Vol 15 | Oct 2020

MEDGENOME

GeKNOWme

Internal Quarterly Newsletter

Special feature

Heart to Heart with Dr Ajit Mullasari, Cardiologist, Madras Medical Mission on CAD & PRS Page 24

Articles

FROM THE FRONTLINE

Rayman Mathoda

CEO, MedGenome, USA

Warm greetings, my dear fellow MedGenomers

I have watched with both awe and pride the amazing progress and contributions that MedGenome has made since 2013, when I joined Sam and Mahesh on their India genomics journey as one of the company's founding investors. Earlier this year, I was delighted to become a full time member of the MedGenome team; I left my career as a CEO in the US finance/real estate sector to lead MedGenome's US focused or driven businesses to the next level of global growth and success.

It has been inspiring the past few years to observe MedGenome's journey towards market leadership in the Indian genomic diagnostics space. Yet, I know that the company and market are still relatively early in their evolution and the untapped opportunity for human and business impact - both within India as well as in other emerging markets - is massive.

I have been equally impressed with the world class quality of scientific research and analysis conducted by our team and their collaborators, as evidenced by key recent high profile publications in Nature, Nature Genetics, Nature Communications, and the Journal of American College of Cardiology. This includes our research as a founding member of the GenomeAsia100K consortium, which has helped create a much needed reference genomes for India and other Asian populations, and expanded global awareness about the need for more research on Non-European populations.

Our India diagnostics capability and infrastructure combined with our clinical partnerships and global research capabilities, creates a new opportunity for MedGenome - the opportunity to build a 'genomic medicines' business that connects US and European Pharma, Biotech, and Academic organizations, skills, and markets with the data, people access and insights from India. Our goal with this business is to generate novel data and insights, to foster new genomic discoveries and solutions for India, and from India for the rest of the world.

One of the first areas of focus for the genomic medicines team has been Parkinson's disease (PD), where we initiated a MedGenome research program in 2016. We recently expanded this program and entered a new discovery collaboration with one of the world's leaders in PD - Denali Therapeutics. Our goal is to work with Denali to make novel PD discoveries, with a goal of enabling the development of new and better therapies for PD patients worldwide.

Further updates will be shared as we roll out additional initiatives, including our proprietary SARGAM genotyping chip which should be operational within a month or so.

I look forward to interacting with the MedGenome Team from both India and USA and with your support, we will continue to expand, grow and impact lives.

Warmly, Ray

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Healthcare

VIEW: Can we learn from COVID-19 testing infrastructure for TB management?

Updated : July 22, 2020 06:23 PM IST

- One of the biggest models India can use from the COVID-19 pandemic is to tackle the eminent problem of deploying a fine TB testing mechanism and infrastructure to progress and address TB testing roadblocks in India.
- A targeted approach to identify the population affected from TB remains the biggest hurdle.
- The current government has set a deadline of 2025 to eradicate TB from India.

DR VEDAM RAMPRASAD
@MedGenome

Indians have largely remained untouched by the epidemics and pandemics the world has seen over the past three decades. India is better placed today to tackle and counter pandemics such as COVID-19. We had our share of failures and learning over decades while managing pandemics such as cholera, plague, influenza, polio, SARS, Japanese Encephalitis, Chikungunya, H1N1, Nipah etc.

In all these decades, more than 30 new infectious agents or pathogens have been detected worldwide. Around 60 percent of these were found to have a zoonotic origin, carried and spread by animals. COVID-19 has resulted in an unimaginable situation with lockdowns and movement restrictions being imposed in many countries. With a death rate of over 2 lakh around the world, countries are racing to develop a vaccine on the basis of the genetic make-up of the virus which is believed to have mutated in 10 forms already.

Apart from this threat at hand we are facing, there are many other infectious diseases as well which continue to claim lives in India, such as malaria and tuberculosis, which have a high mortality rate associated with them. As per WHO, in 2018 India accounted for 27 percent of TB population across the world. The majority amongst this number is the adults (aged > or = 15) population but a significant ratio is that of children who are suffering from pulmonary TB.

Tuberculosis is a multi-faceted challenge the country is facing. The current government has set a deadline of 2025 to eradicate TB from India. Far-fetched but this deadline has led to multiple innovations that can help us overcome various challenges associated with TB. Not only is the country home to the largest TB population and associated deaths, but also faces significant challenges panning out from developing an accurate database of TB patients, keeping the affected population on the medication regime, affordability, as well as accessibility.

