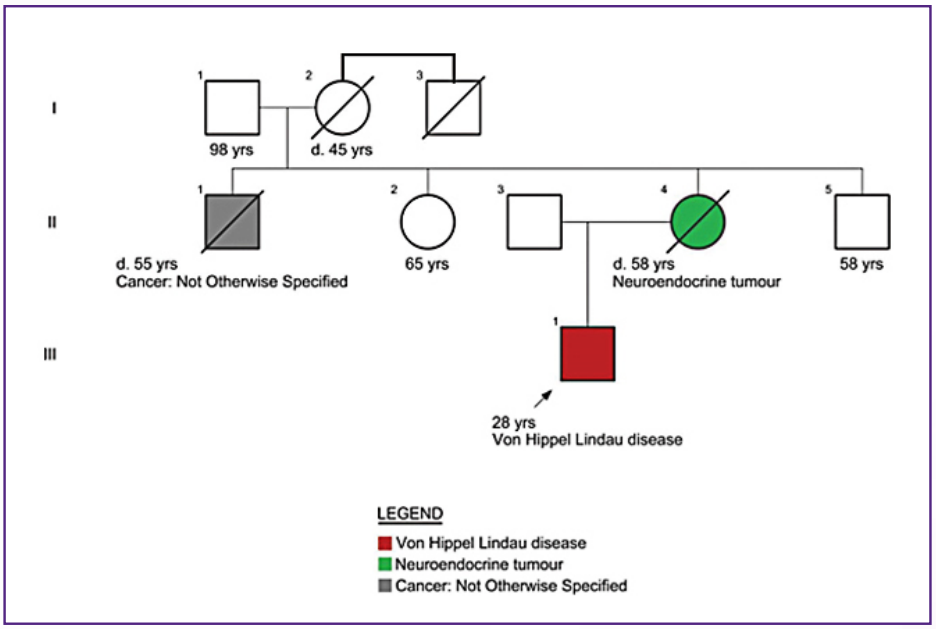
Von Hippel-Lindau (VHL) syndrome is a cancer-predisposing syndrome, marked by the presence of **hemangioblastomas in the brain, spinal cord, and retina, as well as renal cysts and clear cell renal cell carcinoma**. It also includes **pheochromocytomas, paragangliomas, pancreatic cysts**, neuroendocrine tumours, endolymphatic sac tumours, and cystadenomas of the epididymis and broad ligament. It is caused due to heterozygous pathogenic variants in the VHL gene on Chromosome 3.

CASE HISTORY

Mr Y is a 28-year-old man who came to the Genetic Clinic with complaints of numbness and paraesthesia in the upper limbs, mainly over the left shoulder area, for the last three weeks. Lower limbs were unaffected. He had complaints of back and neck pain on and off for the last one year. He has a significant family history—of his mother succumbing to a neuroendocrine tumour at 58 years of age and his maternal uncle succumbing to cancer at age 55. However, the primary site is not known.

The MRI suggested multiple spinal hemangioblastomas. PET CT detected multiple spinal hemangioblastomas, renal tumours, and pancreatic cysts. He underwent C3–C6 laminotomy and D6 and D7 laminectomy—excision of the hemangioblastoma on 23 July 2024.

His genetic test revealed a pathogenic missense variant (c.481C>T) in the VHL gene, confirming the diagnosis of Von Hippel-Lindau Syndrome. He was counselled about the disease and its management and was put on a surveillance protocol.



DISCUSSION

Von Hippel-Lindau Syndrome (VHL) is seen in approximately **1 in 36,000** live births. The majority of the affected individuals have a **positive family history**, however, up to 20% of cases arise from de novo mutations. The pathogenic variants in the VHL gene are **highly penetrant**, meaning that nearly **everyone with such a variant will show symptoms by the age of 65**.

The Cancer Risk for Each Tumour and its Average Age of Onset [1]

Sl. No.	Clinical Feature	Average (range) of presentation (years)	Frequency (%)
1.	CNS hemangioblastoma	30 (9–78)	60–80%
2.	Retinal hemangioblastoma	25 (1–67)	49–62%
3.	Endolymphatic sac tumours	31 (12–50)	6–15%
4.	Renal cell carcinoma or cysts	39 (16–67)	30–70%
5.	Pheochromocytoma	30 (5–58)	10–20%
6.	Pancreatic neuroendocrine tumours or cysts	36 (1–70)	35–70%
7.	Epididymal cystadenomas	Unknown (16–40)	25–60%
8.	Broad ligament cystadenomas	Unknown (16–46)	Unknown

VHLA Suggested Active Surveillance Guidelines [2]

Surveillance Modality (Tumours being screened)	< 5 years	Beginning at age 5y	Beginning at age 11y	Beginning at age 15y	Beginning at age 30y	Beginning at age 65y	Pregnancy
History and Physical Examination	Yearly from age 1 year	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception
Blood Pressure and Pulse (Pheochromocytomas/p paragangliomas)	Yearly from age 2 years	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception
Dilated Eye Examination (Retinal Hemangioblastomas)	Every 6–12 months, beginning before age 1 year	Every 6–12 months	Every 6–12 months	Every 6–12 months	Yearly	Yearly	Prior to conception, then every 6–12 months
Metanephrines (Pheochromocytomas/ paragangliomas)	–	Yearly	Yearly	Yearly	Yearly	Stop routine	Prior to conception
MRI Brain and Spine w/wo Contrast (CNS Hemangioblastomas)	–	–	Every 2 years	Every 2 years	Every 2 years	Stop routine	Prior to conception
Audiogram (Endolymphatic sac tumours)	–	–	Every 2 years	Every 2 years	Every 2 years	Stop routine	–
MRI Abdomen w/ wo Contrast (Renal cell carcinomas, Pheochromocytomas/ paragangliomas, Pancreatic neuroendocrine tumours/ cysts)	–	–	–	Every 2 years	Every 2 years	Stop routine	Prior to conception
MRI Internal Auditory Canal (Endolymphatic sac tumours)	–	–	–	Once	–		

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Case 4

Original Article

The "Good" Future is a Mirage! — Survival in Good Risk Cytogenetics in Childhood Acute Lymphoblastic Leukaemias

Vijayshree Muthukumar[1], Indhumathi Nagarathinam[2], Anupama Nair[1], Anuraag Nalla Reddy[1], Nithya Sheshadri[1], Minakshi[1], Suresh R D[1], Venkateswaran V S[1], Ramya Uppuluri[1], Revathi Raj[1]

[1]Department of Paediatric Haematology, Oncology, Blood and Marrow Transplantation, Apollo Cancer Centre, Teynampet, Chennai, India.

[2]Department of Medical Genetics, Apollo Main Hospital, Chennai, India.

INTRODUCTION

Cytogenetics in Acute Lymphoblastic Leukaemia (ALL) provides a better understanding of the pathways driving the disease. It is the key to disease sub-classification, risk assessment, and optimising management including targeted therapies. Hyperdiploidy and TEL-AML are the most common genetic subtypes in children with Acute Lymphoblastic Leukaemia with a prevalence of around 35%. In multiple studies over several decades, Hyperdiploidy has been associated with a favourable outcome (survival > 90%). Despite this association with good outcomes, the high hyperdiploid ALL subgroup accounts for up to 25% of all relapses.[1] Hence identification of risk factors within this group is clinically relevant. Recent data has shed light on **classical and non-classical hyperdiploidy** and their **impact on relapse**.

