MEDGENOME

GeKNOWme
Internal Quarterly Newsletter
Vol 30 | Jul 2024

NeXI pipeline

A better alternative to genotype arrays in genetic studies and disease risk screening

Scientific article

Non-invasive prenatal testing: interesting case scenarios

Featured article

Complementing strides made with short-reads with PacBio long-read sequencing

Book Review

Neanderthal man: in search of lost genomes

WORDS FROM THE **FRONTLINE**

Dr. Suneeta Bhat
Director - HR

Greetings to all the readers!

My journey started at MedGenome only a month ago, however, with two decades of experience in healthcare, this company did not feel like new to me. The warm welcome extended by the team here makes me feel truly at home.

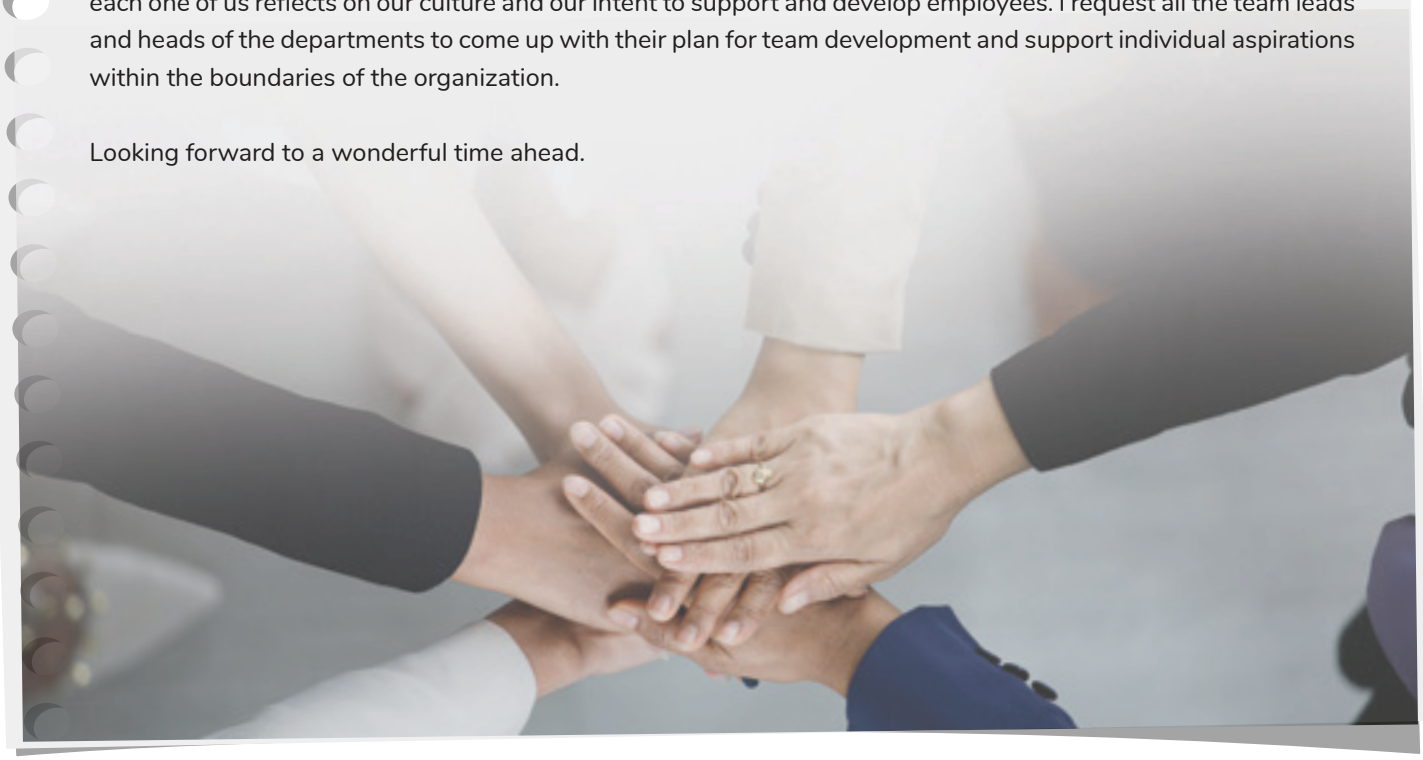
People are the basic building blocks of an organization; they bring unique irreplaceable knowledge and skill to the organization. Hence, as a Human Resources Professional, it brings immense joy and fulfillment to me to enable people to succeed, which in turn helps the organization to grow.

I would like to say that we are committed to making our employees' lives better and will strive to make sure that they have a memorable and successful journey with MedGenome. We all know that HR is responsible for driving recruitment, payroll, and the rest of the transactions related to employment. In addition to that, we are also responsible for driving a transparent and effective performance management system and developing highly engaged and high-performing teams. This is very important in today's competitive world.

Personal development in the workplace is a continuous journey of self-improvement, focusing on enhancing professional skills, expanding knowledge and developing abilities. It is important that we define our short - term and long-term career goals. Every skill that we learn today is an investment for a better tomorrow.

The team leads and the HODs represent the organization to employees on the ground. Hence, it is important that each one of us reflects on our culture and our intent to support and develop employees. I request all the team leads and heads of the departments to come up with their plan for team development and support individual aspirations within the boundaries of the organization.

Looking forward to a wonderful time ahead.



Contents

MedGenome Connect

REPRODUCTIVE GENOMICS

This quarter, we launched several initiatives to boost awareness and engagement. We created an awareness carousel on NIPT and celebrated Mother's Day with a dedicated video and a blog titled "Why Reproductive Genetic Testing Matters? In observance of the International Day of Action for Women's Health, we executed a campaign that included a video, a blog, and interactive polls to highlight the importance of genetic testing. Dr. Priya Kadam did a video byte on the significance of genetic testing in women's health. Additionally, we published a blog titled "Decoding NIPT: What Expectant Parents Need to Know? and did testimonial videos with KOLs to enhance credibility. We participated in FETOVISION Conference, where Dr. E Venkataswamy presented a session on KaryoSeq and we also took part in CME events across India to promote our services. We also did digital mailers for clinicians featuring carrier screening test case studies and other offerings.

Video

Here's what Dr. Vinayak Das, Consultant Maternal Fetal Medicine Specialist at New Ramkrishna Siva Sadan in Siliguri shared about our KaryoSeq test, which utilizes low-pass whole-genome sequencing to provide comprehensive genome-wide information.

Watch the video to find out more.

Video

Here's what Dr. Kusagradhi Ghosh, Consultant of Fetal Medicine and Director at Institute of Fetal Medicine in Kolkata, said about the rising importance of prenatal diagnostics using innovative genetic tests such as KaryoSeq.

Watch the video to find out what he has to say about working with MedGenome for precise sample diagnosis.

Video

Dr. Priya Kadam, Director at MedGenome, shared insightful information on the significance of genetic testing in women's healthcare. From conception challenges to pregnancy, tests like NIPT and carrier screening play a crucial role. Understanding genetic risks, especially for cancers like breast and ovarian, empowers proactive healthcare decisions.

Video

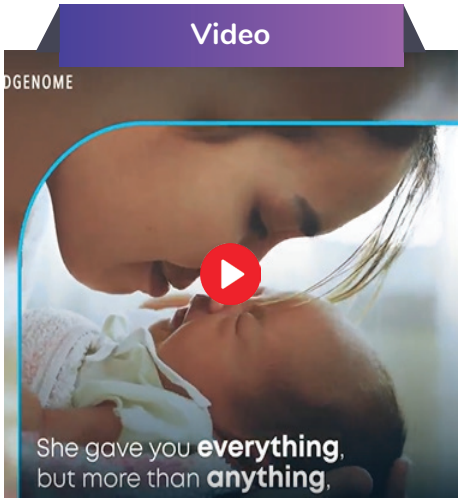
Here's what Dr. Ratnabali Chakravorty, Director of MAGS Medical & Research Centre in Kolkata said about the significance of genetic testing and how MedGenome helped a couple plan their pregnancy better by identifying a genetic defect that enabled targeted treatment for them.

Video

International Day of Action for Women's Health, #WeCare2X focused on women's rising healthcare needs for early detection and targeted therapy.

#MedGenome #Genetics #Genes #Healthcare #Genomics #InternationalDayofActionfor WomensHealth

Video



Mother's Day celebration

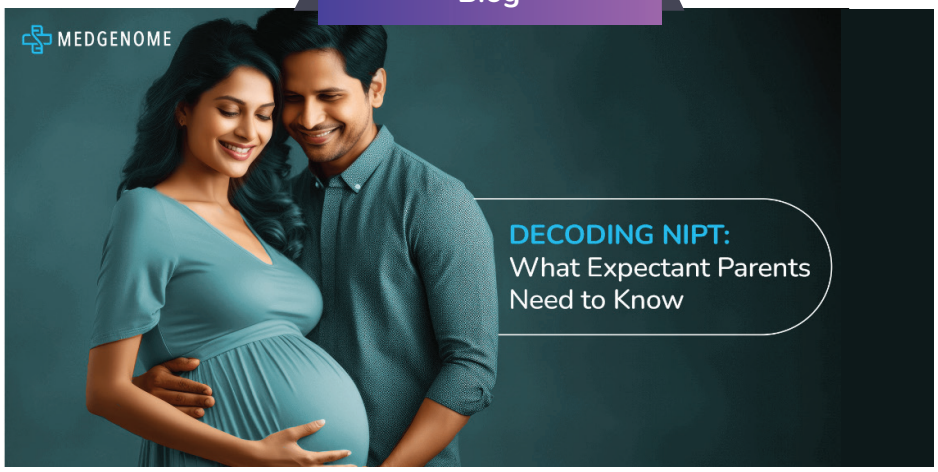
#MedGenome #GeneticLegacy #MothersDay #MothersDay2024 #Mothers #MaternalGenes #Generations #Genes #GeneticTesting #Genetics

Social media post

International Day of Action for Women's Health - raised 2X awareness towards proactive healthcare for two X chromosomes (females). Genetic testing enables women to take preventative measures for reproductive health. The tests provide early detection and targeted treatment for better health outcomes.

#MedGenome #Genetics #Genes #Healthcare #Genomics #InternationalDayofActionfor WomensHealth

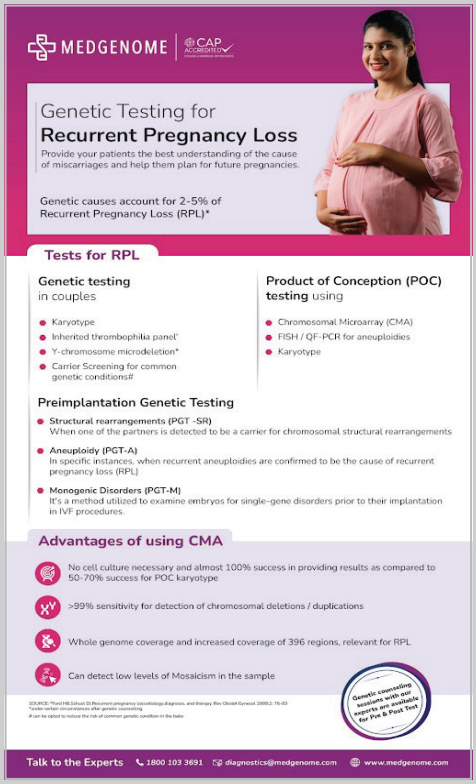
Blog

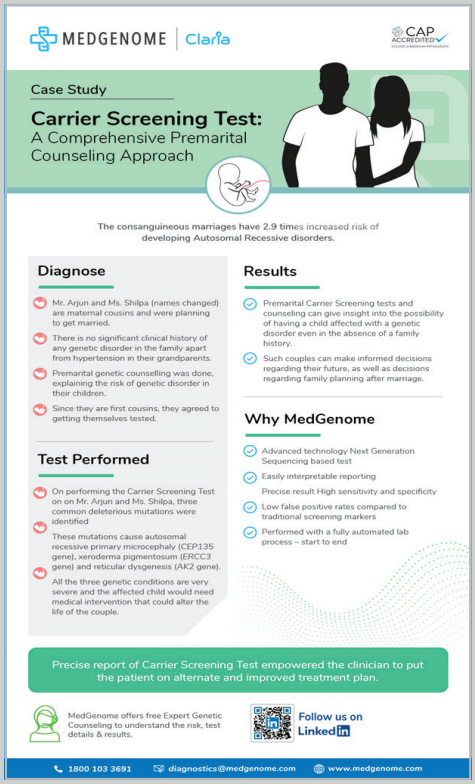


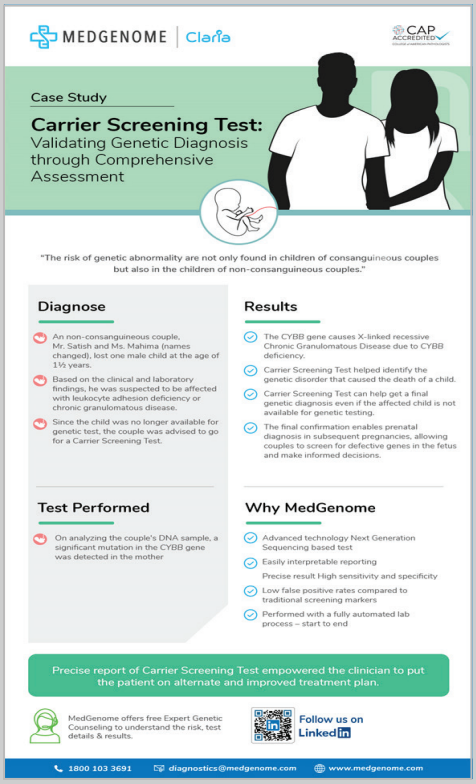
In our latest blog, we demystified Non-invasive prenatal screening (NIPT) - the screening method, offering essential insights for expectant parents. Discover how NIPT provides accurate results without invasive procedures, ensuring peace of mind throughout the pregnancy journey. Click here to read more https://lnkd.in/gWd_DtS6.