A targeted approach to identify the population affected from TB remains the biggest hurdle. The aspect demands to methodically identify individuals who are at risk for new infection as well as individuals at increased risk for reactivation due to associated high-risk conditions.

Now, the Indian population is not proactively surfacing for a check-up due to resources, stigma, consequential treatment cost et al which needs a comprehensive approach altogether. But, at first, identifying this missing TB population through a well-framed testing infrastructure is half battle won! The steps taken to overcome initial stigma and inertia in the case of COVID-19 through large mass communication channels can be replicated to apply for TB.

The public health ecosystem has taken into account infrastructural, economical and socio-political approaches developed by the world's leading forces assigned to overcome the challenge. One of the biggest models India can use from the COVID-19 pandemic is to tackle the eminent problem of deploying a fine TB testing mechanism and infrastructure to progress and address TB testing roadblocks in India. Despite hurdles, key pieces of the necessary data infrastructure for mass TB surveillance and management can be extracted from the COVID-19 model and utilised for collecting data at scale, albeit with gaps, through labs, public and local health agencies.

Once this is deployed, the other giant problem is better and effective drugs that can help people living with MDR and XDR TB. In all these years, USFDA has approved only three drugs that can help in managing TB well including Bedaquiline, Linezolid and now Pretomanid which is yet to be launched in the country.

Genomics has emerged as a next-gen diagnostics arena which is boosting drug and vaccine development basis a relatively new-found scientific basis. In TB specifically, the country saw two big advances last year that could augment the way drugs are developed for the Indian population. One was SPIT-SEQ that sequences the entire genomic make-up of the Mycobacterium Tuberculosis (*Mtb*) and provides intelligence as to which drug will work on the (otherwise naturally resistant) bacteria and the second is Genexpert machine that establishes in a couple of hours whether the patient has resistance to a select list of drugs.

When SPIT SEQ was originally launched in August 2019, it was a research use only (RUO) test with validation studies underway. As a result of successful validation results, the study was published in the *International Journal of Tuberculosis* and hence the test is now available to be used in a clinical set-up.

The COVID-19 environment saw multiple schools of thoughts-where one spoke of advantages of BCG vaccine, the other of using the anti-malaria drug or even anti-arthritis drug. This reflects a uniform strategy to fill gaps until we have a designated vaccine for the coronavirus. Where the learnings from an experience were leveraged in this pandemic, it will be smart to leverage the scaled-up learnings from this outbreak to manage other public health issues the country needs to defeat.

--Dr Vedam Ramprasad is CEO, Medgenome Labs. The views expressed are personal

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Scientists identify vaccine candidate for gallbladder cancer amid COVID-19 pandemic

Health

IANS

Updated Aug 25, 2020 | 10:24 IST

The mutated peptides derived from ELF3 have the potential for use as a cancer vaccine to treat gallbladder cancer patients carrying alteration in this gene.

New Delhi: Amid the Covid-19 pandemic, an international team of scientists has identified the possible vaccine candidates for gallbladder cancer.

In a study, published in the journal *Nature Communications*, scientists from the US- and India-based MedGenome, along with an international team of researchers from India, South Korea, Chile and Australia reported sequencing and analysis of over 150 gallbladder cancer (GBC) samples.

Currently, there are no targeted therapies for treating this cancer. Gallbladder cancer in the US has a higher incidence among Southwestern Native Americans and Mexican Americans. It is more prevalent in South American countries that include Chile, Bolivia, and Ecuador, and in Asian countries such as Korea, India, Pakistan and Japan.

"The work deepens on our understanding of the underlying genomics of GBC, including the identification of new pathways, immune microenvironment and actionable mutations", said study co author Eric Stawiski from MedGenome in the US.

The team performed a comprehensive genomic analysis and identified several targetable genomic alterations. In particular, they identified frequent alterations of the ELF3 gene. They showed that the mutated peptides derived from ELF3 have the potential for use as a cancer vaccine to treat gallbladder cancer patients carrying alteration in this gene.

The researchers obtained whole-exome sequencing data for 160 gallbladder cancer samples, the transcriptomes of 115 samples, and low-pass whole genome data for 146 samples. These samples came from 94 patients from South Korea, 64 from India, and nine from Chile. Overall, based on the exome sequencing data, they identified protein-altering somatic mutations in 10,224 genes, about half of which were recurrent mutations.