Hyperdiploidy (HD) refers to the presence of 52 to 67 chromosomes. Chromosome 21 serves as a marker for the 7 distinct chromosome changes i.e., X, 4, 6, 10, 14, 17 and 18.[2]

The **classical HD** form consists of heterozygous di-, tri-, and tetrasomy. Classical HD has an overall survival (OS) of 95%. This includes trisomies and tetrasomies. **Trisomies** always result from the duplication of either one of the parental chromosomes ("2+1" pattern) and most commonly affect chromosomes X, 4, 6, 10, 14, 17, and 18. **Tetrasomies** always result from the duplication of both parental homologs ("2+2" pattern). The most common, in addition to the obligatory tetrasomy 21, are those of chromosomes X, 14, and 18.[2]

The **non-classical HD** (usually viewed as "duplicated hyperhaploid") contains **only disomies and tetrasomies** and has an OS of 73%. **The disomic chromosomes are always homozygous ("2+0" pattern)**, whereas the tetrasomic ones remain heterozygous ("2+2 pattern"). **Uniparental disomy** is the main feature in non-classical HD karyotypes. They are exact duplicates of the hyperhaploid ones. **Secondary changes in non-classical HD** include Chromosome 1q duplications (10–15%), 6q deletions (5%), Isochromosomes 17q (2–5%) and 7q (1–2%). These 4 changes occur as non-random secondary events in the form of structural abnormalities in a mutually exclusive manner in monoclonal nonclassical HD cases. [2,3]

In our study, we analysed the outcome in children with good risk cytogenetics to help predict outcomes and prevent relapses by optimal risk stratification.

PATIENTS AND METHODS

We performed a retrospective study in children diagnosed with B acute lymphoblastic leukaemia from January 2012 to December 2021 to enable a minimum 18-month follow-up. All children were risk-stratified and treated as per the UKALL Protocol 2011 . We performed karyotyping and cytogenetic analysis by FISH at diagnosis and termed hyperdiploid and TEL-AML as good risk cytogenetics. Children with duplicated hypohaploids with the following five structural changes namely: chromosome1q duplication, chromosome 6q deletion, isochromosome 17q, isochromosome 7q, and tp53 mutation were classified as **non-classical hyperdiploidy**.[2,3] We collected data from **retrospective chart reviews on day 28 of bone marrow and MRD, relapse, HSCT, and mortality on day 28** to analyse the **difference in outcomes between the classical and the non-classical hyperdiplody, and the TEL-AML groups**.

RESULTS

A total of 396 children were treated for Acute Lymphoblastic Leukaemia from 2012 to 2021. Of these, 139 Children (35.1 %) had good risk cytogenetics and were included in the study. Of the 139 children with good risk cytogenetics, 30 (21.6%) relapsed, 14 (10%) haematopoietic stem cell transplant, 18 (12.9%) succumbed and 13 (9.3%) were MRD positive at the end of induction and had a regimen escalation. Despite the regimen escalation at the end of induction, 11 of the 13 MRD-positive children (84.6%) relapsed.

Of the 139 children with good risk cytogenetics, 80 (57.5%) had classical hyperdiploidy, 39 (28%) had non-classical hyperdiploidy, and 20 (14.3%) were TEL-AML. Representative classic and non-classic hyperdiploidy images are given in Fig. 1A, 1B, and 1C, respectively.

— Among the 80 children with classical hyperdiploidy, 8/10 80 (10%) had regimen change after induction due to MRD positivity, 17/80 (21.3%) had relapsed, 8/80 (10%) had underwent HST, and 12/80 (15%) succumbed.

— Among the 39 children with non-classical hyperdiploidy, 5/39 (12.8 %) had regimen change after induction due to MRD positivity, 10/39 (25.6%) relapsed, 5/39 (12.8%) underwent HST, and 6/39 (15.4%) succumbed.

— Among the 20 children with TEL-AML, none needed a regimen change after induction due to MRD positivity, 3/20 (15%) relapsed, 2/20 (10%) underwent HSCT, and 1/20 (5%) succumbed.

DISCUSSION

The original definition of high hyperdiploidy was based on the number of chromosomes, using 51 as the threshold. However, using DNA index or cytogenetic combinations gives an understanding of masked hypoploidy and classical hyperdiploidy. HD stratification is achieved by determining the DNA content, the overall chromosome number, and/or the copy numbers of selected chromosomes with FISH. [3] These laboratory tests are available in most centres across India.

Because of the dissimilar clinical impact of classical HD and near-triploid cases, the proper assignment of such ambiguous cases is important for appropriate treatment stratification. If high hyperdiploidy is to be utilised as a criterion to identify patients eligible for treatment de-intensification, it is crucial to remove high hyperdiploid poor- risk patients from this group, as they have an intermediate prognosis and should be considered for treatment intensification. [4]

Many clinical trials now use high hyperdiploidy in combination with MRD to assign patients to risk groups. [3] Several studies are exploring the application of specific chromosome numbers that are duplicated and co-relating the clinical outcomes.[5] As attempts are being made to understand why hyperdiploid cytogenetic children relapse, this study shows the need to classify children as true hyperdiploids and those masquerading as hyperdiploidy and leading to inferior outcomes.[3]

Even if these tests are made available, adapting them in the risk stratification upfront in practice has the following practical issues:

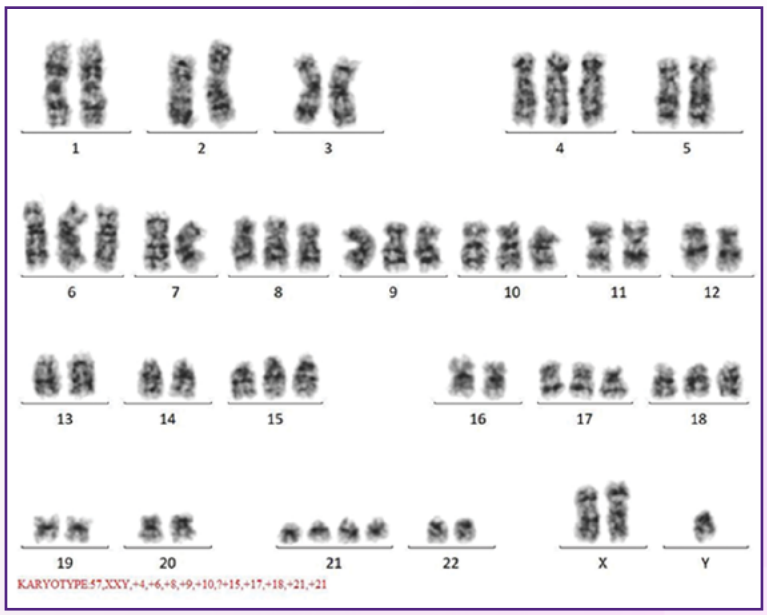
- Applicability: Whether such a detailed threshold definition is technically feasible routinely, and worthwhile to implement routinely, remains to be seen.
- Availability: The need for specialised molecular laboratories makes access a challenge.
- Affordability: The cost of these tests for risk stratification adds to the economic burden in resource-limited settings.
- There is a need for more prospective data on whether upgrading treatment regimens for children with non-classical hyperdiploidy upfront results in better outcomes.