#MedGenome #Prenatalscreening #pregnancy

Mailer







Social media post

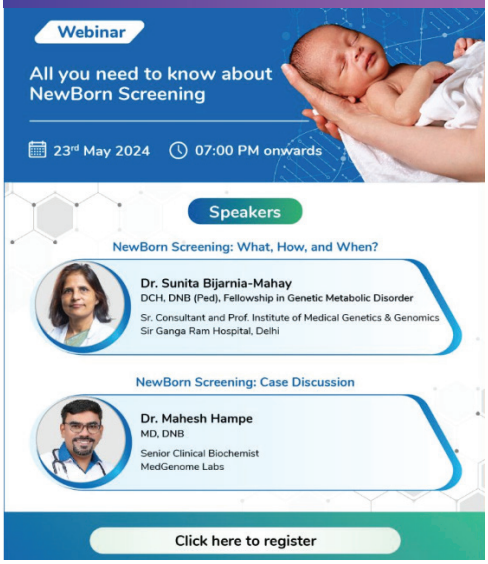
Empower your journey to motherhood with knowledge! Our latest blog explores how reproductive genetic testing empowers women with valuable insights, promoting informed decisions and healthy pregnancies.

#MedGenome #Mothers #MothersDay #HappyMothersDay #ReproductiveGenetics #Women #Healthy

RARE INHERITED DIEASE GENOMICS

In the past quarter, we hosted three engaging webinars: Dr Anup covered the Genetics of Gastroenterology, Dr Sunita and Dr Mahesh discussed Newborn Screening, and Dr Jacky Ganguly presented on Parkinson's disease. Additionally, we introduced two ground-breaking tests - WGS Reflex OGM at the NIMHANS conference and India's first Blended Genome Exome Test. We were honoured to receive a testimonial from Dr Vikram Holla praising our genetic services. Furthermore, our campaign on thalassemia also received good response.

Webinar



Webinar

Social media post

#WorldThalassemiaDay

With the right genetic counselling, you can assure better health outcomes.

#GeneticTesting #WorldThalassemiaDay #MedGenome #Healthcare #Genes #Genetics #Genomics

Doctor testimonial

Dr. Vikram V Holla, Assistant Professor of Neurology at the Institute of Mental Health and Neuro Sciences in Bengaluru, shared his experience with MedGenome. He emphasizes on how precise and accurate genetic diagnosis by MedGenome has helped in better patient management.

#MedGenome #Testimonial #Clinicians #Doctors #Patients #Accuracy #Results #Precision

CANCER GENOMICS

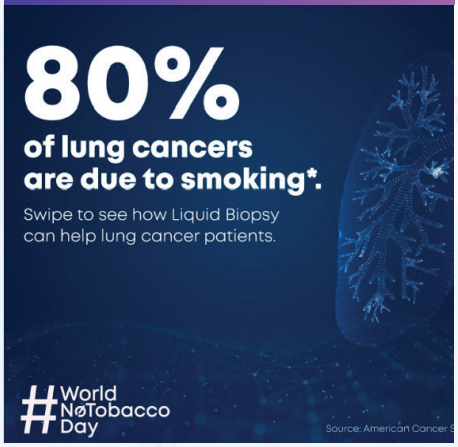
On International Day of Action for Women's Health, we focused on the top five cancers impacting women. For World No Tobacco Day, we addressed the detrimental effects of tobacco and showcased how our liquid biopsy test can aid in the detection of lung cancer. We also spotlighted ovarian cancer - often referred to as the silent killer - by discussing its early symptoms, preventive measures, and how our genetic tests can support patients. Additionally, we ran a distinct campaign for Father's Day.

Social media post

#WorldOvarianCancerDay, created awareness about the importance of early detection and help women take better charge of their health.

#GeneticTesting #WorldOvarianCancerDay #WorldThalassemiaDay #MedGenome #Healthcare #Genes #Genetics #Genomics

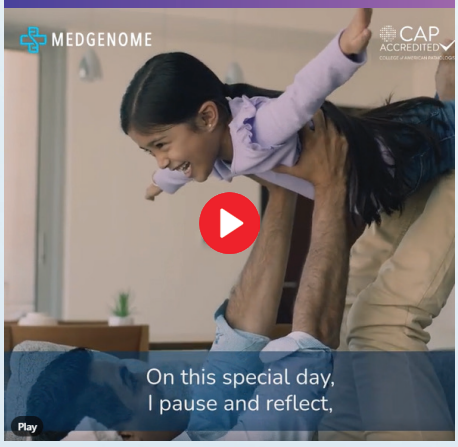
Social media post



#WorldNoTobaccoDay, created awareness about the harmful effects of smoking and urged people to stop using tobacco.

#MedGenome #Liquidbiopsy #lungcancer #Healthcare #NoTobacco

Social media post



#fatherday #MedGenome #Genetics #Genes #Healthcare #Genomics

INFECTIOUS DISEASE GENETICS

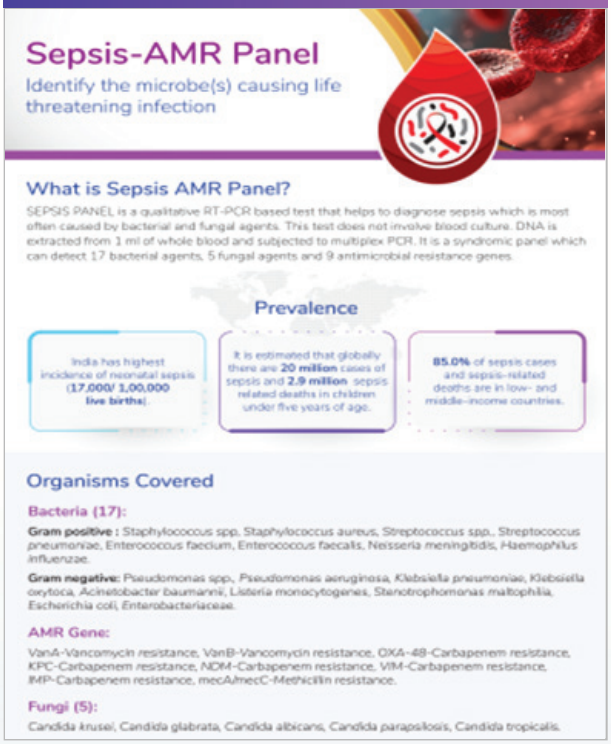
The last quarter was very encouraging and has been highly active one for Micra with a focus to engage a good number of clinicians with test specific mailers and brochures like Sepsis AMR Panel along with social media posts. We have also completed the World Malaria Day campaign in the month of April successfully. We also posted Testimonials video of Dr. Chhavi Gupta, DM - Infectious Disease, Senior Consultant at Yashoda Super - specialty hospital, Ghaziabad on all social media platforms. We also conducted online polls for the awareness during the World Malaria Day.

World Malaria Day- Dr. Chhavi Gupta

Dr. Chhavi Gupta, DM - Infectious Disease, Senior Consultant at Yashoda Super-specialty Hospital, Kaushambi, Ghaziabad, highlighted the progress made in the field of malaria this World Malaria Day. She emphasizes the role of the RT-PCR based Tropical Fever panel, used for testing various pathogens including malaria. Watch the video for more details.

#MedGenome #Testimonial #Clinicians #Doctors #WorldMalariaDay #Accuracy #Precision #TropicalPanel

Sepsis AMR Panel Brochure

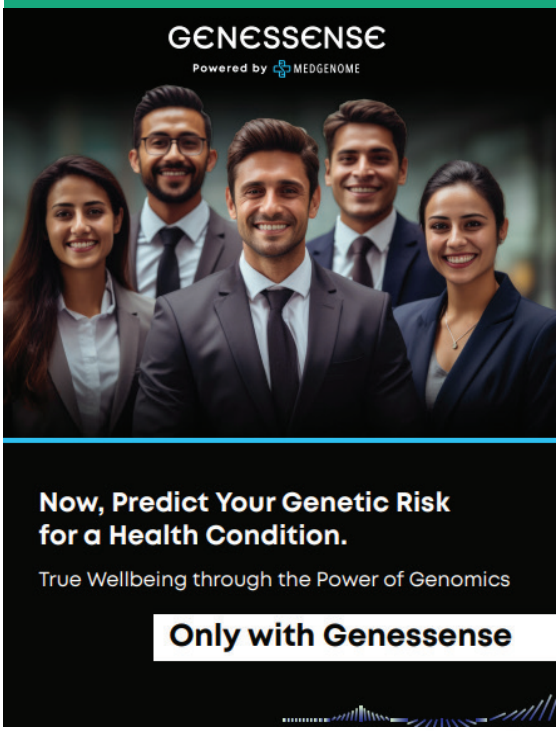


Sepsis AMR Panel Brochure

GENOMIC WELLNESS

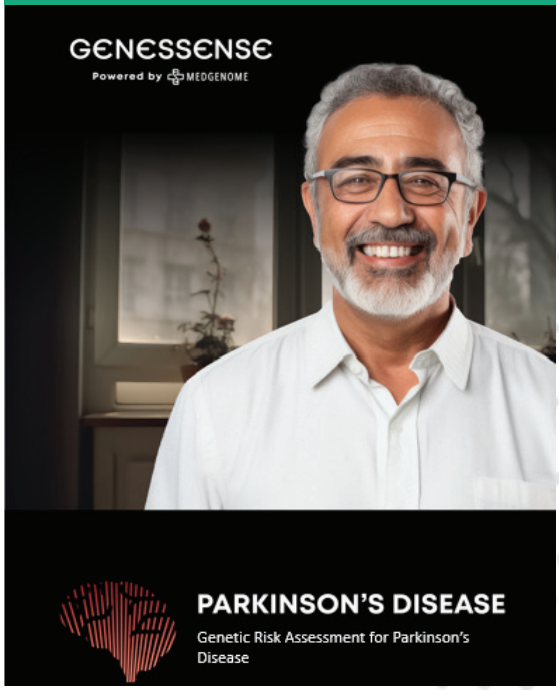
We continued to evolve the various tests being offered under the Genessense portfolio in this quarter. We focused on forging partnerships with a few aggregators & conversations were initiated with some of the major players in this space. We are also revamping our Genessense website with individual tests, blogs, along with scientific insights. We have worked on various tests brochures and reports under Genessense such as comprehensive flyer, Hepasense report and Parkinson's report.

Genessense Flyer



Hepasense Report

Parkinson's Report



What's new

Research publications

Results of comprehensive genetic testing in patients presenting to a multidisciplinary inherited heart disease clinic in India

Journal : *Indian Heart Journal* Read more

CNS-wide repopulation by hematopoietic - derived microglia - like cells corrects progranulin deficiency in mice

Journal : *Nature Communications* Read more

Phenotype - genotype correlation of a cohort of patients with congenital myopathy: a single centre experience from India

Journal : *Journal of Neuromuscular Diseases* Read more

Early detection and diagnosis of cancer with interpretable machine learning to uncover cancer-specific DNA methylation patterns

Journal : *BIOLOGY Methods & Protocols* Read more

Clinical exome sequencing unravels the diverse spectrum of genetic heterogeneity and genotype - phenotype correlations in hypertrophic cardiomyopathy

Journal : *International Journal of Cardiology* Read more

Tests launched

- HPV screening panel
- TumorFocus panel by NGS
- TRIO - whole exome sequencing (80-100x) + couple carrier analysis
- TRIO exomeMAX (Enhanced whole exome sequencing) + couple carrier analysis
- WGS reflex OGM

Announcement

MedGenome has expanded its footprint in East India with the acquisition of majority stake **in GenX Diagnostics, Odisha.**

MEDGENOME | GENX Diagnostics
Results you can trust

MedGenome's, state-of-the-art advanced science and technological capabilities, combined with GenX's diagnostics leadership in the East, will empower the clinicians in Odisha with actionable insights from genetic data and enable them to prescribe targeted treatment for patients, improving healthcare outcomes.