They specifically homed in on 25 significantly mutated genes, which included well-known oncogenes like ERBB2 and KRAS; tumour suppressor genes like TP53 and ARID2; and other less well-established cancer-linked genes like ELF3.

"Our scientists were able to show the potential for use of ELF3-derived mutant peptides as a cancer vaccine for treating GBC and shows the value of the platform for the identification of cancer vaccine candidates," said Rayman Mathoda, CEO, MedGenome.

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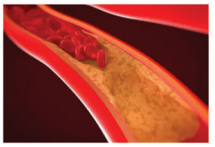
ealthworld.com

Economic Times

Experts develop a breakthrough genetic risk score for Heart Disease in South Asia

MedGenome collaborated with researchers to conduct a first-ever research capturing the PRS of disease for South Asia populations and its findings are now published in the Journal of the American College of Cardiology (JACC).



Bengaluru: MedGenome Lab has conducted a first-ever study on Indian population that validates a novel 'CAD-PRS' (coronary artery disease-genome-wide polygenic risk score) to precisely predict the risk of developing a coronary artery disease/myocardial infarction (MI) using a person's genetic makeup.

MedGenome collaborated with researchers from Broad Institute of MIT and Harvard; Massachusetts General Hospital, Boston; Narayana Health, Bangalore; Eternal Hospital, Jaipur; Madras Medical Mission, Chennai; KMCH, Coimbatore and a few other institutes to conduct this first-ever research capturing the PRS of disease for South Asia populations and its findings are now published in the Journal of the American College of Cardiology (JACC).

Dr. Vedam Ramprasad, CEO, MedGenome Labs said "Looking at all the available scientific evidence and our study results we are convinced that there exists a good opportunity to combine both clinical and genetic risks (polygenic risk score based) and significantly improve the primary prevention of coronary artery disease (CAD)."

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Spectrum

Friday, 25 September 2020

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Exploring NGS test for ophthalmic diseases

08 September 2020 | Views

The diagnostic yield of the NGS testing in ophthalmological diseases is about 50-70%

Image credit- shutterstock.com

The purpose of the genetic testing is to identify the underlaying genetic defect in the affected case or family. Firstly, it answers the cause of the disease.

Second, if the disease casing mutation/gene is identified, it reveals the pattern of inheritance, autosomal or X-linked, dominant or recessive, thereby facilitating in risk prediction of the disease in the family. This opens the possibility of offering prenatal genetic diagnostics wherever appropriate.

With time researchers and scientists are constantly evaluating the in-depth genetic information available to understand the progression and prognosis of the disease. Though most of the inherited ophthalmic diseases do not have a cure, the requisite for any patient to be eligible for gene therapy is to know the underlying genetic defect which can be known by genetic testing.

In case of a patient who is diagnosed with cancer of the retina, genetic testing in retinoblastoma helps in prognosis of the disease to determine whether it is familial or sporadic.

This information changes the recurrence risk of the disease in the family members and the next generation and in turn helps in disease management, surveillance, and follow-up.

The benefits of next generation sequencing (NGS) based testing is that it offers targeted panel testing (only disease specific candidate genes are screened), clinical exome (all clinically significant genes), whole exome (WES) or whole genome sequencing (WGS) (currently more under research testing). The diagnostic yield of the NGS testing in ophthalmological diseases is about 50-70%.

In earlier days, diagnostic genetic testing was not comprehensive because screening all the candidate genes for a given disease was time-consuming and expensive. With advancement in technology and innovation in science the process of NGS has evolved to offer comprehensive, affordable genetic testing with a very short turn-around time of 3-4 weeks.

Though genetic testing for risk prediction of age related complex ophthalmic diseases like age related macular degeneration, glaucoma, diabetic retinopathy, is currently not available, case-control studies on very large cohorts across the globe over the years have generated vast data and polygenic risk score (PRS) for these diseases are slowly emerging which would be available soon.

Dr. N Soumittra, Disease Head, Ophthalmology, MedGenome, Bengaluru

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ENGLISH | தமிழ் | বাংলা | മലയാളം | हिंदी | मराठी

The Indian EXPRESS

Friday, September 25, 2020

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Parents, here's what you need to know about inborn errors of metabolism

It is a class of diseases, where the normal metabolic activity of a person is disrupted due to a genetic defect in his or her DNA that leads to the disruption in normal bodily function.