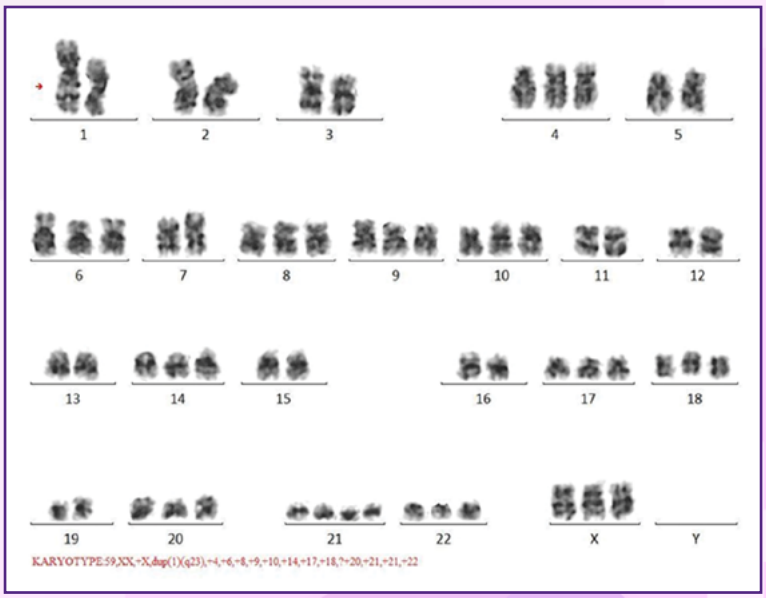
CONCLUSION

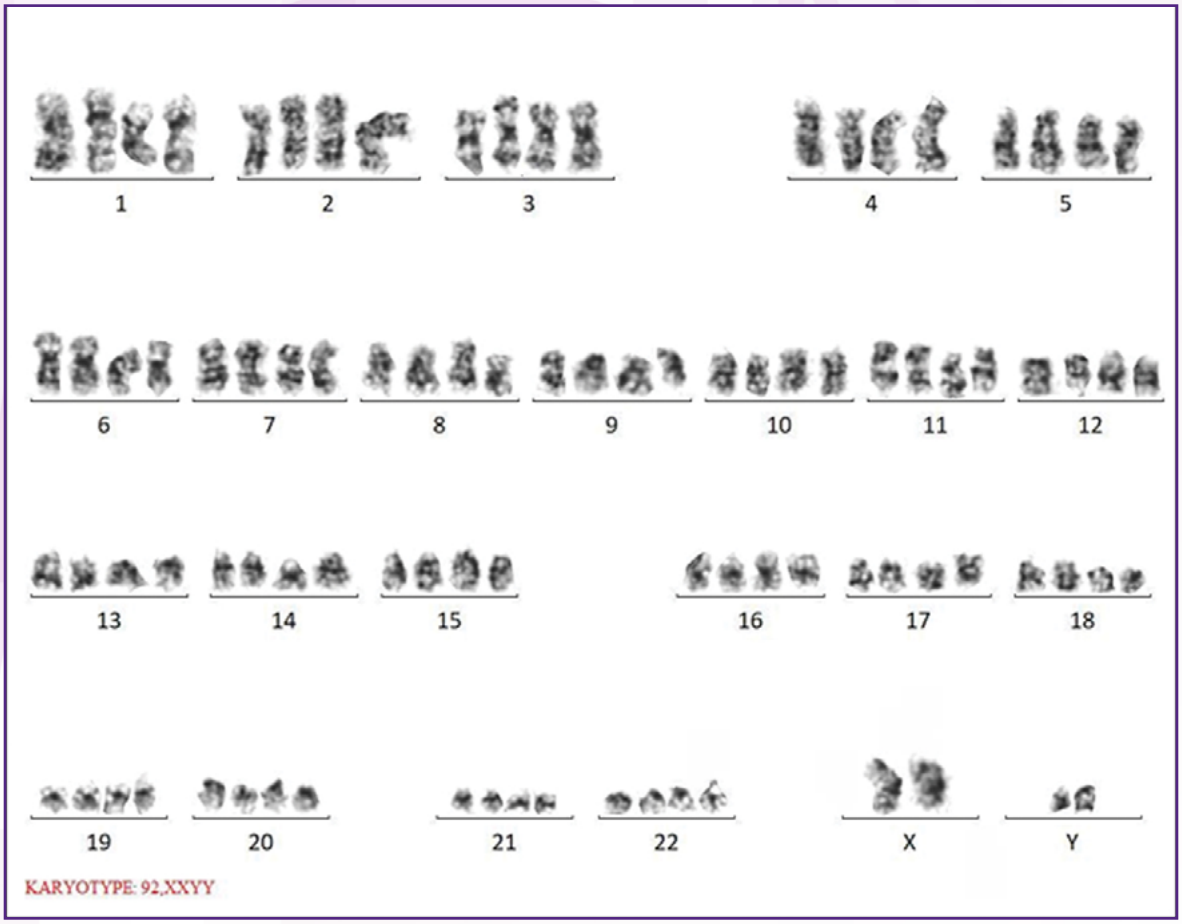
Our study has helped a deeper understanding of basic data from cytogenetics and FISH in children with ALL. Aggressive therapy upfront with optimal risk stratification could have prevented relapses in good-risk children. All good- risk cytogenetics children need a second look during the decision-making on Day 28. It is important to identify all patients with hypodiploidy at the time of diagnosis for timely administration of intense consolidation and continuation therapy.

A wealth of knowledge from simple cytogenetics remains underutilised in LMICs. MDT discussion of every single child on Day 28 in LMICs will help individualise therapy with FISH/cytogenetics / MRD as the backbone and prevent relapses. NGS-based assessment and additional targeted therapy may be beneficial in MRD-positive hyperdiploid children as the relapse risk is exceedingly high in this category.

We recommend including duplicated hyperhaploids chromosome 1q duplication, chromosome 6q deletion, isochromosome 17q, isochromosome 7q and TP53 mutation within those with hyperdiploidy for augmented therapy upfront as they are associated with a higher chance of inferior outcomes when compared to the classical hyperdiploid children.







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Case 5

Genetics in Cancer—A Clinical Perspective

Targeted Mutation Therapy in Cancer: Precision Hits for Personalised Treatment

Dr. Priya Ranganath

Medical Geneticist, Apollo Hospitals Bannerghatta Road, Bengaluru.

INTRODUCTION

Over the past two decades, targeted therapies have revolutionised cancer treatment. Advances in sequencing technology have revealed the mutational landscape of human cancers, leading to the identification of targetable mutations. Unlike conventional chemotherapy, **targeted therapies specifically act on abnormal proteins produced by mutated genes, sparing healthy cells and minimising side effects**. These therapies offer rapid tumour regression with fewer toxicities.

CASE STUDY

Mrs X, a breast cancer patient initially resistant to chemotherapy, experienced a remarkable turnaround after undergoing targeted therapy. Molecular profiling revealed HER2neu amplification (30% MAF) and a BRCA1 mutation (15% MAF). Based on these findings, she was treated with a combination of trastuzumab and pertuzumab (HER2-targeted agents), along with olaparib (a PARP inhibitor). Within months, her tumour size decreased significantly, and her overall health improved. She remains in a stable condition with non-remittent disease. Cases like Mrs X's highlight the transformative impact of personalised treatments in cancer care, offering hope to many patients.