From Our US Office

We are happy to share that we have now added the PacBio Long-read sequencing capability to our existing portfolio of services making us the first commercial provider in the San Francisco Bay Area to offer this full suite of cutting-edge capabilities in-house.

This acquisition helps MedGenome to strengthen its long-read sequencing capabilities, thus providing unparalleled insights into complex genomic regions that were previously inaccessible with short-read technologies. With the PacBio Revio, we can offer end-to-end solutions for applications such as:

Improved Genome Assembly: Achieving complete and contiguous de novo genome assemblies for even the most complex organisms.

Enhanced Transcriptome Profiling: Revealing novel transcripts and isoforms, providing a detailed view of gene expression down to the single-cell level.

Comprehensive Variant Detection: Identifying a wider range of genetic variations, including structural variants and repeat expansions, crucial for understanding diseases like cancer.

As a testament to our capabilities, we are collaborating with **Dr. Lauren Esposito** from the California Academy of Sciences, and PacBio on an exciting project to sequence the genome of the Dune Scorpion, *Smeringurus (Paruroctonus) mesaensis*. This project aims to deepen the understanding of scorpions and their venom at a molecular level.

Dr. Lauren Esposito

Smeringurus (Paruroctonus) mesaensis

Our recent participation in the Festival of Genomics conference was a remarkable success. We were pleased to receive enthusiastic feedback about our value-added services, which underscored our role as a trusted research partner. Attendees appreciated our commitment to delivering not just data, but comprehensive support and collaboration, affirming our position as a leader in advancing genomic research.

From Our US Office

Additionally, MedGenome played a significant role in a recent publication in Nature Communications, led by **Pasqualina Colella** (Senior Research Scientist, Stanford University) and colleagues. This study, supported by MedGenome's technical consultation and single-cell sequencing expertise, presents an optimized brain conditioning regimen for robust microglia replacement, offering new potential for improving HSCT efficacy in neurological disorders.

Read more about the study here: https://www.nature.com/articles/s41467-024-49908-4

Stay updated with our evolving blog, featuring fresh and informative articles on a variety of topics:

01

Melanoma & Skin Cancer Awareness Month: Genomics for Developing Effective Therapies

02

Navigating Spatial Data Analysis for Publishable Research

03

Complementing Short-Reads with PacBio Long-Read Sequencing

Explore our latest blog articles at **MedGenome Research Blog.**

We value your insights and invite you to share your viewpoints and articles of interest at mgus-blog@medgenome.com.

pipeline facilitates low-pass whole genome sequencing as an alternative to genotype arrays in genetic studies and disease risk screening

(One XI)

Dr. Ramesh Menon, PhD
Asso. Director, Genomic Medicine & Personal Genomics Division
Bioinformatics Department

Introduction

Whole genome genotyping is a widely used technology for genetic research including gene-disease associations, disease risk scoring, ancestry inference, etc. Till recently, the genotyping arrays stood as an irreplaceable solution as the cost of the whole genome sequencing is way higher compared to it. Genotype imputation is a crucial step in any genome-wide analysis as the directly genotyped markers are limited. For example, the Illumina's Global Screening Array (GSA) has about 650,000 markers which is scaled with a reasonably good accuracy to ~150 times by imputation resulting in more than 100 million markers. The accuracy of imputed sites depends on the quality of genotype data, the method used for imputation and more importantly, the imputation reference panel.

Low pass whole genomes (lp-WGS) and blended genome-exome (BGE)

A standard high coverage human whole genome sequence at 30x average coverage will have 90 Giga bases of data. The low pass WGS typically has the sequencing depth ranging from 0.5x to 5x. Recently, ultra-low pass sequencing based studies are also conducted which has average coverage below 0.5x (<1.5 Gb data). However, the reliability of variants identified is questionable in case of ultra-low pass sequencing without imputation. The blended genome-exome is a combination of whole genome library and targeted exome library at a specific ratio. Typically sequence libraries are pooled at 1:3 ratio (33% targeted region, 67% whole genome library). The data is generated according to the requirements. For example, clinical grade diagnostics will require 20Gb data is generated where targeted region will have 80-100x and whole genome region will have the average coverage of 4-5x. For research usage, typically 10Gb data is generated in BGE, where 40-60x targeted coverage is achieved and whole genome coverage will be 2-3x. In both cases, the whole genome data generated is low pass, which requires accurate imputation for any analysis.

Comparison of NGS and whole-genome genotyping array

As low-pass whole genome has inherent advantages of NGS such as scalability, operational efficiency, cost-effectiveness etc. (use image for each yellow word and create a collage) The data generated from genotyping array has fixed content at a given time but subjected to content revision by the manufacturer from time to time. For example, MedGenome's coronary artery disease multi-centric study spanned from 2017 to 2019, where 3 versions of Global Screening Array (GSA) was used. During each content revision from the Illumina Inc, some markers are removed or added. So, for the consolidated data in the study, we could used only markers common across three versions of GSA. Very recently, the fourth version is also released from Illumina, which has again a revised content. This makes data generated from genotyping array non-future proof.

Genotyping array has no option to add more data points "top-up" for a given sample in future as the content is fixed once the data is generated. Genotyping array also suffers from operational efficiency and scalability. For example, our present bandwidth is 96 samples in 3-4 days. If we get 100 samples, we can't run it altogether and the remaining 4 samples has to wait for another week. Also, running the Illumina iScan for 4 samples is not cost-effective, so we may need to wait for samples to fill-up the array to perform the experiment which can cause TAT delay. On the other hand, the low-pass (3Gb) or BGE (10Gb or 20Gb) solutions are highly scalable and future proof. For example, any WGS with 15Gb data (5x for human) generated, needs only a top-up run to generate to reach 30x coverage. That means data generated once is future-proof.

	High coverage WGS (~90Gb)	Genotype array	Low-pass WGS (3Gb)	Blended Genome-Exome (10Gb or 20Gb)
Cost	High	Low	Low	Reasonable
Clinical grade whole genome reporting	Yes	No	No	No
Clinical diagnostics from exome region	Yes	No	No	Yes, 20Gb BGE
Rare variant discovery	Yes	No	No	Yes
Operational efficiency / scalability	Good	Poor	Good	Good
Data top-up feasibility	Yes	No	Yes	Yes
Future proof data	Yes	No	Yes	Yes
Accuracy of imputed sites	NA	Fair	Good	Good

Fig. 1: Features and applications of WGS (30x, low pass, BGE) and Genotyping array

Current solution	Replacing solution	Applications
Whole genome genotyping array (GSA/GDA etc.)	Low-pass whole genome (3Gb)	• Polygenic risk scores • Genome-wide association studies • Population genomics
Whole exome or targeted NGS panels + Whole genome genotyping array or WGS	Blended genome-exome (20Gb or 10Gb)	• Clinical diagnostics & research • Rare variant association & gene burden • Polygenic risk scores • Genome-wide association studies • Population genomics

Fig.2: OneXI enables replacement of Genotyping arrays for various applications

Therefore, for applications such as disease risk scores, genome-wide association study (GWAS), populations genomics studies 1x WGS can replace whole genome to genotyping. For clinical diagnostic and research involving exonic markers BGE is the alternative where 20Gb version can be used get to 80-100x targeted region coverage and 4-5x genome coverage. The BGE-10Gb can be used for research studies involving rare and common variants, where ~60x targeted region coverage and 2-3x genome coverage is present. A recently published multi-centric study on Young-onset Parkinson's disease from MedGenome, in collaboration with Denali Therapeutics, USA and PRAI (Parkinson's Research Alliance of India), the data was generated for about 700 PD cases using 3 methods: 100 30x whole genomes, 600 whole exomes. Whole genome genotype data was also generated. This involved lot of operational efforts, time and cost. BGE is the one-stop solution for such clinical research studies. Now with the OneXI pipeline, we can impute low pass whole genome data with a better accuracy compared to that of genotype arrays.

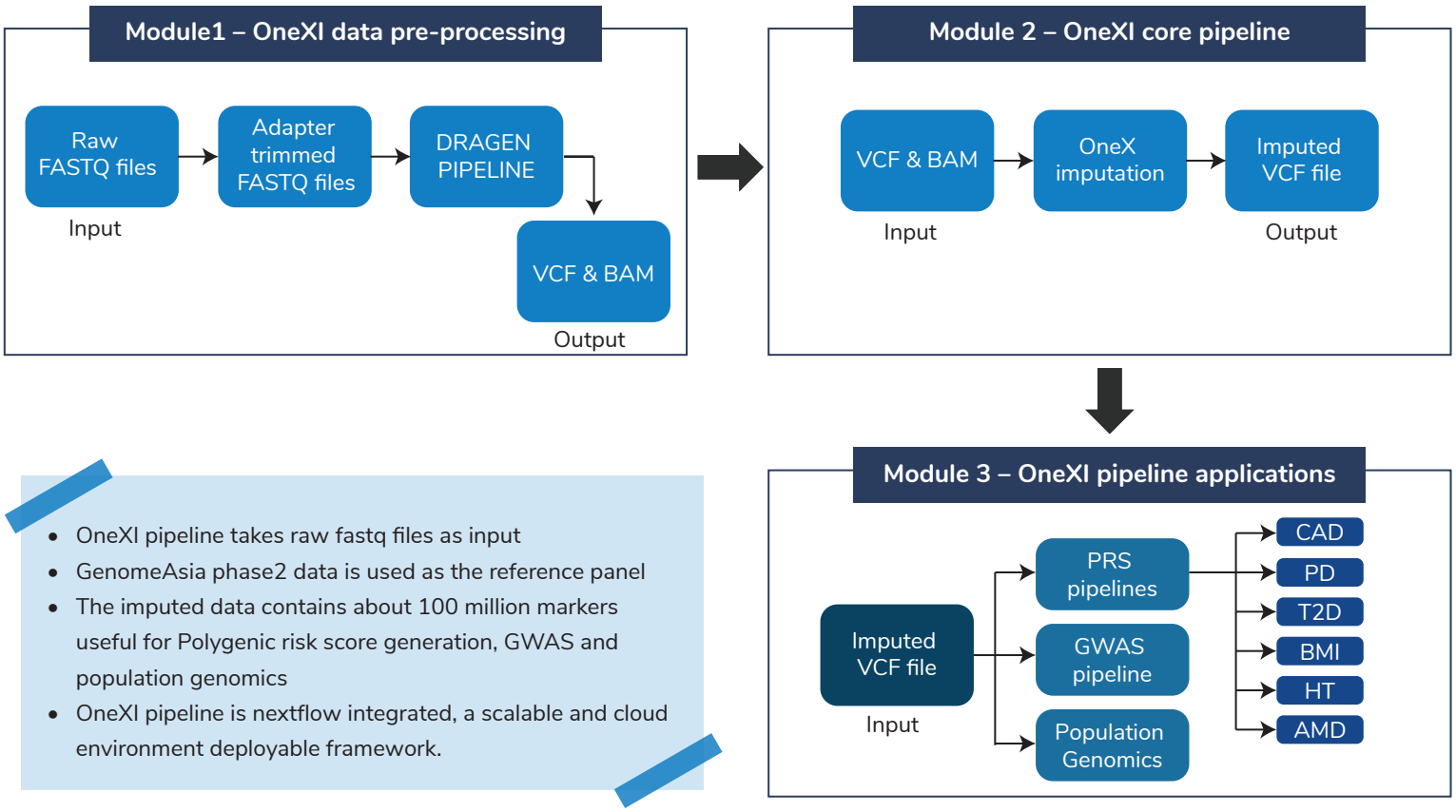


Fig.3: Nextflow enabled OneXI pipeline modules

OneXI pipeline is developed in-house utilizing the latest published methods, it optimised and validated in South Asian datasets. The pipeline has 3 modules. The first one is the data preprocessing step in which takes the raw fastq file as input which is processing through the DRAGEN, a hardware accelerated data analysis platform from Illumina which the bioinformatics team uses presently for processing whole genomes. The output from module 1 is the compressed alignment file (bam) and variant file (VCF). The module 2 of OneXI pipeline takes these files as input does the phasing and haploid imputation based on GenomeAsia phase 2 reference haplotypes. The module 3 of OneXI pipeline is an application layer where the output of module 2 can be plugged into applications such as Polygenic risk score predictions, GWAS, Population genome analysis etc.

The OneXI pipeline is nextflow integrated with for scalable and portable application that can be deployed in a cloud environment or can be run in a local parallel computing environment.

Low-pass imputed data accuracy benchmarking with Genotyping arrays

From the published Young-Onset Parkinson's disease study, we selected 24 samples where we had 30x whole genomes, and genotype data was generated using GSAv3 and SARGAM arrays. The WGS down - sampled data was generated with various coverage such as 1x and 0.5x and 0.25x. The low-pass data were imputed using OneXI pipeline and genotype data were imputed using the regular genotype imputation pipeline. The imputation accuracy of genotype arrays and 1xWGS were compared at various allele frequencies.