Modern genetic screening techniques such as Next Generation Sequencing (NGS) have made the job of analysing a person's DNA a doable process. (Source: Pixabay)

By Dr Sunita Bijarnia-Mahay

The human body is a marvel of natural engineering and runs like a well-oiled machine. The blueprints of this machine are etched in our DNA and are replicated like clockwork from parent to offspring. But every now and then, this clockwork breaks down and errors in the blueprint creep in. These errors can disrupt the normal functioning of a body and lead to impairment and death. Some of these mistakes are classified into what is known as Inborn Errors of Metabolism (IEM). IEMs are a class of diseases where the normal metabolic activity of a person is disrupted due to a genetic defect in his or her DNA that leads to the disruption in normal bodily function.

IEMs tend to cause significant morbidity and mortality and are responsible for 1-10 per cent of ICU admissions and 35-50 per cent of mortalities. Their global prevalence is approximately 50 per 1,00,000 births and a case fatality ratio, among those requiring ICU care, of 13-33 per cent (Donald Waters, 2018).

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

What's New?

Publications & collaborations

Pathbreaking Study Paves the Way for Preventive Healthcare using Polygenic Risk Score (PRS) for Coronary Artery Disease (CAD) Diagnosis.

This study has been published in the **Journal of the American College of Cardiology.**

Actionable targets and potential immunotherapy strategies to treat gallbladder cancers have been identified.

This study has been published in the journal **Nature Communications.**

MG has formed a strategic collaboration with Denali therapeutics on applying genomics to identify and analyse novel genes and variants associated with Parkinson's Disease, with an aim to develop new therapies.

Dx Test launches

COVID-19 test by CBNAAT and Rapid Antigen Test in partnership with Dr Iravatham's Clinical Laboratory, Hyderabad and **Hepatitis C Virus** (HCV) quantitative PCR test.

KardioGen - Polygenic Resk Score Test for Coronary Artery Disease.

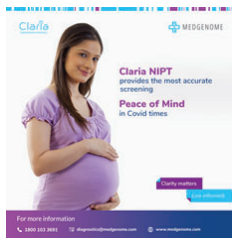
Pharmacogenomics panel to use genomics for drug response.

MedGenome connect

Claria
Reproductive Genetics

The highlight for Claria over the past quarter has been the press coverages that we received on the occasion of World IVF day. Dr Priya Kadam and Dr Venkatswamy were featured in the New Indian express giving their take on the need to PGS screening of all embryos. The 2nd coverage was even more significant as it was based on a case study about a 36-year-old woman *L1CAM* variant and how MedGenome, Kushi Fertility and Dr. Preetha Tilak came together to help this woman have healthy twin girls (details in the case study section). This coverage was featured in the New India Express, The Hindu and other vernacular papers. This case study was featured in a 30 min program on TV9 news channel.

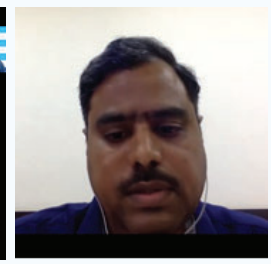
Two of our genetic counsellors won poster awards at the Board of Genetic counselling India 5th annual e-conference in early July. We posted congratulatory message on our social media platforms to celebrate their achievement.

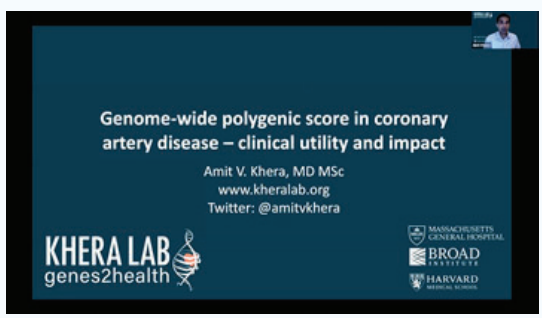


Due to the lock down and the subsequent spike in Covid-19 cases, the number of pregnant women visiting hospitals for their routine first trimester screening had significantly reduced. In order to highlight the benefit of NIPT as a safe non-invasive method of screening for trisomy's compared to invasive procedures, we came up with a Facebook campaign.