DISCUSSION

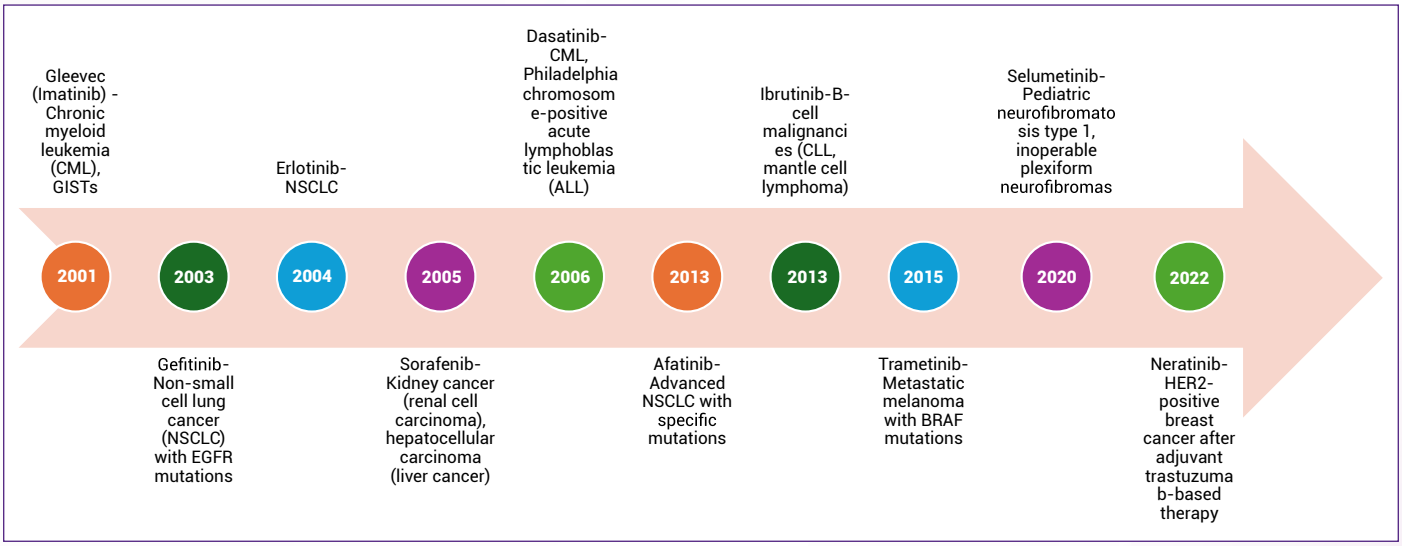
The discovery of the BCR-ABL fusion gene, which characterises chronic myelogenous leukaemia (CML), and the subsequent development of the BCR-ABL inhibitor imatinib marked a watershed moment in targeted drug therapy. Since then, numerous targeted therapies have been approved by the U.S. FDA, and many more are in development [FIGURE 1].

Current targeted therapies include monoclonal antibodies and small-molecule inhibitors, which act on specific proteins within cancer cells. Monoclonal antibodies are lab-engineered versions of antibodies that recognise proteins in cancer cells. They can block growth signals (e.g., angiogenesis inhibitors), enhance immune responses (e.g., in immunotherapy for brain cancers), or deliver toxic payloads directly to cancer cells. Small-molecule drugs bind to specific targets within cancer cells. Examples include proteasome inhibitors and signal transduction inhibitors, which interfere with cancer cell growth, division, and survival.

Examples of Targeted Therapies [TABLE 1]

- **Angiogenesis Inhibitors:** These block signals that promote the growth of blood vessels in tumours and are used in cancers such as colorectal, kidney, and lung cancers.
- **Proteasome Inhibitors:** These drugs target proteasomes, the enzymes that degrade proteins in cancer cells, and are effective in multiple myeloma and certain lymphomas.
- **Signal Transduction Inhibitors:** These disrupt the pathways that cancer cells rely on for survival. Tyrosine kinase inhibitors, such as imatinib, are a prime example and are used in the treatment of chronic myeloid leukaemia.

Target	Examples of Targeted Drugs	Cancer Types	Type of Genetic Alteration
ALK	Crizotinib , Alectinib	Non-small cell lung cancer	Fusion
ATM	Olaparib	Various cancers (PARP inhibitor)	Mutation
BCR-ABL	Imatinib	Chronic myeloid leukemia (CML)	Fusion
BRAF	Vemurafenib, Dabrafenib	Melanoma, thyroid cancer	Mutation
BTK	Ibrutinib, Acalabrutinib	B-cell malignancies (e.g., CLL, lymphoma)	Mutation
CDK4/6	Palbociclib, Ribociclib	Breast cancer, liposarcoma	Amplification
CHEK2	Not applicable	Various cancers	Mutation
CSF1R	Pexidartinib	Tenosynovial giant cell tumor (TGCT)	Mutation
EGFR	Erlotinib , Gefitinib	Lung cancer, colorectal cancer	Mutation
ERBB2 (HER2)	Trastuzumab , Pertuzumab	Breast cancer, gastric cancer	Amplification
EZH2	Tazemetostat	Follicular lymphoma, diffuse large B-cell lymphoma	Mutation
FLT3	Midostaurin	Acute myeloid leukemia (AML)	Mutation
KIT	Imatinib, Sunitinib	Gastrointestinal stromal tumor (GIST)	Mutation
KRAS	Sotorasib	Non-small cell lung cancer (NSCLC)	Mutation
MET	Capmatinib	Non-small cell lung cancer, other solid tumors	Amplification
NTRK	Larotrectinib , Entrectinib	Various cancers with NTRK fusions	Fusion
PDGFRA/B	Imatinib	Gastrointestinal stromal tumor (GIST)	Mutation
PIK3CA	Alpelisib	Breast cancer	Mutation
PML-RARA	All-trans retinoic acid	Acute promyelocytic leukemia (APL)	Fusion
RET	Selpercatinib	Thyroid cancer, lung cancer	Fusion
ROS1	Entrectinib	Non-small cell lung cancer, solid tumors	Fusion
TRK	Larotrectinib , Entrectinib	Various cancers with NTRK fusions	Fusion
VEGF	Bevacizumab, Ramucirumab	Various solid tumors (e.g., colorectal, renal)	Expression



Challenges in Targeting Mutations

Despite the promise of targeted therapy, several challenges remain in identifying suitable drugs for individual patients. This includes genetic heterogeneity and understanding protein conformation. Every patient's tumour harbours unique mutations, making it essential to perform comprehensive genomic analyses to identify actionable mutations. Understanding the conformation and function of proteins is critical to developing mutation-specific therapies.

Importance of Mutation-specific Databases

Mutation-specific therapy databases are vital for advancing precision medicine by consolidating information on cancer-associated mutations and their corresponding therapies. One such resource, developed in India, is MUSTARD. It provides structured, well-annotated data on mutation-specific therapies, gene fusions, and overexpressed genes—empowering clinicians, patients, and researchers alike. Other important databases include the Catalogue of Somatic Mutations in Cancer (COSMIC) and The Cancer Genome Atlas (TCGA), which play key roles in identifying potential therapeutic targets.

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‘Don’t be scared of finding cancer. Be scared of not finding it.’

Vani Agarwal

Intern, Apollo Genomics Institutes, Indraprastha Apollo Hospitals, New Delhi, India

Our bodies are always talking to us, hinting at the future to come. 15000 km from home, Gabriela recognised the critical value of listening to hers.

“Because of my family history, I was always very aware of my health, and I also have a very close relationship with my body, in a sense that I'm always paying attention to what's happening." This proactive approach led Gabriela to discover a lump under her right armpit during a routine self-examination, two months before her diagnosis. Despite the initial ultrasound showing nothing of concern, Gabriela couldn't shake the feeling that something was wrong. She knew her body too well.