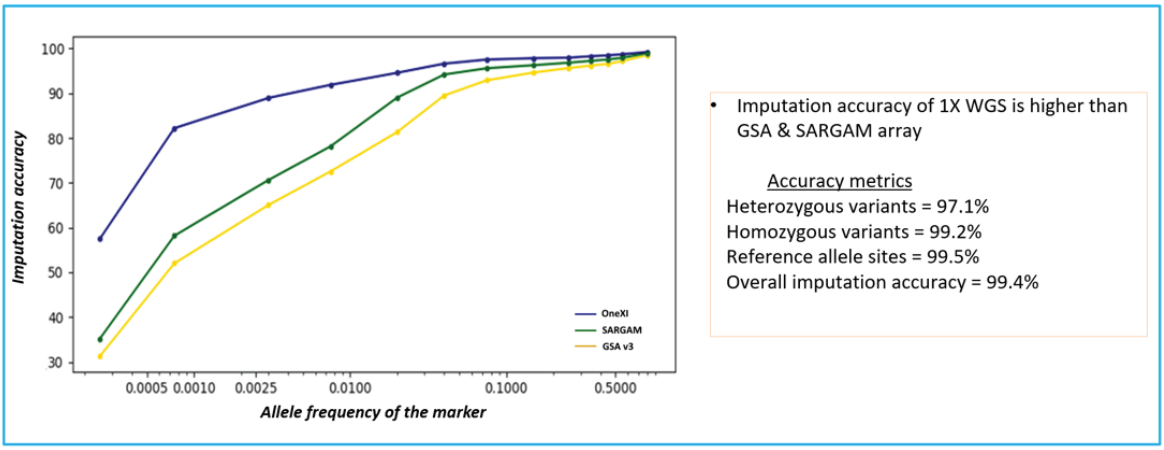
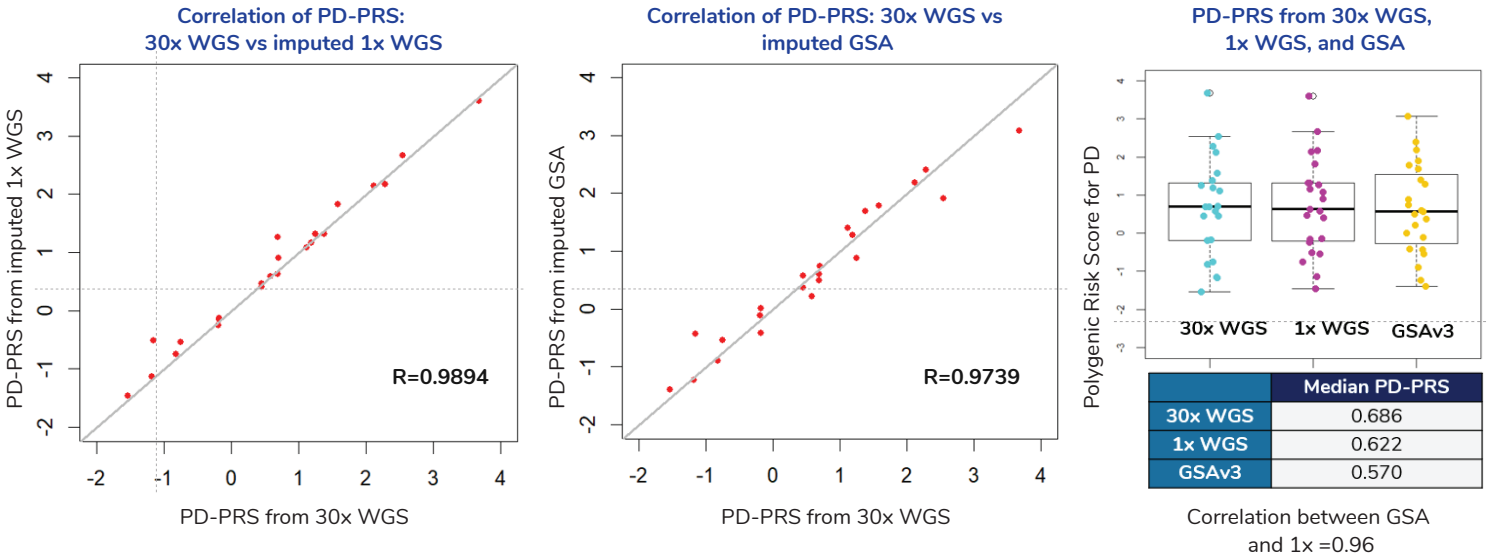


Fig.4: Accuracy benchmarking of low pass WGS imputed OneXI and genotyping arrays

The imputation accuracy was found highest in imputed 1x WGS followed by SARGAM array and GSA v3. As the test samples are of South Asian origin the imputation accuracy is expected to have been better in SARGAM array compared to GSA v3. Here, 30x WGS data was used as the gold-standard reference data. The marker level accuracy was also separately calculated for Heterozygous (97.09%) , Homozygous (99.29%), and Reference (99.56%) genotypes. Overall the median sample wise concordance was found to be 99.55%.

Application level validation of OneXI pipeline

As the samples chosen for validations was from Parkinson's disease (PD) study, we generated PD-PRS for the samples using 30x WGS, 1x WGS and GSA for the same 24 samples. The PD-PRS generated from GSAv3 and 1x WGS highly correlating with the 30xWGS (0.97 and 0.98 respectively). A slight improvement in the median PD-PRS was observed in 1x WGS compared to that generated from GSAv3, when compared to the 30x WGS.



	Median PD-PRS
30x WGS	0.686
1x WGS	0.622
GSAv3	0.570

Correlation between GSA and 1x =0.96

Fig.5: PRS of Parkinson's disease samples of data generated from 30x WGS, OneXI and GSA

Conclusion

With the bioinformatics solution such as OneXI, the low-pass whole genome sequencing can now replace genotype arrays for genomic studies involving PRS, GWAS and population genomics. The blended genome-exome (BGE) can be offered as a one-stop solution for clinical research studies where clinical grade variants reporting as well as whole genome analysis can be performed using the OneXI pipeline and improving operational efficiency, accuracy, scalability in a cost-effective manner.

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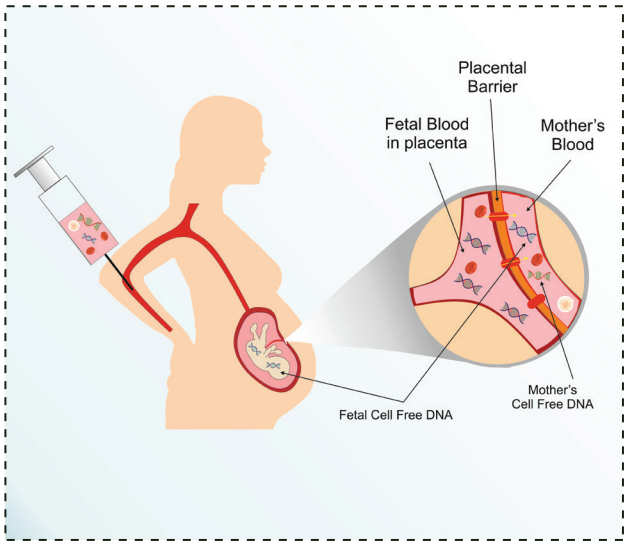
Non-Invasive Prenatal Testing: Interesting case scenarios

Angela Devanboo
Senior Genome Analyst & Genetic Counsellor

The introduction of Non-invasive Prenatal Testing (NIPT) in prenatal care has revolutionized the field of fetal medicine worldwide. In 1997, Dennis Lo and his colleagues detected the presence of cell free fetal DNA circulating in the maternal blood. NIPT utilizes the cell free fetal DNA originating from the placenta to detect chromosomal abnormality in the fetus. In 2011, NIPT was introduced in clinical practice and since then, the clinical utility of NIPT has been evaluated and scrutinized worldwide.



NIPT has been established to be the most sensitive screening test compared to conventional screening methods for screening common chromosomal aneuploidies such as Trisomies 21, 18 and 13 in the fetus. The non - invasive nature of the test, high sensitivity & specificity, low false positive rates and high negative predictive values are the reasons why this test is most preferred by both the clinicians and pregnant women. International committees such as the American College of Medical Genetics and Genomics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) agree that this cell-free DNA - based test is the most sensitive and specific screening test and is offered to all pregnant women regardless of age.

NIPT employs different technologies which either have a targeted or genome-wide approach. Based on the technology, the test can detect whole chromosomal abnormalities, sub - chromosomal abnormalities, microdeletions/duplications and fetal genotyping in Rh - negative mothers. Currently, research is being carried out to extend the use of NIPT or in this case Non - invasive prenatal diagnosis (NIPD) in detecting single nucleotide variations in the fetus.

The implementation of NIPT in all pregnancies irrespective of the background risk has proven to be beneficial for good pregnancy outcome. However, some challenges and limitations need to be considered. Though the concordance between the NIPT result and the fetal genotypic status is high, discordant NIPT results have been known and reported. The discordant results can be attributed to certain biological reasons namely, confined placental mosaicism, twin demise, maternal chromosomal mosaicism, true fetal mosaicism and maternal malignancy. Therefore, high-risk NIPT results should always be investigated further.

NIPT at MedGenome

MedGenome Labs was the first laboratory to introduce end-to-end NIPT in India in the year 2015. We were also the first to validate NIPT in Indian population. MedGenome has experience in handling two technologies i.e. target based NIPT (SNP-based NIPT) and genome-wide based NIPT (Counting based NIPT). Currently, we offer Claria NIPT i.e. Illumina's VeriSeq v2 (Counting based NIPT) which provides a comprehensive view of fetal genome.

Claria NIPT can be offered to pregnant women with gestational age of 10 weeks and above. The test can be performed on singleton, twins and surrogate pregnancies. Since the launch of Claria NIPT in 2019, we have encountered a few interesting clinical case scenarios wherein the maternal background influenced the NIPT results. This is because the cfDNA present in the plasma of pregnant women contains both placental, which is considered fetal and maternal DNA.

	Case 1	Case 2	Case 3
Maternal age	23 years	30 years	36 years
Marriage	Non consanguineous	Non consanguineous	Non consanguineous
Gravida	Primi	Primi	Primi
Mode of conception	Spontaneous	Spontaneous	- - - - -
GA	18 weeks	18 weeks	16 weeks
Clinical indication	The mother herself has Down Syndrome	1:27 risk for T21 on DMT & 1:161 risk for T21 on combined FTS	- - - - -
NIPT result	High risk for Trisomy 21, Fetal fraction - 8.2%	Fetal fraction - 7.4%, Common Trisomies - Low Risk & Sex chromosomal aneuploidies - Inconclusive	Trisomies in chromosomes 2, 5, 9, 14 and Monosomies in chromosomes 1, 4, 6, 10, 15, 18, Fetal fraction - 5.9%
Confirmatory tests	FISH & KT - Normal set of chromosomes	QF - PCR & CMA done on the amniotic fluid sample - Normal chromosomes QF - PCR & CMA done on the mother - Mosaic XXX (70% of cells has XXX)	- - - - -
Antenatal history	- - - - -	- - - - -	Normal first-trimester scan, intermediate risk on Double Marker Screening, & 2 soft markers detected on anomaly scan
Clinical presentation of the mother	- - - - -	- - - - -	Fever & cough for 4 weeks. Suspected of bronchopulmonary aspergillosis. Did not respond to broad - spectrum antibiotics
Investigations done	- - - - -	- - - - -	Chest X-ray - no definitive lesion detected CT Chest (with abdominal shield) - a few enlarged mediastinal lymph nodes Endobronchial ultrasound-guided biopsy (EBUS) - reported necrotic cells (started on antitubercular therapy) CT-guided biopsy (done based on NIPT results) from the enlarged mediastinal lymph nodes - confirmed Hodgkin's lymphoma

Cases 1

Demonstrates the importance of genetic counselling while offering NIPT to the patient. During the pre-test genetic counselling, the possibility of maternal genetic background influencing the NIPT result was discussed, and that high-risk result should be investigated further. The patient insisted on NIPT due to the non - invasive nature of the test. As expected, the NIPT result was high risk for Trisomy 21. Since the significance of the confirmatory testing was discussed, the pregnancy was investigated further i.e. amniocentesis followed by FISH & KT.

Cases 2 & 3

Illustrate that in certain scenarios, non-reportable or unusual NIPT results can lead to an incidental finding of a maternal sex chromosomal abnormality (SCA) or maternal malignancy respectively. Case 2 further highlights the importance of careful analysis when reporting results for SCAs on NIPT. In recent years, the possible detection of incidental maternal malignancy through genome-wide NIPT has been gaining attention worldwide. Reporting such unusual NIPT results as seen in case 3 can help asymptomatic pregnant women by offering them early intervention leading to a good prognosis.

In conclusion, NIPT is a highly sensitive test and any unusual results on NIPT require proper and thorough investigations before considering the option of termination of pregnancy. Furthermore, it is imperative that the expectant couple undergoes a comprehensive pre-test and post-test genetic counselling while offering NIPT. Topics such as the type of NIPT results, the possibility of a repeat sample along with the pros and cons of the test should be discussed with the patient. The importance of further investigations in case of high-risk or unusual NIPT results should be emphasized before taking any irreversible clinical decisions.