ACTIA
Inherited Genetics

Actia saw the addition of another test to its basket in the form of Polygenic Risk Score test for Coronary Artery disease. This test was made possible by the publication of our validation study in the prestigious Journal of The American College of Cardiology. We organised a virtual press conference to announce the publication of the study and this was attended by eminent cardiologists from Narayana Institute of Cardiac Science, Madras Medical Mission, Eternal heart institute. This press conference received good coverage online and in the press.





This was followed up with a webinar by one of the leading proponents of the PRS concept Dr. Amit Khera of Harvard Medical School. The webinar was presided over by two leading cardiologists Dr. HK Chopra and Dr. Rakesh Gupta.

MedGenome connect

Prima Cancer Genetics

We as a “new” normal, continued to focus on digital platforms and leveraged it for various activities such as online symposiums and social media banners. September being the Leukemia awareness month, we conducted a successful symposium on Leukemia and Minimal Residual Disease where we had eminent speakers - Dr Rahul Bhargava (Fortis, Gurgaon) and Dr Joseph John (CMC, Chandigarh) share their clinical experiences, along with Dr Arun Kumar (MedGenome) talking about newer techniques for MRD. The talks were followed by an interesting panel discussion, moderated by Dr Rahul Bhargava with Dr Nilesh Wasekar (HCG, Nasik), Dr Prathamesh Kulkarni (Nanavati Hospital, Mumbai) and Dr Shruthi P S (MedGenome) as the panelists. The symposium was well received and well attended.

We also did a social media awareness campaign around the broad applications of genetic testing in leukemia - Targeted treatment, Prognosis, Disease relapse monitoring and Diagnosis.

mycra Infectious Disease Genetics

We continued our efforts on spreading awareness about COVID-19 at various fronts. A couple of catchy videos on how to wear a mask properly were made for public awareness.

https://www.youtube.com/watch?v=VZZm5FF_Oqc

We also launched the COVID-19 test by CBNAAT and Rapid Antigen Test in partnership with Dr Iravatham’s Clinical Laboratory, Hyderabad. Along with this, we also launched the Hepatitis C Virus (HCV) quantitative PCR test.

From our US office

This quarter owing to our continued business efforts despite the ongoing pandemic situation, we were able to launch new services such as “Metagenomics Service using Loop Genomics technology” and “Denovo Genome Assembly Solutions”.

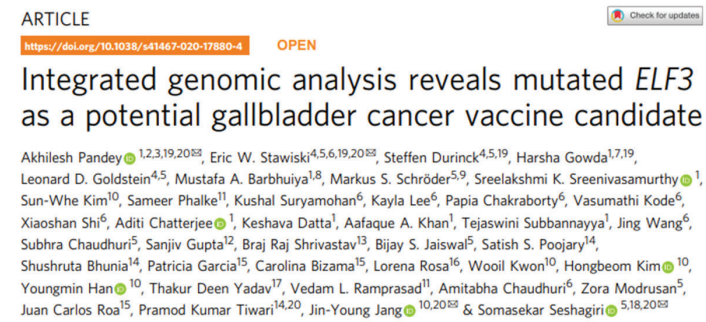
More details and important information regarding these services are available on our website under the Resources section. Please follow the below link to know more:

https://research.medgenome.com/white-papers/

nature COMMUNICATIONS

We are happy to share that our proprietary OncoPept™ platform has been successfully used to identify potential gallbladder cancer vaccine candidate and the same was duly cited in the prestigious journal “Nature”.

For more information, refer link:
https://www.nature.com/articles/s41467-020-17880-4



ARTICLE

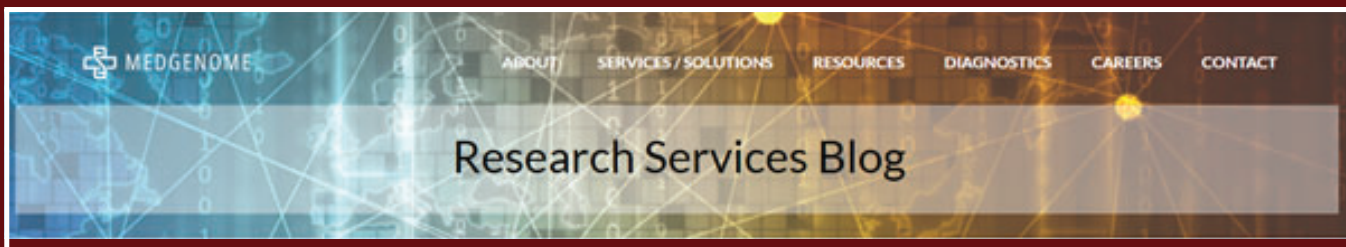
https://doi.org/10.1038/s41467-020-17880-4 OPEN