> *“It’s very new, and I’m still processing,” she admits, “Right now I’m just focusing on the fact that there’s a 10 to 30% chance that I could have it in the future (the other cancers, specifically ovarian), but 70 to 90% that I won’t!*

Months later, on an Ayurveda retreat in India, Gabriela felt a lump again. This time, it was in her left breast, and it was different—swollen, tender, and pressing uncomfortably against her skin- like a “pimple”. “That's when I felt like… what's going on?" she recalled. She knew she immediately had to seek help.

So, in a foreign country, and all alone, Gabriela was thrust into a medical system she barely understood. Yet her resolve was unyielding. “When I went to the doctor, I did act in an instinctive way. I had a very high sense of urgency inside me…maybe because it was a foreign country, maybe because I was feeling that this could be serious." There is a slight note of amusement in her voice as she narrates the story in hindsight, “I think everybody may know me in the hospital. Because when you see a foreigner crying in the middle of the corridor shouting, ‘Give me a mammogram!', you know, that's probably an image that they'll remember."

Nevertheless, Gabriela's sense of urgency paid off; the diagnosis came swiftly—stage one breast cancer. Alone in a doctor's office, Gabriela found herself staring at a piece of paper that suddenly made her world tilt on its axis. A quick Google search of “carcinoma" had already filled her mind with the darkest possibilities. “I had to hold myself up with the counter, because I was… super, super, super scared," Gabriela says, her voice catching slightly.

But there was no time to succumb to fear, and the doctors didn't let her. Quality medical advice and the reassurance she received from doctors were key to her remaining calm. “They (the team of oncologists) were assuring me, since the beginning, saying, ‘You are the perfect patient, so everything will be okay. We want everybody to come to us like you—because this is stage one, you are going to be super fine.' This professionalism and the speed with which the doctors moved to surgery—within three days—were critical to providing Gabriela with a sense of relief, amidst the storm of uncertainty that her treatment held.

The suggestion of genetic testing was something raised at multiple points of the journey. For one, long-term management of hereditary cancer depends on the specific results of the genetic tests, making them crucial. Moreover, given her Ashkenazi Jewish background—where BRCA1 and BRCA2 mutations are more prevalent — doctors urged her to consider it. The idea of a hereditary predisposition to cancer was daunting. It wasn't just about surviving this battle; it was about future wars she might have to wage.

The statistics are stark: women with BRCA mutations face up to an 85% risk of developing breast cancer by age 70, compared to 12% in the general population. This knowledge was a double-edged sword for Gabriela.

It gave her a roadmap for the future, allowing her to proceed with more rigorous surveillance. But at the same time, it opened a new front in an already exhausting battle.

"It's very new, and I'm still processing," she admits, "Right now I'm just focusing on the fact that there's a 10 to 30% chance that I could have it in the future (the other cancers, specifically ovarian), but 70 to 90% that I won't! I have to behave with awareness of the 10 to 30%, but I think, with my positive attitude, and holistic healthcare, I may just be between the 70 and the 90%."

Gabriela's journey was shaped not just by her diagnosis, but by the environment she found herself in. The efficiency and care she received in India were unexpected, a stark contrast to the chaotic emotions swirling inside her, "The doctors want the best for you. They're there to save you, to help you, to cure you. So, you can just trust them, trust the medicine."

Now, as she continues to navigate the aftermath, Gabriela has become an advocate for self-awareness, emphasising the importance of proactiveness with enthusiasm. "People feel scared of finding cancer, and I feel scared of... not finding it. Because if you find it, then it's fine, you're gonna take a medicine that has a little bit of a strong side effect and makes our hair fall, but that's it! I think many people see something, and they may postpone a visit to the doctor thinking, 'Oh my God. What if it's something?' And it's like, well, if it's something, then you need to go find help!"

And if the mental taxation of cancer is what you fear, Gabriela insists, "Cancer is much scarier in the media than in reality. It's going to pass. We are stronger than we think. We just go through it and that's it. And yes, you're going to think things like 'Oh my God, I'm going to die!' But don't dwell on those thoughts. Don't stay in that mindset. Have a simplistic and positive attitude."

So, if you think your body is saying something to you at this very moment, don't be scared to listen. And even if it turns out to be nothing, the best cure is mitigation: "Just give good things to your body. Regular check-ups, relaxed environments, nutritious food, good sleep, and mindfulness!"

ACKNOWLEDGEMENT

I would like to thank the Genetic team and Oncology team (Dr. Manish Singal, Medical Oncologist) for providing the opportunity to interact with Gabriela. And grateful for Gabriela for her narrative.

Opinion Piece

Molecular, Not Mutational Oncology! Role of a Clinical Geneticist in Tumour Boards

Dr. Surya Balakrishnan

Consultant Medical Geneticist
Apollo Hospitals, Jubilee Hills, Hyderabad

Tumour boards are a routine exercise in any oncological establishment. It is an effort to combine multidisciplinary expertise to optimise care for cancer patients and their families. Genetics, the most recent addition, is nevertheless the most transformative. Over the years, the field of oncology has learnt to harness this dimension to develop novel testing strategies and treatment options. But questions remain: Are we doing enough? Are we doing it the right way?

Medical or Clinical genetics is now a recognised sub-specialty, with a tangible impact across various medical branches. However, a geneticist is yet to find a firm footing in oncology, despite widespread genetic testing and prevailing non-familiarity with key genetic concepts. These are a few pointers from a geneticist's perspective, to facilitate fruitful collaborations between oncology and genetics, which, in turn, will ensure the most updated, appropriate cancer care for our patients.

We play by zones. And they have to merge seamlessly!

Modern medicine is moving towards sub-specialties & our respective areas of expertise are shrinking. While this design guarantees depth and reveals novel solutions, it can also blindside us with its extremely myopic/ reductionist approach. Therefore, an integrated view requires a cooperative ecosystem, where our respective roles are well-defined & we diligently seek support from fellow specialists, when dealing with our blind spots.

Genetic testing only for Targeted therapy – a low-hanging fruit!

Yes, therapy based on genetic testing is important & must be a priority in every case. However, the potential of genetics in solving mysteries must not be overlooked. Every patient phenotype is probably trying to teach us as to what is unique in our populations or if there are seemingly disparate things that don't necessarily fit! It is these 'anomalies' that uncover insights, spark curious conversations & propel research. Research doesn't happen in a unicorn case, it must happen in every case.

Collaborate & grow

"Collaboration allows us to know more than we are capable of knowing by ourselves." Cancer is a multi-dimensional fight, therefore, our expertise needs to be multi-dimensional too. We often miss things because of limitations in time, experience or expertise. The quickest way to overcome all three is to collaborate! We are heavily reliant on Western data for report interpretations & treatment. Steady & long-term partnerships between Oncologists & Geneticists are necessary to understand the Indian onco-genomic landscape & redesign our strategies.

Geno-Iatrophobia!

We often see this among patients & clinicians alike, although the underlying reasons are different. And the simplest way to deal with it is to talk to us, geneticists. The subject is relatively new & concepts may be difficult, but not everyone knows everything. Also, give the patients the benefits of genetic counselling before ordering a genetic test. They will co-operate much better & will be grateful that you took a step beyond, in their best interests.

It's all about family!

In Genetics, it's not just about the patient! It is also about the relatives, who are suddenly faced with an unpleasant situation. Patients are increasingly being offered genetic testing, without a relevant discussion as to how it might impact them or their families. Lack of appropriate pre-test or post-test counselling will sabotage precious opportunities for pre-symptomatic testing, surveillance & prenatal diagnosis. When you are able to impact more lives, why choose only one?