Sneak Peek into the World of Science

Complementing strides made with short-reads with PacBio long-read sequencing

Michelle Vierra Balakrishnan
Associate Director
Product and Marketing
MedGenome (USA)

Short-read sequencing technologies have, without a doubt, revolutionized genomics. The ability to look at genetic variants at the base pair level and compare gene expression levels between normal and other conditions has made it possible to diagnose more diseases, develop more robust crops, and protect the biodiversity here on Earth.

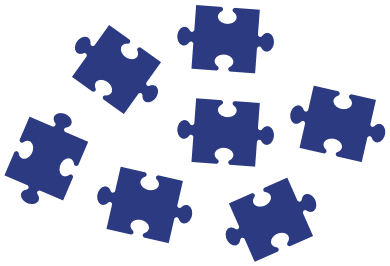
However, short reads are inherently limited and often fall short in fully characterizing complex genomes and transcriptomes. Short reads struggle to resolve repetitive regions, assemble complex structural variants, and fully capture isoform diversity. This is where the power of PacBio long - read sequencing comes into play.

PacBio HiFi sequencing delivers highly accurate long reads, enabling us to more fully profile not only the bases involved, but the context in which genetic variation exists. The ability to sequence every base in a genome or transcriptome opens doors previously blocked by extreme GC content, repeat rich regions, and long stretches of homozygosity. And as scientists dedicated to making the world a healthier place, MedGenome now offers researchers an unparalleled ability to delve deeper into the intricacies of genomes and transcriptomes with both short - read and long - read sequencing solutions.

Short-read sequencing

Smaller pieces requiring more context for connecting pieces correctly

Long-read sequencing



Larger pieces give additional context for connecting pieces correctly

A comprehensive suite of PacBio solutions

1. **De novo genome assembly and annotation solution:**
    - Generating high-quality, contiguous genome assemblies for any organism, regardless of complexity.
    - Identifying and annotating genes, isoforms, and regulatory elements with greater accuracy than ever before.
    - Understanding the complete genomic blueprint of an organism, crucial for evolutionary studies, conservation efforts, and agricultural advancement.

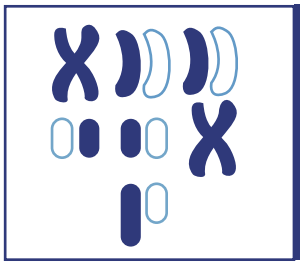
2. Comprehensive human variant detection solution:

- Detecting all types of genetic variation, including SNVs, Indels, SVs, and variants in complex regions, with high confidence.
- Providing haplotype-resolved variant information, crucial for understanding inheritance patterns and disease mechanisms.
- Enabling more accurate diagnosis, personalized treatment strategies, and a deeper understanding of human health and disease.

3. Full-Length RNA sequencing solution:

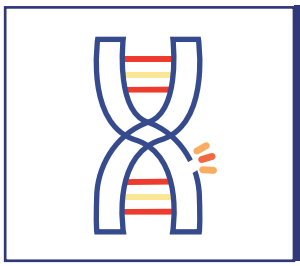
- Capturing the complete length of RNA transcripts, providing a comprehensive view of isoform diversity.
- Identifying novel transcripts and fusion genes, crucial for understanding disease mechanisms and identifying potential drug targets.
- Offering both bulk and single-cell full-length RNA sequencing, enabling researchers to dissect cellular heterogeneity and unravel the complexities of gene expression at single - cell resolution.

Combined capabilities – your omics superpower



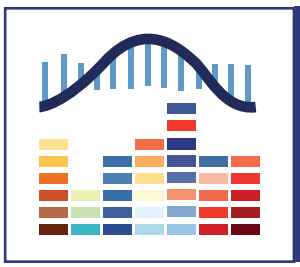
Genome assembly and annotation

Long reads provide a high-quality reference genome and short reads enable population scale screening



Comprehensive variant detection

Long reads detect large structural rearrangements and repeat expansions and short reads capture SNVs



Transcriptome characterization

Long reads detect individual isoforms uniquely and short reads quantify expression

From strategy to publication: crafting omic insights with your research in mind

At MedGenome, we believe in the power of comprehensive genomic exploration. That's why we offer both short-read and PacBio long-read sequencing services, allowing you to choose the best strategy for your specific needs or combine both for unparalleled insights. Whether you're assembling complex genomes, characterizing cryptic genetic variation, or unraveling the complexities of the transcriptome, our expert team is here to guide you every step of the way. Contact us today to discuss how our comprehensive suite of sequencing solutions can empower your next breakthrough discovery.

Case study Liquid Biopsy

MedGenome laboratory developed OncoTrack Advance **Liquid Biopsy** Test identifies

FGFR2::WAC Fusion

A Case of Cholangiocarcinoma

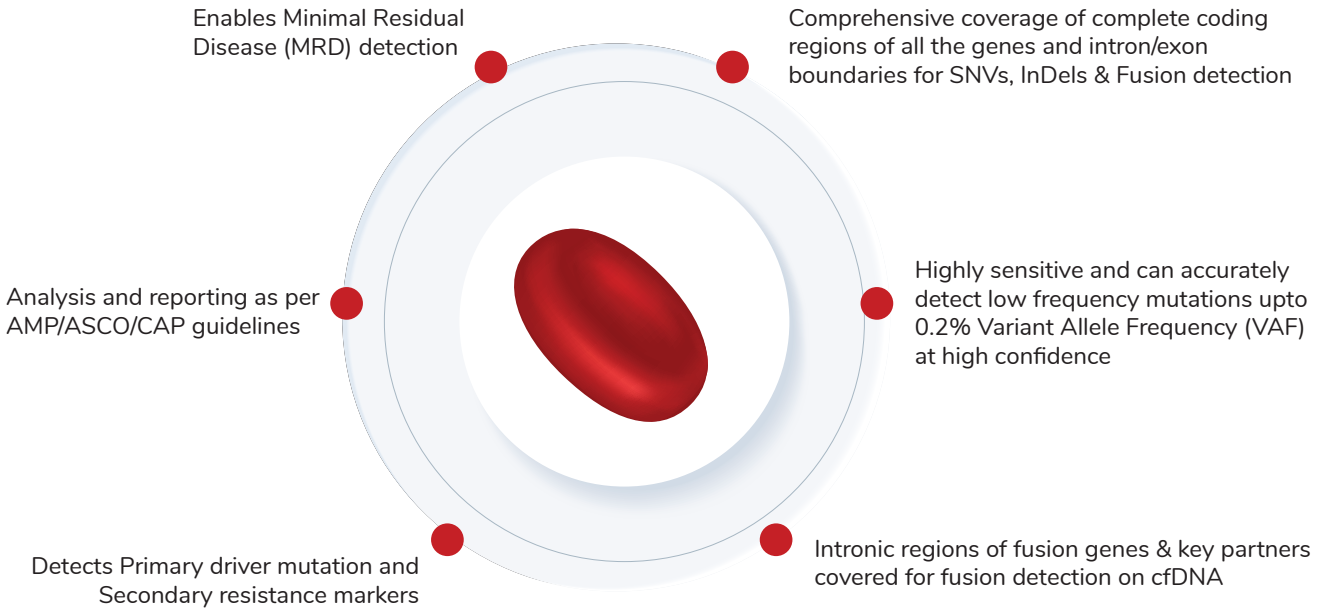
A 34-year-old male diagnosed with intrahepatic cholangiocarcinoma (ICC), where tissue biopsy was unavailable and genomic profiling was conducted on liquid biopsy

Considering ICC's rarity and poor prognosis, comprehensive genomic analysis was employed to identify potential molecular targets with diagnostic, prognostic, and therapeutic implications for precision medicine

Next-Generation Sequencing (NGS) based Liquid Biopsy Test was used to identify somatic alterations in the patient's blood plasma. Peripheral blood samples were collected using streck tubes, and circulating cell - free DNA (cfDNA) was isolated from the plasma

Test Performed

OncoTrack Advance Liquid Biopsy Test, tumor agnostic assay covering 117 Pan cancer actionable genes as recommended by guidelines (FDA, NCCN, ASCO, ESMO etc.) for diagnostic and prognostic (SNVs, InDels & 15 genes for fusion).

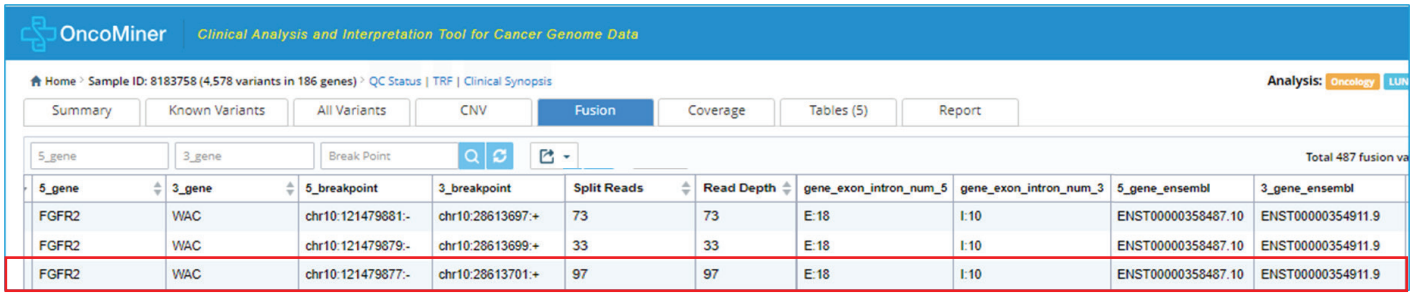


Quality Control passed UMI - libraries undergo sequencing on an Illumina platform at a raw depth of >20,000X. Sequences are processed using a customized and validated analysis pipeline designed to accurately detect all genomic alterations (SNVs, InDels, and Fusions).

Analysis & Interpretation through Proprietary Software Platform

Variants are annotated using an in - house annotation pipeline, and the annotated varimat file is analyzed by genomic experts using **Oncominer, a platform for interpretation and reporting developed at MedGenome Labs**.

Reportable genomic alterations and fusions are prioritized, classified, and reported following AMP - ASCO - CAP and NCCN guidelines.



Analysis & interpretation using proprietary variant interpretation & analysis software - Oncominer

Clinical Report

Result - POSITIVE

CLINICALLY RELEVANT VARIANT/S DETECTED

AMP Classification^	CDS variant details	Interpretation	Treatment Recommendations	$Treatment Response
***FGFR2/WAC* (FUSION)** Total Read depth - 73x				
Tier I	NA	Oncogenic	Futibatinib and Pemigatinib	Effective

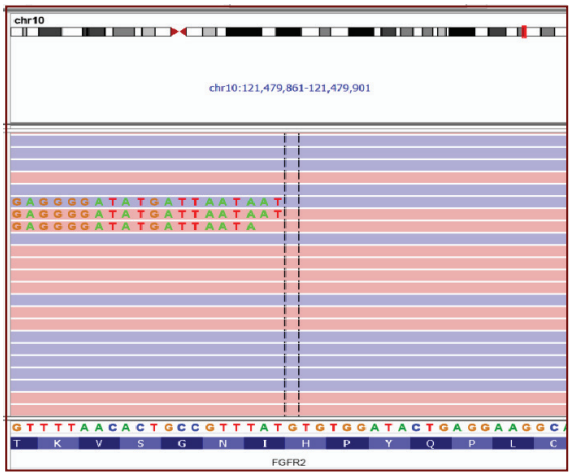
This gentleman with unresectable intrahepatic cholangiocarcinoma (ICC) received Gemcitabine + Oxaliplatin treatment but experienced disease progression. This test identified an *FGFR2*::*WAC* fusion at 73X depth.

FGFR2 fusions occur in up to 14% of ICC cases. Activation of *FGFR2* typically involves *FGF* - induced receptor dimerization. In fusion events involving *FGFR2*, the gene acts as the 5' fusion partner, introducing additional dimerization domains from 3' fusion partners, which can affect downstream signaling pathways. In this case, intact dimerization domains were observed.

The Food and Drug Administration (FDA) has granted accelerated approval to futibatinib and pemigatinib for adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (*FGFR2*) gene fusions or other rearrangements.