Integrated genomic analysis reveals mutated *ELF3* as a potential gallbladder cancer vaccine candidate

Akhilesh Pandey[1,2,3,19,20✉], Eric W. Stawiski[4,5,6,19,20✉], Steffen Durinck[4,5,19], Harsha Gowda[1,7,19], Leonard D. Goldstein[4,5], Mustafa A. Barbhuiya[1,8], Markus S. Schröder[5,9], Sreelakshmi K. Sreenivasamurthy[1], Sun-Whe Kim[10], Sameer Phalke[11], Kushal Suryamohan[6], Kayla Lee[6], Papia Chakraborty[6], Vasumathi Kode[6], Xiaoshan Shi[6], Aditi Chatterjee[1], Keshava Datta[1], Aafaque A. Khan[1], Tejaswini Subbannayya[1], Jing Wang[6], Subhra Chaudhuri[5], Sanjiv Gupta[12], Braj Raj Shrivastav[13], Bijay S. Jaiswal[5], Satish S. Poojary[14], Shushruta Bhunia[14], Patricia Garcia[15], Carolina Bizama[15], Lorena Rosa[16], Wooil Kwon[10], Hongbeom Kim[10], Youngmin Han[10], Thakur Deen Yadav[17], Vedam L. Ramprasad[11], Amitabha Chaudhuri[6], Zora Modrusan[5], Juan Carlos Roa[15], Pramod Kumar Tiwari[14,20], Jin-Young Jang[10,20✉] & Somasekar Seshagiri[5,18,20✉]

On July 22, MedGenome hosted a virtual South San Francisco Computational Biology Meetup for scientists and bioinformaticians in the Bay Area. Dr Andy Peterson (GenomeAsia100K) and Dr Eric Stawiski (VP, Bioinformatics) gave a presentation titled "The hidden genetic treasures of India: Why you should care about South Asian medical genetics." In this talk, Dr Peterson presented early results from Phase 2 of GenomeAsia100K effort which elucidates fine-scale population structure within South Asia. Dr Stawiski further talked about how MedGenome collaborated with ThermoFisher to design the South Asian Research Genotyping Array (SARGAM) based on MedGenome's proprietary data and GenomeAsia100K data.

Video Link: **https://research.medgenome.com/videos/**



We have also added new articles on our Research Blog. MedGenome colleagues are encouraged to take initiative and contribute towards the blog. You can share your view points and articles with Vinay and Hiran at **mgus-blog@medgenome.com**

Proud moment

Congratulations

To our Genetic Counselling team for awards at the Board of Genetic Counselling India 5th annual e-conference held from 2nd to 4th July 2020

Angela Devanboo,

won the joint second prize for case presentation for the poster titled

Challenges in genetic counselling involving mosaic embryos obtained post PGT-A – A case report.

Angela Devanboo and Dr Priya Kadam

Shweta Mahalingam,

won the joint second prize in the category 'others' for the poster titled

Implications of language barrier in genetic counselling in the era of telegenetics.

Shweta Mahalingam, Angela Devanboo, Prachi Inamdar, RijuNair, Dr Madhavilatha GK, Dr Priya Kadam and Dr Sheetal Sharda

Making a difference

36-year-old woman realises her dream of a normal motherhood after Dr Rashmi Yogish and her team of embryologists at Khushi Fertility & IVF centre along with leading geneticists Dr Preetha Tilak and MedGenome Labs implement a multipronged genetic testing protocol to eliminate a genetically inherited condition in her embryos leading to the birth of healthy twin girls.

Case Discussion

In a first-of-its-kind multidimensional IVF treatment in the country, Khushi Fertility and IVF Centre, a pioneering city-based fertility centre specialising in the latest Assisted Reproductive Technologies (ART), and MedGenome labs, India's leading genetic diagnostic company implemented Clinical Exome Sequencing (CES) ,

Pre-implantation Genetic Diagnosis (PGD) and Pre-Implantation Genetic Screening (PGS) procedures on the embryos of a patient after Intra Cytoplasmic Sperm Injection (ICSI) to rule out an inherited genetic disease arising from inheritance of an abnormality in the parents' gene.