Panels are not always perfect

While panels named after cancers have made it easier for oncologists to order genetic tests, they are not always infallible. Panels are not standardised across companies, may not cover all types of genetic defects & may not be cost-effective in some cases. The type of test ordered also depends on whether the primary clinical question pertains to cancer diagnosis, prognosis or therapy. There are quite a few instances in oncology, where unique tests may have to be performed. These situations are best dealt with the help of a Geneticist.

The message....

Genetic testing has immense potential beyond the simple mutational testing that is currently practiced in oncology. Involving a clinical geneticist in tumour boards and oncology in general, can accelerate learning across both departments and ignite interesting discussions. Genetic testing/counselling is a critical need in the treatment paradigm of cancer patients and must be facilitated via a qualified medical or clinical geneticist for optimised outcomes.

Recent Updates in Oncogenetic Diagnostics and Therapeutics

Dr. Ambika Gupta
Apollo Hospitals, Ahmedabad

1. Lesser-known Facts on the Genetics of Prostate Cancer

Source: Updates from National Cancer Institute, July 2024

Carcinoma of the prostate is the third most common cancer in Indian males and 1 out of every 125 men is likely to get it in their lifetime. Prostate cancer heritability (when considering low, moderate, and high-penetrant genetic factors) can be as high as 57% (95% CI, 51%–63%). Genetic variants that contribute to this risk are continuously being identified. Germline genetic testing may be used to assess prostate cancer risk and/or inform therapeutic decision-making in men diagnosed with prostate cancer. Clinically Relevant Genes for Prostate Cancer include: BRCA1, BRCA2, HOXB13, ATM, TP53, DNA mismatch repair genes (MLH1, MSH2, MLH6, PMS2, and EPCAM), CHEK2, and NBN.

Indications for germline testing in prostate cancer include (NCCN, 2023) men affected with prostate cancer who have the following: ≥1 FDR (First-Degree Relative), SDR (Second-Degree Relative), or TDR (Third-Degree Relative on the same side of the family) with—

- Breast cancer at age ≤50 years
- Colorectal or endometrial cancer at age ≤50 years
- Triple-negative breast cancer at any age
- Male breast cancer at any age
- Ovarian cancer at any age
- Exocrine pancreatic cancer at any age
- Metastatic, regional, very-high-risk, high-risk prostate cancer at any age
- Prostate cancer at any age and Ashkenazi Jewish ancestry

2. PARP Inroads in Neuroblastoma Management

Source: Link CM et al. N Engl J Med 2024;391:659-661, DOI: 10.1056/NEJMc2403316

Patients with relapsed or refractory high-risk neuroblastoma have a poor prognosis. A recent study identified BARD1 as the gene with the most enriched pathogenic or likely pathogenic germline variants in neuroblastoma patients, leading to homologous recombination repair (HRR) deficiency and sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors. The authors reported a case of a child with high-risk neuroblastoma and a BARD1 germline mutation who responded to the PARP inhibitor talazoparib. After multiple therapies, including chemotherapy, stem-cell transplantation, and radiation, the patient's disease progressed to 30% bone marrow involvement. Whole-exome sequencing revealed a pathogenic BARD1 frameshift variant, leading to treatment with talazoparib and irinotecan. The patient achieved complete bone marrow response by cycle 2, with stable disease maintained for 32 months post-therapy. Immunohistochemistry confirmed somatic BARD1 protein loss, and RNA sequencing suggested biallelic BARD1 loss in the tumour. Synthetic lethality analysis indicated that PARP2 inhibition, rather than PARP1, likely drove the response. This case highlights the therapeutic potential of targeting HRR deficiencies in paediatric cancer and supports ongoing clinical trials evaluating PARP inhibitors in children with recurrent or refractory tumours harbouring HRR gene alterations.

3. Bezultifan in VHL Management

Dr. Surya Balakrishnan
Consultant Medical Geneticist
Apollo Hospitals, Jubilee Hills, Hyderabad

INTRODUCTION

von Hippel Lindau syndrome is a highly penetrant, familial cancer syndrome characterised by multi-focal benign & malignant tumors. Bezultifan (Welireg, Merck) is a small molecule drug, which was FDA approved in 2021, for VHL associated tumors not requiring immediate surgical intervention. It inhibits the **Hypoxia inducing factors (HIFs)** & prevents a multitude of downstream, aberrant cellular processes.

MODE OF ACTION

In short, a functional VHL protein **hijacks & destroys the HIFs**, which otherwise enter the nucleus & trigger tumorigenesis. Normally, VHL protein is a part of the E3 ubiquitin ligase complex & mediates the oxygen-sensitive proteasomal degradation of HIFs. Loss of function VHL variants lead to persistence & hetero-dimerization of various HIFs, which stimulate the HIF-mediated transcription & tumorigenesis, by binding to hypoxia response elements (HREs).

INDICATIONS

Belzutifan inhibits HIF-2a & is currently approved for VHL associated clear cell renal cell carcinoma (ccRCC), CNS hemangioblastomas (CNS-HB) and pancreatic neuroendocrine tumors (pNET). The therapy is expected to improve outcomes by reducing the need for morbid surgeries & prevention of organ dysfunction. The VEGF-targeted therapy in the same setting is usually associated with significant toxicity, requiring drug discontinuation in many cases. There is also the risk of haemorrhage especially in CNS-HBs, due to excessive vascular fragility.

In advanced ccRCC refractory to VEGF targeted therapy, Bezultifan was shown to have an ORR of 25%. Its potential role as a single agent/ combination therapy is also being explored across several phase III trials, in adjuvant and metastatic setting.

CLINICAL TRIALS

The benefits of the drug were studied in a single-arm phase II study named 'LITESPARK'. Bezultifan was given at a dose of **120 mg orally once daily, until disease progression or unacceptable toxicity**. Primary end-point was ORR in renal neoplasms, and secondary

end-points were safety and ORR in extra-renal tumours. Objective response in terms of volume reduction were noted in 91% renal (56/91), 77% pancreatic (47/61) & 30% PNETs (15/50), over a follow up period of 21.8 months. The number of surgical interventions reduced dramatically following Bezultifan therapy (only 3 against 64 interventions prior to therapy).

ADVERSE EFFECTS

The adverse effects, although noted in all patients, were mostly grade 1, 2 & included fatigue, headache, anaemia, and dizziness. It is also teratogenic & therefore effective contraception is critical in women of childbearing age.

CONCLUSION

Belzutifan offers durable responses in VHL associated renal and extra-renal tumors & may be administered with **minimal adverse effects**.

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Liquid Biopsy: A New Focus in Diagnosis, Prognosis, and Future of Cancer Treatments

Dr. Saswati Mukhopadhyay

Consultant Clinical Geneticist, Apollo Multispeciality Hospitals, Kolkata

Molecular profiling of tumours obtained from individual patients has improved the selection of personalised cancer treatment therapies, patient responses, detection of drug resistance, and monitoring of tumour relapse[1,2]. Profiling tumours initially involves analysing resected tumour samples by **invasive surgeries. However, such invasive procedures may not yield adequate tumour samples for initial analysis, subsequent monitoring of response to therapy, and relapse**[3]. The **heterogeneity** of resected tumour samples limits the use of invasive methods[4]. In the case of metastasis, where tumours evolve in response to treatment over time, multiple invasive biopsies may be required.