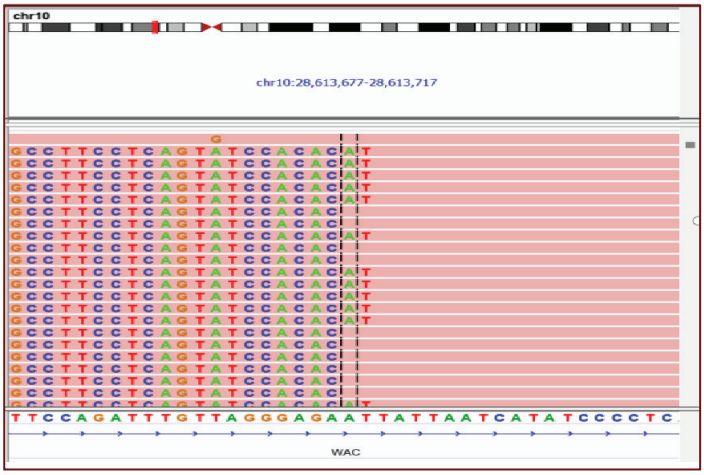
FGFR2

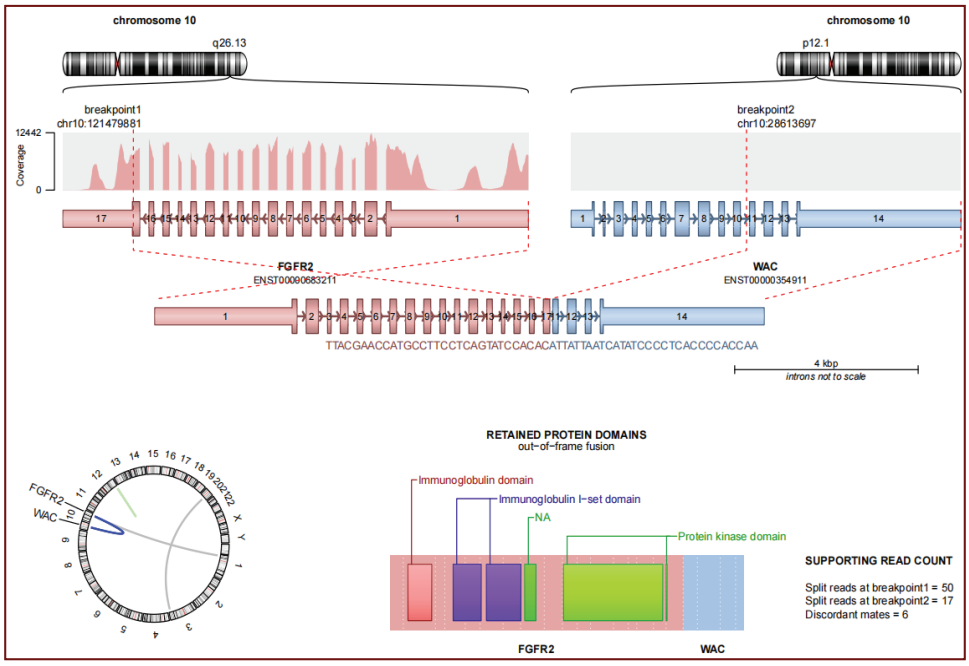
5'Chromosome Breakpoint (hg38):
chr10:121479881:/ Exon18



WAC

3'Chromosome Breakpoint (hg38):
chr10:28613697:+/Intron10





Arriba tool verification of *FGFR2*::*WAC* fusion which was found to be in-frame

This clinical case illustrates the depth of investigation necessary to fully characterize the functional significance of the breadth of alterations identified through genomic analysis.

This case was referred by **Dr. Senthil J. Rajappa**, HOD, Medical Oncology, Basavatarakam Indo American Cancer Hospital & Research Institute, Hyderabad

Case study Lung Cancer

Lung Cancer Panel identifies rare ALK fusion

PRKAR1A::ALK

46-year-old male, presented with right pleural effusion, diagnosed with adenocarcinoma of lung as per biopsy examination in March 2023

Biopsy sample was sent for Next Generation Sequencing (NGS) based Lung Tumor panel to identify actionable biomarkers

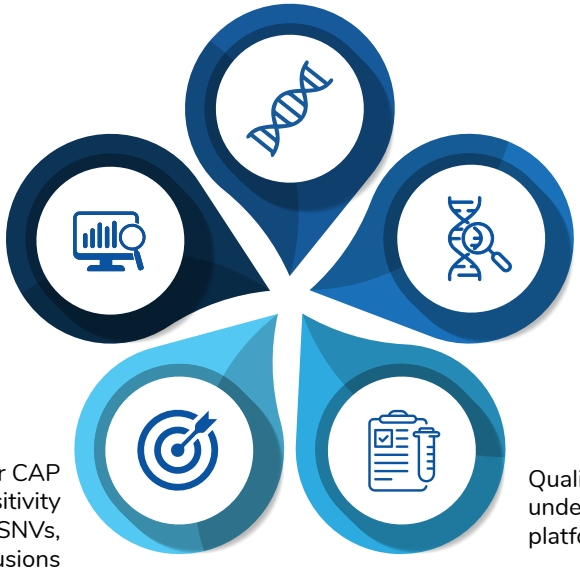
Testing was carried to screen for SNVs, InDels, CNVs and Fusions in 18 genes

Test Performed

NGS based lung cancer tumor panel which detects SNVs, InDels, CNVs and Fusions in 18 genes.

Comprehensive coverage of complete coding regions and intron / exon boundaries of the included genes *EGFR, KRAS, BRAF, ERBB2, MET, RET, ALK, ROS1, NTRK1/2/3, KEAP1, MAP2K1, NRAS, PIK3CA, STK11, TP53, FGFR3.*

CNV detection in *MET, ERBB2* & *EGFR* WITH >90% sensitivity



Analysis and reporting as per AMP / ASCO / CAP guidelines

Fusions and splice variants assessed via RNA sequencing, known / unknown partners are detected

Well validated as per CAP guidelines; 100% sensitivity and specificity for SNVs, InDels, CNVs and Fusions

Quality Control passed UMI - libraries undergo sequencing on an Illumina platform at depth of >250X

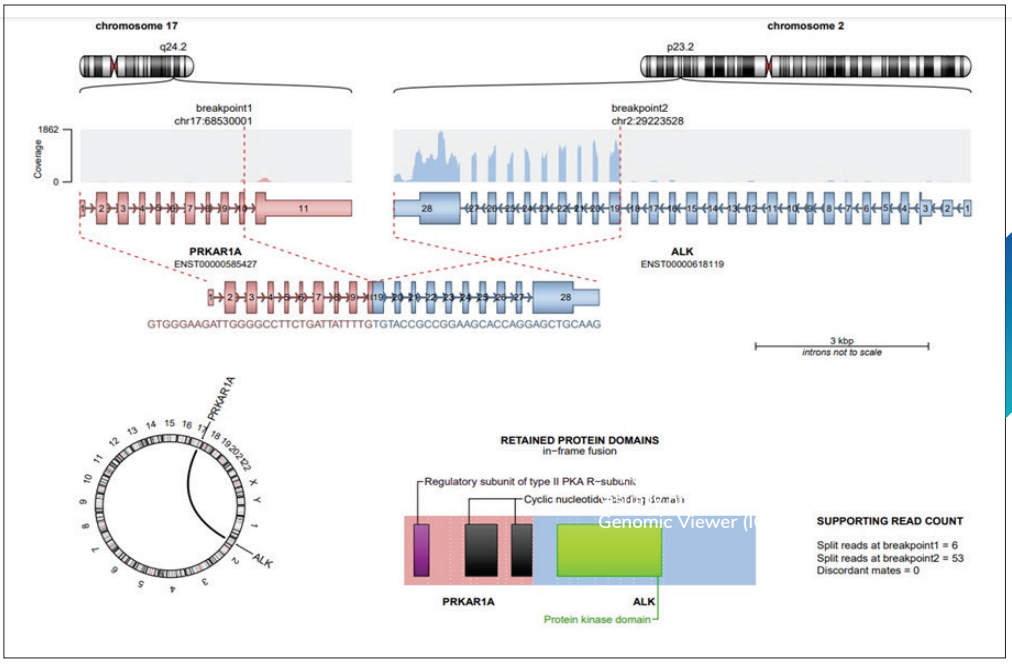
This case was referred by **Dr. B S Ankit** (MBBS, MD, DM Medical Oncology), Consultant Medical Oncology, HCG Cancer Centre, Jaipur

Test results

NGS based lung cancer tumor panel which detects SNVs, InDels, CNVs and Fusions in 18 genes.

PRKAR1A::*ALK* fusion detected

Result – POSTIVE CLINICALLY RELEVANT VARAINT/S DETECTED				
AMP Classification[^]	CDS variant details	Interpretation	Treatment Recommendations	[$]Treatment Response
PRKAR1A/ALK(FUSION) Total Read depth - 59x				
Tier 1	NA	Oncogenic	Sensitive to ALK TKIs	Effective
PD-L1 IHC (SP263)- 2% TPS				



Fusion is confirmed to be in-frame

Fusion is verified visually on Integrative Genomic Viewer (IGV)

The junction sequence blast results matched with *PRKAR1A* (exon 10) and *ALK* (exon 20)

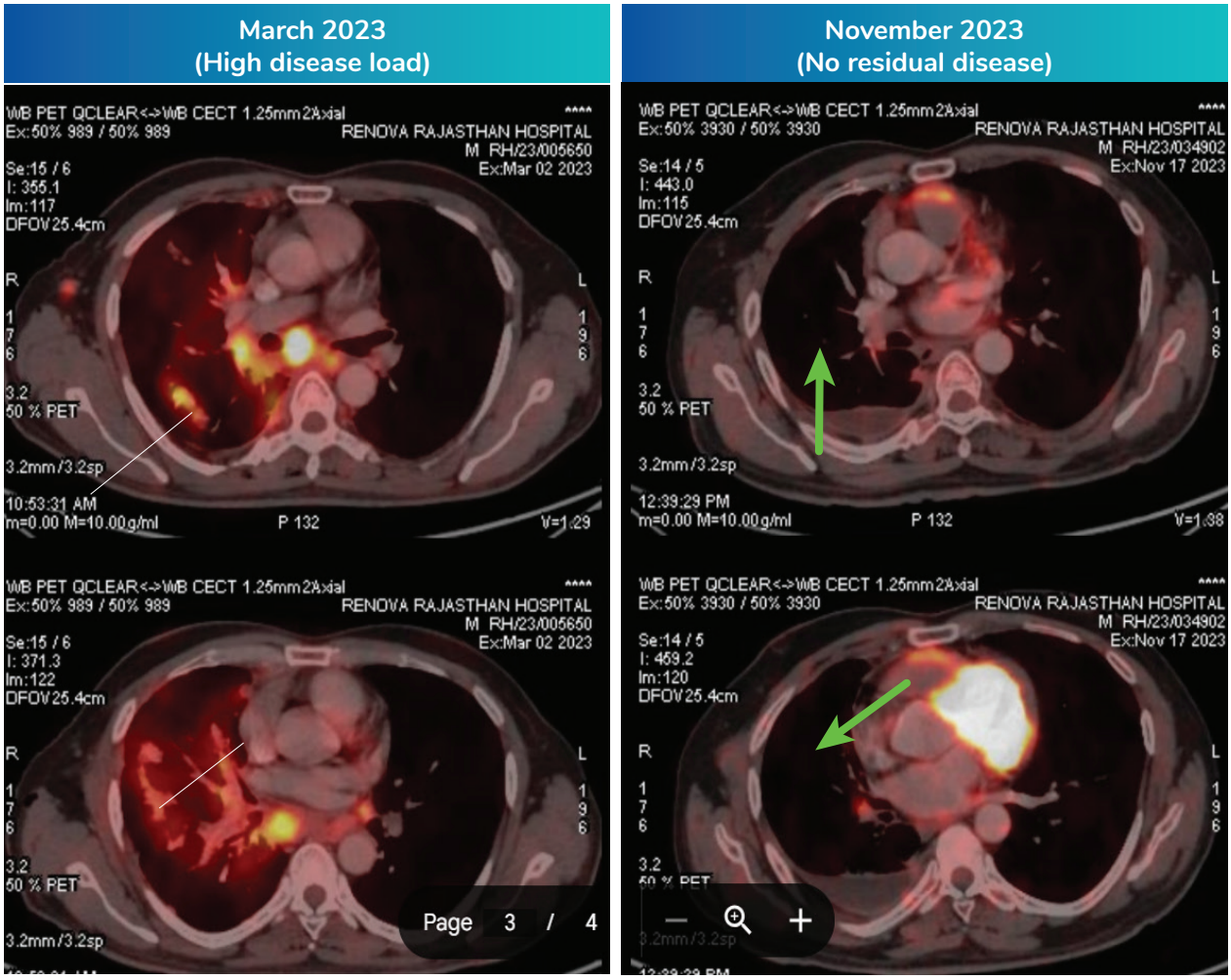
Treatment selection based on *ALK* fusion partners

- All Tyrosine Kinase Inhibitors do not show the same efficacy for different *ALK* - fusion partners.
- 5' *ALK* - fusion partners affects the biochemical and cellular properties of the *ALK* fusion protein which includes kinase activity, protein stability & transformative potential thus affecting the response to *ALK inhibitors*.
- **Lorlatinib was administered to this patient as it was reported to be most effective in literature for *PRKAR1A::ALK* fusion**

Ref: Mol Cancer Res. 2018;16(11):1724-1736. doi:10.1158/1541-7786.MCR-18-0171

Clinical response

PET scan comparison before and after Lorlatinib treatment



March 2024 - PET findings (No Residual Disease)

- Non FDG avid mild soft tissue thickening in peribronchial region, along right lower lobe bronchus - likely burnout disease
- FDG avid multiple subcentimeter sized lymph nodes in right axillary region. Most of them having preserved fatty hilum - infective / inflammatory etiology more likely. However keep in close follow up.
- Loculated right mild pleural effusion with pleural thickening is sorted
- There is no other metabolically active lesion noted elsewhere in the whole-body PETCT survey

In comparison to previous PETCT dated 17/11/2023

- Right axillary lymphadenopathy increased in metabolic activity
- Otherwise no significant interval change noted
- Clinical histopathological correlation is required

Patient Outcome Journey

Patient diagnosed with stage 4 ADCC NSCLC in Mar 2023 showing right pleural effusion

Tumor biopsy was sent to perform 18 gene lung tumor panel by NGS *PD-L1* testing at MedGenome Labs

PRKARIA/ALK fusion detected
PD-L1:2% TPS
Loraltinib TKI was selected

On follow - up in Nov 2023 & Mar 2024, patient has shown complete response to Loraltinib and has no residual disease

This clinical case illustrates the diagnostic yield of MedGenome lung tumor panel by NGS. A rare *ALK* was identified and specific *ALK* inhibitor was used for treatment which showed positive response. This establishes functional and clinical benefit through comprehensive approach.

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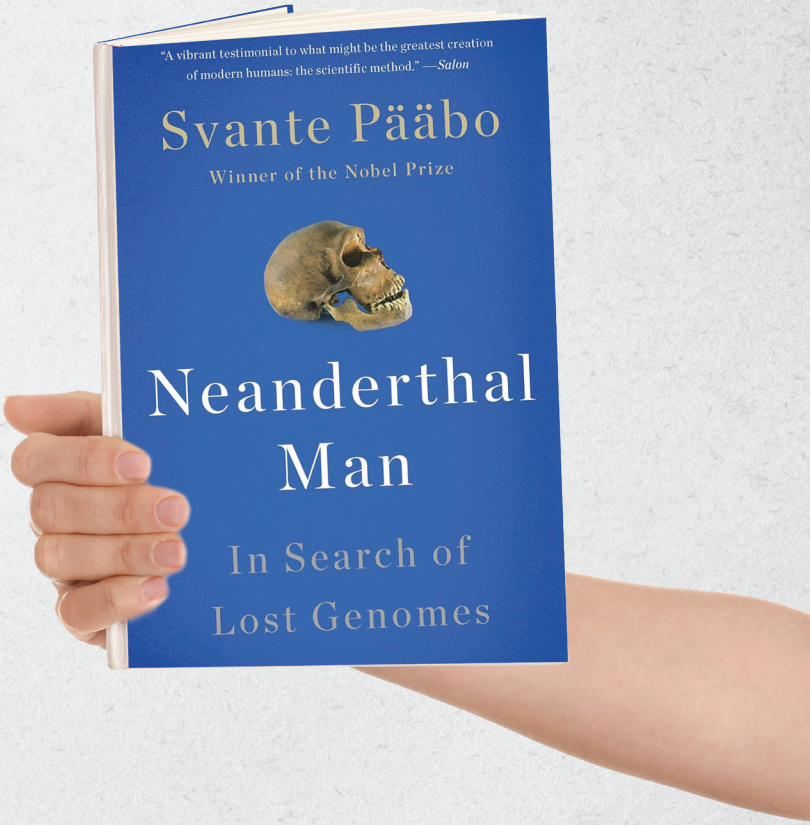
Book Review

By

Avinash Pradhan, PhD
Associate Scientist

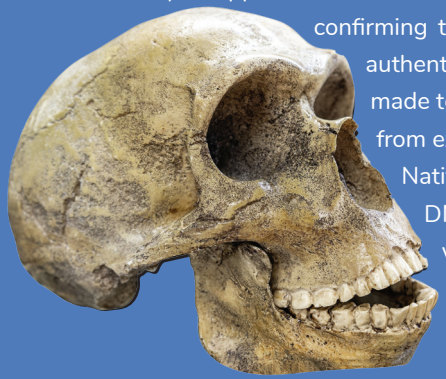


The book describes Pääbo's research into the DNA of Neanderthals, extinct hominins that lived across much of Europe and the Middle East. It is written in the style of a memoir, combining scientific findings with personal anecdotes.

On 12 February 2009, researchers at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, led by Svante Pääbo, announced in a press conference that they had completed a first draft of the Neanderthal genome, the first to be sequenced from an extinct type of human. This book is Pääbo's account of how that remarkable scientific achievement came about. But it is much more than that. It is also the brilliantly written account of the founding of an entirely new scientific discipline (paleogenomics), an instructive case study of the power of the scientific method and the story of Pääbo's own scientific career with all its twists, turns and serendipities, along with occasional glimpses of the sometimes happy but often complicated and messy personal life of its author. This review will focus on Pääbo's scientific story.

Chapter 1 begins with the moment that Pääbo and his team realized they had managed to retrieve mitochondrial DNA (mtDNA) from a Neanderthal bone. We are then introduced to the Neanderthals and the questions that arose concerning their relationship to modern humans following their discovery in the nineteenth century. The author explains the problem of post-mortem DNA degradation, meaning that very little DNA is present in most ancient samples, and the dramatic advance represented by the development in 1983 of the polymerase chain reaction (PCR). This technique allowed a single piece of DNA to be "amplified", generating thousands to millions of copies. However, one of the biggest challenges in ancient DNA studies is minimizing the contamination of samples, thus ensuring that what is being amplified is DNA endogenous to the individual or organism being studied. The problem of contamination becomes a recurring theme of the book and serves to highlight just what an achievement the sequencing of the Neanderthal genome really was.

In Chapter 2 the reader is taken back to the earliest stages of Pääbo's scientific career, when he was a medical student at the University of Uppsala in Sweden. His interest in ancient DNA began as a secretive sideline, with "proof-of-principle. experiments confirming that DNA could be extracted from artificially mummified calf liver and subsequently from authentic Egyptian mummies. During Pääbo's time as a postdoc at UC Berkeley improvements were made to the PCR method, and Chapter 3 charts his successful application of the method to samples from extinct animals (the quagga and the thylacine), to museum specimens of kangaroo rats and to Native American remains. Pääbo also notes his growing awareness of the limitations of ancient DNA preservation and the techniques for extracting and studying it. In the early 1990s Pääbo was increasingly frustrated by "lashy" publications in high-profile journals claiming, for instance, that DNA had been retrieved from Miocene magnolia leaves, from insects in Dominican and Lebanese amber, and even from dinosaur bones.



In Chapter 4, he explains his dismissal of these claims of “super - old” or “antediluvian” DNA, especially when attempts to replicate the findings under more rigorous laboratory conditions proved to be a failure. He and his colleagues introduced what they called “criteria of authenticity”, procedures that had to be carried out before a DNA sequence obtained by PCR could be regarded as truly old. Eventually, Pääbo and his team decided to ignore the dubious results and concentrate on their own work. The next chapter describes Pääbo’s sequencing of the mtDNA of the extinct giant ground sloth, in order to elucidate its evolutionary relationships with modern tree-dwelling sloths. The field of ancient DNA studies had become sufficiently well - established by the mid - 1990s that Pääbo could return to the challenge of human remains, applying sequencing methods to Oetzi the Ice Man and to mummies from the American southwest.

Chapter 5 concludes with Ralf Schmitz of the Bonn Museum in Germany agreeing to provide a small piece of the right upper arm bone of the Neanderthal type specimen, from which the groundbreaking mtDNA sequence was retrieved. Chapter 6 resumes the story following publication of the Neanderthal mtDNA sequence. An immediate priority was to sequence mtDNA from other Neanderthals to establish how much mtDNA variation was present in the group as a whole. Small samples of Neanderthal and cave bear bones from the Vindija cave in northwestern Croatia were obtained for this purpose. However, Pääbo and his colleagues were beaten to publication by a UK-based group reporting a second Neanderthal mtDNA sequence from Mezmaiskaya cave in the northern Caucasus. With three sequences now available, it became clear that Neanderthal mtDNA showed little variation, suggesting that the Neanderthals, like modern humans, had expanded from a small population.

Pääbo tells the story in Chapter 7 of how he was invited by the Max Planck Society to set up a new evolutionary anthropology institute in Leipzig. The new facility included custom-designed clean rooms for ancient DNA extractions. Chapter 8 recounts the reactions of multi regionalists to the Neanderthal mtDNA results, which broadly supported the out-of-Africa model of modern human origins. In particular, Erik Trinkaus argued that the mtDNA results might be biased if DNA sequences resembling those of modern humans were erroneously discarded as contaminants. This chapter shows how Pääbo’s team was able to demonstrate that Trinkaus’ concerns were misplaced. The focus then shifts in Chapter 9 towards the need to sequence the Neanderthal nuclear genome. Initial attempts were made to extract nuclear DNA from the Vindija cave bear bones, rather than the scarcer and more valuable Neanderthal bones. However, these efforts failed. Success was achieved with Pleistocene mammoths recovered from the Alaskan permafrost, but this was discouraging because there were no Neanderthals preserved in permafrost! Despite these setbacks, Pääbo was convinced that nuclear DNA had to be present in Neanderthal bones even if the PCR could not retrieve it. Two alternative approaches presented themselves: second-generation sequencing and the cloning of DNA in bacteria. Chapter 10 outlines the decision to test both approaches head to head using Neanderthal DNA. To this end, collaborations were established with Michael Egholm of biotech company 454 Life Sciences and Eddy Rubin of the Lawrence Berkeley National Laboratory in California. The chapter concludes with Pääbo setting out a “roadmap” for sequencing the entire Neanderthal genome at the Cold Spring Harbor genome meeting in 2006. Chapter 11 describes Pääbo’s dawning realization that the bacterial cloning method was too inefficient to get the project done and the termination of his collaboration with Eddy Rubin. Pääbo nevertheless boldly promised at a press conference in July 2006 to sequence the entire Neanderthal genome within two years. The urgent quest for more and better Neanderthal bones is the theme of Chapter 12. The right upper arm bone from the Neander Valley had yielded 4% Neanderthal DNA, and it was hoped that other bones might yield as much or even more.

However, analyses of additional samples from the Neander Valley and other sites did not prove encouraging. Yields from these bones ranged from 0.1 to 1.5 percent Neanderthal DNA. Then a developing collaboration with the Croatian Academy of Sciences and Arts led to the acquisition of eight more bones from Vindija. Nearly all contained Neanderthal DNA; three yielded more than 1% Neanderthal DNA and one almost 3%. Every step in the laboratory procedures was re - evaluated to minimize the loss of DNA during processing. Chapter 13 explains that the result was a “game - changing advance” with the development of a protocol that was several hundred times more efficient than the previous one. Another significant advance was the use of restriction enzymes to separate bacterial DNA in the bone extracts from endogenous Neanderthal DNA. This increased the yield of Neanderthal DNA from 4% to 20%. Chapter 14 moves on to the next challenge the team faced: mapping the genome by matching the short Neanderthal DNA fragments to a human reference sequence. This required the development of mapping algorithms that struck a careful balance between being too stringent (which would make the Neanderthal genome look too similar to the modern genome) and too permissive (which would make it look too different to the modern genome). Next, the mapping algorithms were tested by sequencing and mapping all the nucleotides in the Neanderthal mtDNA (Chapter 15). However, the accumulation of nuclear DNA sequences was going much more slowly than hoped, and in mid-2008 this led to the termination of the collaboration with 454 Life Sciences.