Recent oncology research has shifted its focus toward analysing various biological fluids rather than whole tissues for tumour-derived components—a technique referred to as liquid biopsy (LB). LBs mostly involve **blood** sampling, but other body fluids like **mucosa, pleural effusions, saliva, urine**, and cerebrospinal fluid (CSF) are also analysed[5]. Thus, LB helps in early diagnosis, and repeated sampling can be done throughout the treatment conveniently and in a non-invasive way[6].

LB assesses a wide array of tumour-derived moieties, such as circulating tumour cells **(CTCs)**, shed by both primary and metastatic tumours, circulating tumour DNA

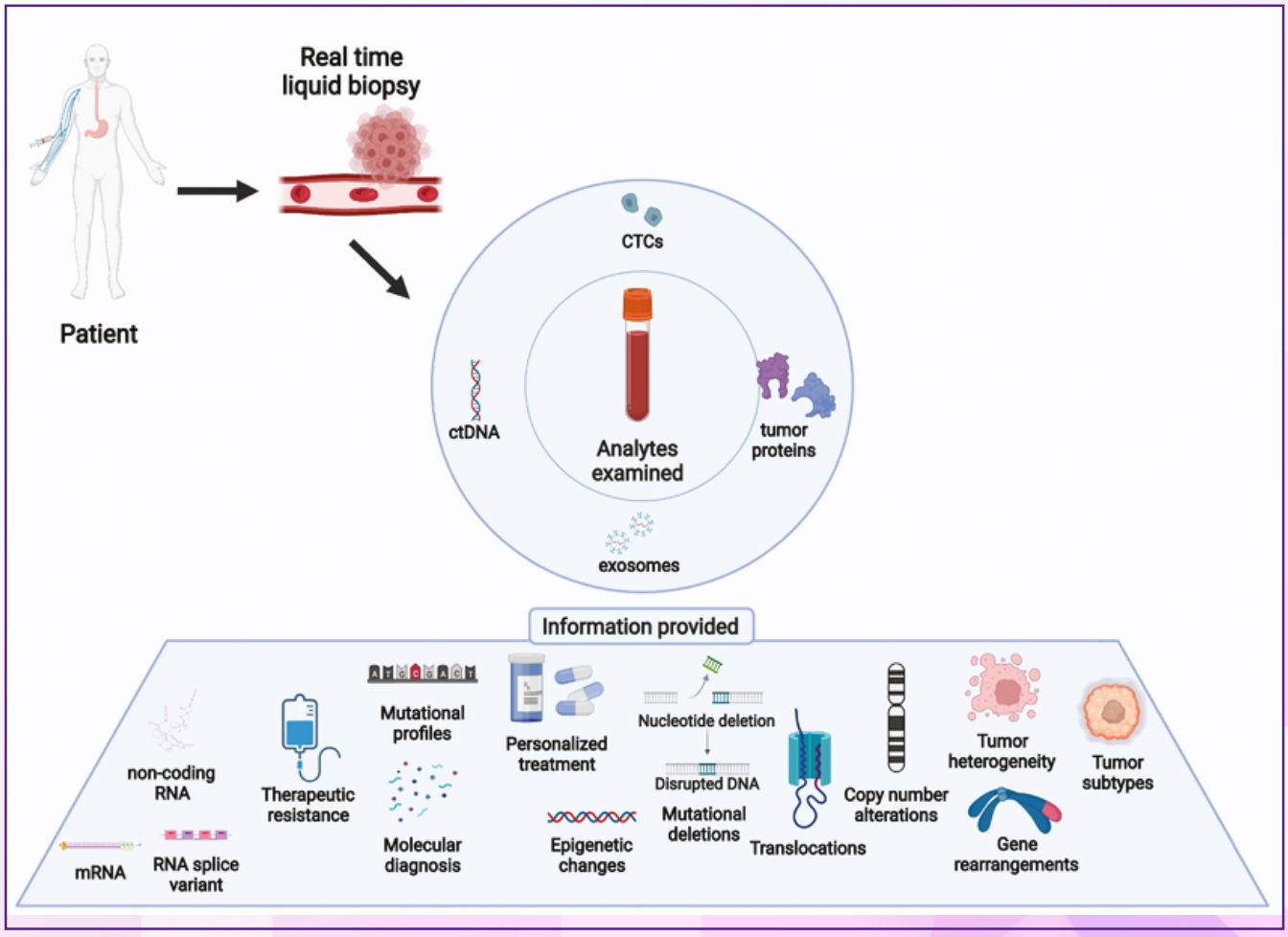

Fig. 1 Entities analysed in liquid biopsies and their application.

(ctDNA), tumour-derived extracellular vesicles **(EVs)** that are composed of nucleic acids/proteins, tumour educated platelets **(TEPs)**, and circulating cell-free RNA (cfRNA). LBs encompass information like DNA mutations, copy number alterations (CNAs) of crucial genes [4], transcriptome/proteome profiling, epigenetic alterations [7], metabolite profiling, etc. (Fig. 1)

In addition to plasma or serum, various other body fluids like saliva, urine, etc. have significant applications in liquid biopsy. Sampling saliva and urine is easy, non-invasive, and cost-effective—even more so than plasma or serum—making them useful candidates in LBs, particularly where repeated sampling is required to monitor tumour progression and therapeutic outcomes.

The major **limitation of LB is the lack of sensitivity and precision** to identify various **tumour types** compared to tissue biopsy. Moreover, an LB may not provide a representative sampling of all genomic clones within an individual tumour or a specific sub-region of the tumour. Also, the number of CTCs, ctDNA, RNA, progenitor and mature endothelial cells, and tumour-educated platelets are relatively rare compared to other haematological components in the blood, which makes LB's detection ability challenging.

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Events and Updates from Apollo Genomics Institutes

Two-day Hands-on Workshop on Karyotyping, FISH & M-FISH











Snippets of the Second Hands-on Workshop on Karyotyping, FISH & M-FISH at Apollo Multispeciality Hospitals, Chennai (2nd and 3rd August 2024)

Apollo Chennai Medical Genetics Lab organised its second comprehensive cytogenetics workshop in alliance with Metasystems, India. The two-day hands-on workshop was attended by 12 participants from various parts of the country.

The workshop was inaugurated by Dr. Mamta Soni, Quality Manager and HOD – Department of Hematology and Clinical Pathology, and Dr. N. Indhumathi, HOD – Department of Medical Genetics, AMH.

The participants not only acquired knowledge of cytogenetic techniques, analysis, and troubleshooting skills but also learned the application of Karyotyping, FISH, and M-FISH in patient care for better diagnosis and prognosis.

They were given hands-on exposure to the following techniques: cell culture of peripheral blood, culture termination, harvesting, slide preparation for karyotyping, FISH, M-FISH, GTG Banding, FISH Slide Process (pre-/post-washes), denaturation of target and the hybridisation of the probe. It also focused on the analyses and interpretation of Karyotyping, FISH and M-FISH slides.

The workshop concluded with a certificate distribution ceremony by Dr. Dhanalakshmi, Senior Consultant, HOD – Department of Biochemistry, AMH.

Comprehensive Genetic Workshop in Collaboration with PCNI-IAP and Apollo Genomics Institutes

A comprehensive genetic workshop was held in collaboration with PCNI-IAP and Apollo Genomics Institutes.

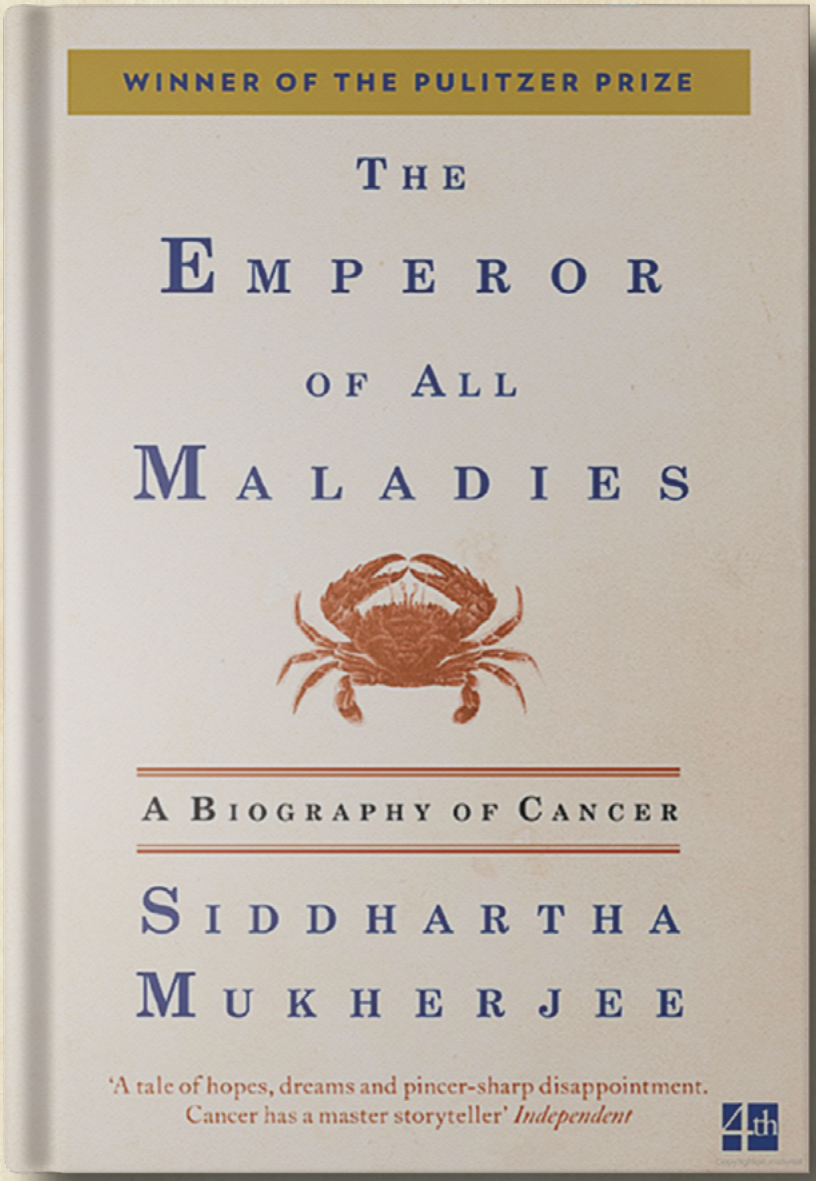
This workshop included talks on various components, such as:

- **Initial Patient Assessment**, where clinicians collect family history and evaluate potential red flags for genetic conditions (e.g., developmental delays, dysmorphic features, etc.).
- **Genetic Testing Considerations**, which outlines the criteria for selecting appropriate tests, such as karyotyping, chromosomal microarrays, or next-generation sequencing panels, based on clinical suspicions.
- **Pre-test and Post-test Counselling** that emphasises the importance of explaining test implications, potential outcomes, and ethical considerations with family members, as well as discussing the results and post-test management and treatment options.
- **Genetic Testing and Interpretation**, which focuses on the process of sending tests to the lab, followed by analysing results with a particular focus on variant classification and ACMG guidelines.

The workshop also showcased case capsules and inspiring patient stories to serve as reminders of why we strive to get a diagnosis for patients and their families suffering with rare disorders.

The Emperor of All Maladies: A Biography of Cancer
— *Siddhartha Mukherjee*

Siddhartha Mukherjee is an Indian-American physician, biologist, and author. He is currently a professor of Medicine at Columbia University Irving Medical Centre, USA. This was his first book, and it won him notable literary prizes including the 2011 Pulitzer Prize for General Non-Fiction and the Guardian First Book Award.



He calls this book a biography of cancer, which he deems the emperor among all illnesses known to mankind. The author tracks the first historical glimpses of the disease, the development of treatment regimens, the role of prevention, and the biological mechanisms by which cancer proves detrimental in every patient's life.

The author narrates the various ways by which modern science discovered the genes and genetic mechanisms that play a role in causing cancer. He also delves into the history of the tobacco industry and how cigarette manufacturers and their cartels never wanted the research that smoking causes cancer to be made public. He also goes on to make us, ordinary people, understand how drugs for cancer treatment were discovered, the monopoly of some pharma giants, and the role of American politics in this entire saga.

In short, this book has to be read to know what I am trying to say! Once you start, you will put it down only after you read it till the end because there is so much we never knew until now.

The simple language used by the author helps clear all fundamental doubts, whether you are a person of science or not. It is a lesson in genetics, biology, evolution, and anthropology all rolled into one.

Siddhartha Mukherjee wins readers with his inimitable style, which has resulted in all his subsequent books doing so well. Though many of his masterpieces have been published in the following years, this one continues to rule as only an emperor can!

Reviewed by
Mrs. Reena Trivedi

Senior Genetic Counsellor,
Apollo Hospitals, Gandhinagar

New Members of the Apollo Family

Dr. Kathirvel. M

MBBS, MD Paediatrics (JIPMER)
DM Medical Genetics (AIIMS, New Delhi)
Associate Consultant, Medical Genetics, Apollo Hospitals, Chennai

Email: kvel564@gmail.com

Member
Indian Society of Inborn Errors of Metabolism; Society for Indian Academy for Medical Genetics; Molecular Pathology Association of India

Fields of Interest
Artificial Intelligence (AI) in Medicine, Neurogenetics, Oncogenetics, Genome Analysis and Variant Interpretation

Ms. Khyati Arora

B.Tech Genetic Engineering (SRM IST)
M.Sc. Genetic Counselling (KMC), Level 1 BGCI certified
Genetic Counsellor, Apollo Hospitals, Hyderabad

Email: khyati.arora1999@gmail.com

Member
Board of Genetic Counselling, India

Fields of Interest
Prenatal and Paediatric Genetics, Neurogenetics, Genome Analysis and Variant Interpretation

Dr. Vishaka Kothiwale

MBBS, MD (Paediatrics), DM (Medical Genetics), Associate Consultant,
Department of Genomics, Apollo Multispecialty Hospitals, Kolkata

Email: vkdec20@gmail.com

Member
Indian Academy of Paediatrics
Society for Indian Academy of Medical Genetics

Fields of Interest
Inborn Error of Metabolism, Skeletal Dysplasia, Dysmorphology Neurogenetics, Oncogenetics

Ms. Shilpa Kamble

M.Sc. Biomedical Genetics (VIT University) Level 1
Genetic Counsellor (Board of Genetic Counselling of India)
Apollo Hospitals, Navi Mumbai

Email: shilpakamble88@gmail.com

Fields of Interest
Prenatal, Paediatric and Cancer Genetics, Psychological Aspects of Genetic Counselling, Genetic Variant Interpretation