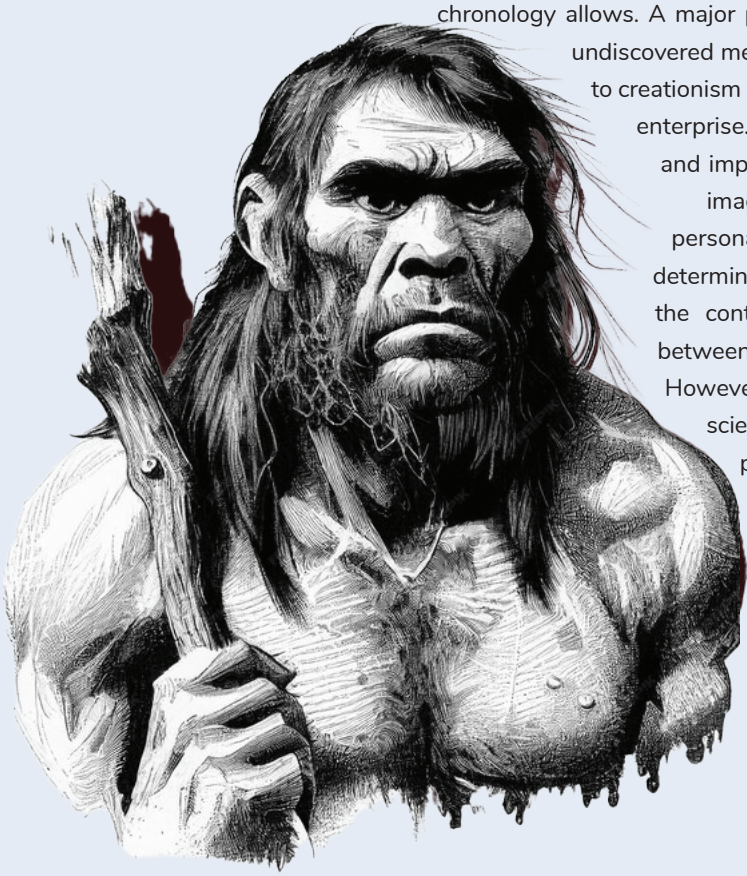
New technology acquired by biotech company Illumina would allow completion of the nuclear genome sequence within reasonable time. Both Science and Nature began to court Pääbo’s team for the Neanderthal genome paper. Chapter 16 begins with all the nuclear DNA needed to complete the project now sequenced. This achievement allowed important questions to be answered, such as whether Neanderthals had contributed DNA to people living today, especially in Europe where Neanderthals are known to have coexisted with early modern humans. The mtDNA data and the first nuclear genome analyses suggested no admixture, but could only exclude a very large genetic contribution from Neanderthals. By February 2009, however, there was strong evidence that Neanderthal genomes more closely resembled those of modern non-Africans than Africans and that interbreeding outside Africa must therefore have taken place. At a research meeting in Croatia, Pääbo and his colleagues hammered out how they would analyse and publish the genome paper (Chapter 17). Their studies had confirmed that the data quality was excellent, with estimated levels of contamination in the mtDNA data of about 0.3% and in the nuclear DNA data of less than 1%. Chapter 18 describes additional work confirming that Neanderthals and early modern humans had interbred. Furthermore, the data suggested that the direction of gene low had been from Neanderthals into modern humans. If gene low had occurred in the other direction it was now undetectable.

One outstanding puzzle was thrown up by the data: Neanderthal DNA seemed to be present not only in modern Europeans, but also in the Chinese and in the inhabitants of Papua New Guinea. Pääbo’s solution to this puzzle was the “Middle Eastern” scenario, in which early modern humans leaving Africa mixed with Neanderthals in the Middle East and then carried Neanderthal DNA into regions where the Neanderthals had never been present. Chapter 19 discusses the “Middle Eastern” scenario in a little more detail. Fossil evidence shows that early modern humans had coexisted with Neanderthals for some time in the Carmel mountain range of present-day Israel. The two populations shared the same stone tool technology and in all likelihood interbred with one another. But then a “replacement crowd” of more expansive early moderns with a more sophisticated tool technology spread out rapidly from Africa and absorbed the modern human populations that already existed in the Middle East. In this way, Neanderthal DNA passed indirectly into the replacement crowd and through them into modern European and Asian populations. In 2009, work began to construct a catalogue of the genetic differences between modern humans and Neanderthals (Chapter 20). This was seen as a crucial step in understanding what sets the two groups apart. However, there were limitations to how complete the catalogue could be since only 60% of the genome had been sequenced at that time.

Chapter 21 tells the story of the publication of the Neanderthal genome and the reception it received from the scientific community. Science published the paper on 7 May 2010, along with 174 pages of supplementary material. At the same time, the reconstructed genome was made freely available in online databases. Most reactions from fellow scientists were positive, although Erik Trinkaus was a notable exception. Pääbo even notes the welcome given to the paper by young-age creationists, almost all of whom consider the Neanderthals to be “fully human”, while old-age creationists (and speciically Hugh Ross’ Reasons to Believe organization) did not like the discovery that Neanderthals and modern humans had interbred, regarding this as evidence of “animal bestiality” in human history.

In Chapter 22 the book turns from the Neanderthals to the discovery of another extinct type of human. Early in 2009, Pääbo's team had acquired a minuscule fragment of finger bone that had been found in Denisova Cave in the Altai Mountains of southern Siberia. Sequencing of its mtDNA revealed that it represented neither a modern human nor a Neanderthal, but seemingly another extinct human group. During a research visit to Russia an unusual molar tooth from the same cave was also acquired. The mtDNA analysis of the finger was published in Nature in April 2010. The final chapter describes the nuclear DNA sequencing of the finger bone, which contained surprisingly low levels of contamination (Chapter 23). An entire mtDNA sequence was also reconstructed from the molar tooth. The results indicated that the finger bone and the tooth came from different individuals but the same type of human, subsequently named "Denisovans". Analysis of the nuclear DNA sequence revealed that the Denisovans were more closely related to Neanderthals than to modern humans, although, as with the Neanderthal genome, there was evidence of gene low from Denisovans into the ancestors of some modern populations.

The team concluded that "low levels of mixing with earlier humans seemed to have been the rule rather than the exception when modern humans spread across the world" (p.246). So what do we now know as a result of this extraordinary research project? 1) We have a pretty good idea of what the Neanderthal genome was like and how it differed from the modern human genome. A near-complete catalogue has now been compiled of nucleotide positions that distinguish modern humans from Neanderthals, Denisovans and living apes, and it contains 31,389 changes, 125 insertions and a few deletions. What is not yet known is the functional significance of these differences. On page 208 Pääbo highlights what he calls "the dirty little secret of genomics", the fact "that we still know next to nothing about how a genome translates into the particularities of a living and breathing individual."2) We have strong evidence that both the Neanderthals and the Denisovans contributed a small percentage of genetic material to modern-day populations. In the case of the Neanderthals, this flow of genetic material into early modern humans most likely happened while the two groups coexisted in the Middle East, early modern humans then carrying the Neanderthal DNA with them when they migrated into regions where no Neanderthals had ever been present. In the case of the Denisovans, it seems likely that early modern humans met and mixed with them while migrating out of Africa and along the southern coastlines of Asia. 3) Like modern humans, the amount of mtDNA variation in Neanderthals is very low, suggesting that both groups began as small populations that later underwent expansion. From a young-age creationist perspective, the data from these genome studies (and from the fossil record) are consistent with the claims that human diversity was significantly greater in the early post-Flood period than today and that both the Neanderthals and the Denisovans were members of the human baramin. What is not clear is how the genetic differences between these groups arose so quickly after the Flood (and, presumably, after Babel).



Conventional estimates of divergence times suggest much longer time scales than the Biblical chronology allows. A major prediction of the young-age model is that there must be as-yet undiscovered mechanisms of rapid genomic change. A few other points pertinent to creationism can be drawn from the book: 1) The human nature of the scientific enterprise. On page 191 the author writes: "Science is far from the objective and impartial search for incontrovertible truths that non scientists might imagine. It is, in fact, a social endeavor where dominating personalities and disciples of often defunct yet influential scholars determine what is 'common knowledge.'" Pääbo makes these comments in the context of the once-prevailing consensus that no interbreeding between Neanderthals and modern humans had ever taken place. However, his words serve as a useful and more general reminder that scientists are subject to biases of many kinds (not least worldview, philosophical and religious biases).

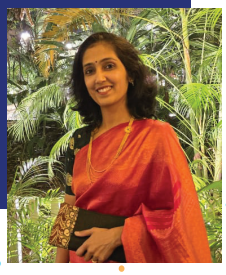
2) The excitement of the scientific enterprise. This book reads like a detective story and vividly conveys the excitement of a life in science. As in any life, there are ups and downs, successes and failures. Advances in scientific knowledge are hard - won. But overall, science is a joyous and fulfilling activity, and one that brings glory to God as we study the Creator's handiwork. One of our tasks as creationists is surely to cultivate in the church a healthy attitude to scientific discovery, and help to dispel the fear and suspicion that too often prevails. 3) The practical realities of the scientific enterprise. There are also lessons for us in this book about how good science is done. Pääbo's story helps us to see the importance of developing and testing our own models (not simply criticizing those of our opponents), the need for self - criticism, the value of collaborations with others, the necessity of rigorous peer review, and the unfortunate way in which headline - grabbing (but ultimately wrong-headed) ideas can eclipse more careful, systematic work. Of course, as creationists we can only dream of having a research budget of $6 million and the facilities of the Max Planck Institute at our disposal, but there is much to learn here despite our limited resources! One final thought: the Neanderthal genome project challenges the popular creationist claim that "origins" science is somehow inferior to "operations" science, by showing that multiple competing hypotheses about observable past events (e.g. the Neanderthals did/did not contribute genetic material to modern humans) can be successfully evaluated in terms of how well they explain observable phenomena in the present.

While there may be some differences in methodology (e.g. Cleland 2001), it is difficult to maintain that there is a hard - and - fast distinction between "historical" science and "experimental" science. This is an unfinished story, as the postscript to the book makes clear. Indeed, as I was writing this review the latest edition of Nature landed on my desk, with a report by Pääbo and colleagues of nuclear DNA sequenced from bones found in Sima de los Huesos in northern Spain, which may have belonged to Homo heidelbergensis (Meyer et al. 2016). About the same time, Pääbo's team published a further analysis of Denisovan and Neanderthal DNA persisting in modern individuals from the Pacific Melanesian islands (Vernot et al. 2016). As creationists we ought to welcome the results of such research as we seek to develop young-age models to explain the fossil record of early humans. In this endeavour, more data is better than less and it is clear that new and exciting discoveries await us.

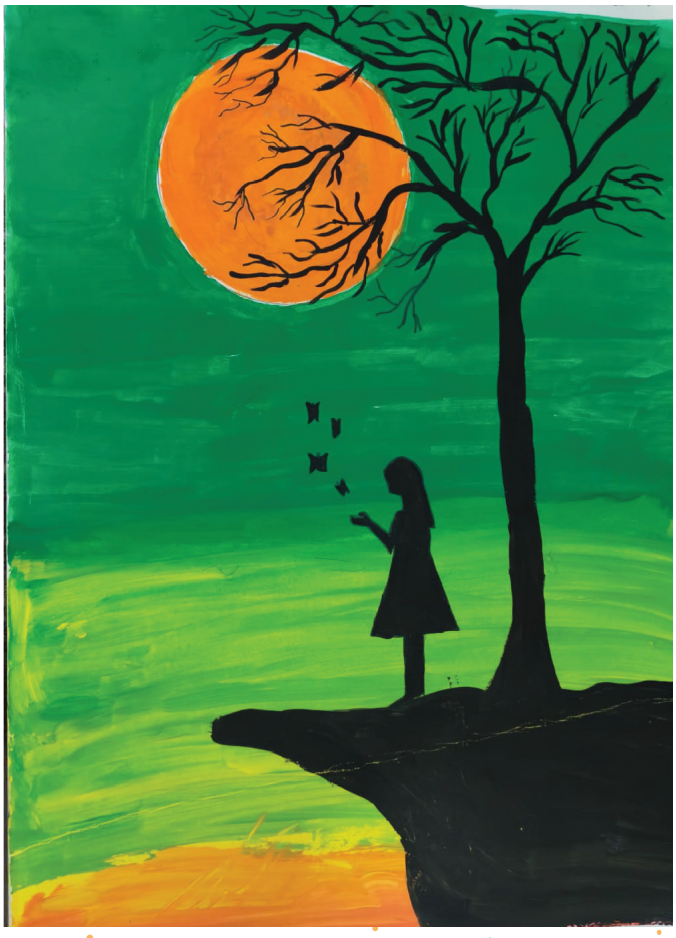
From our Colleagues

Art meets Science

The most beautiful thing we can experience is the mysterious. It is the source of all true art and science.
— Albert Einstein



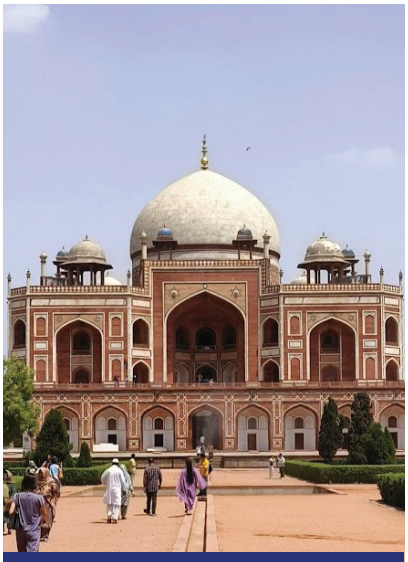
By:
Dr. Shruthi PS, MBBS, MD Pathology
Senior Hematopathologist



From our Colleagues

By:
Annesha Roy
Genome Analyst Trainee

Night view of the Lenin Cruise, Kolkata



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Vishnu Jayaraj

Photo Feature

Triple panga Celebrations

Following the triumph of the 2023 Triple Panga Challenge, we're thrilled to bring the next round of this exciting tournament. Our colleagues were competing fiercely in Chess, Carrom, and Dumb Charades this year, and the enthusiasm and energy with which everyone has participatied was truly commendable. A special shoutout goes to those who came out to support and cheer for their peers and team members.

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