In 2017 at the age of 33, Ramya had given birth to her first child who presented with several neurological symptoms and missed several developmental milestones. Ramya was both terrified and hopeful of having a normal baby the second time and hence decided to consult before going through the second pregnancy. She consulted Dr Preetha Tilak in Bangalore, who suggested her to undergo Carrier Screening test to check if she is the carrier of any genetic mutations. The test results from MedGenome Labs revealed she was a heterozygous carrier for the L1CAM variant that was found in her first child and thus caused the abnormality in the child.

In 2018, Ramya was pregnant again and went for prenatal genetic test which revealed the fetus had the same genetic variant as the first baby and was likely to have a similar outcome. Due to this, the couple took the painful decision to go in for a medical termination of the pregnancy. Her hope and fear of conceiving again intensified with the unfortunate loss of her son due to the genetic condition.

L1CAM gene in its normal state performs the critical function of providing instructions to produce a type of protein present on nerve cells. Abnormalities of the L1CAM gene, which is inherited from the mother, can cause any one of L1CAM spectrum disorders abbreviated as CRASH syndrome (Corpus callosum hypoplasia, Retardation, Adducted thumbs, Spasticity and Hydrocephalus), leading to conditions such as developmental delay, paralysis and delayed speech. Most importantly, the lifespan of children affected by L1 Syndrome is short lived and many are unable to even survive a few years after birth.

Ramya was devastated when she approached Dr Rashmi Yogish at Khushi Fertility & IVF Centre for treatment. Dr. Yogish prescribed specific genetic tests, starting with Pre-PGD work up of the couple and then Pre-implantation Genetic Screening (PGS) on the embryos created by performing ICSI.

A total of 11 Grade A blastocysts formed during 1st and 2nd IVF cycle were biopsied, frozen and sent to MedGenome for an analysis where PGD was performed on the embryos to detect L1CAM mutation. The test revealed that 4 of the embryos were free of the L1CAM mutation and these 4 were further analysed using a technique called PGS to check for any chromosomal abnormalities. Using these two techniques 2 out of the 11 embryos were identified as normal.

After an uneventful pregnancy, during which confirmatory testing was done to further confirm the diagnosis through Amniocentesis, Ramya gave birth to full-term twin daughters.

PGD involves taking a biopsy of the embryo fertilised to screen for a particular genetic abnormality which has already been detected in one or both parents. The embryos are frozen until the results are processed. Carrier Screening on the other hand is prescribed blood test to identify a genetic problem that is present in one or both partners or is a common to both parents. This test is recommended in the case of consanguineous marriages, in couples having recurrent pregnancy loses or in cases where one or more children are born with an inherited genetic abnormality where the risk of passing on a genetic disease is significantly higher.

Dr Priya Kadam
Associate Director, Reproductive Genomics, MedGenome labs

"Clinical exome can help identify genetic causes of certain inherited diseases. Tests such as PGD or PGT-M can help couples like Ramya and her husband achieve normal pregnancies. More needs to be done to make people aware of these technologies".

Dr Rashmi Yogish,
Founder Medical Director and Lead IVF Consultant, Khushi Fertility & IVF Centre

"We are extremely delighted to help Ramya have healthy babies!! PGD and CES are new technologies that are helping IVF couples with debilitating genetic conditions have normal, healthy children. With an accuracy rate of 95 to 97%, they reduce the emotional and financial burden on the parents."

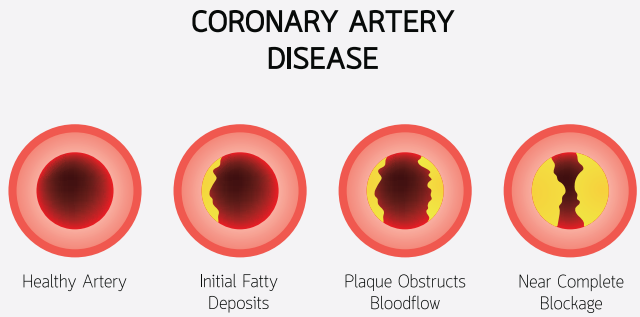
Genome-wide polygenic score for coronary artery disease in South Asians

Coronary Artery Disease in South Asians

Dr Sanghamitra Mishra,
Senior Scientist, Operations Department, MedGenome (INDIA)

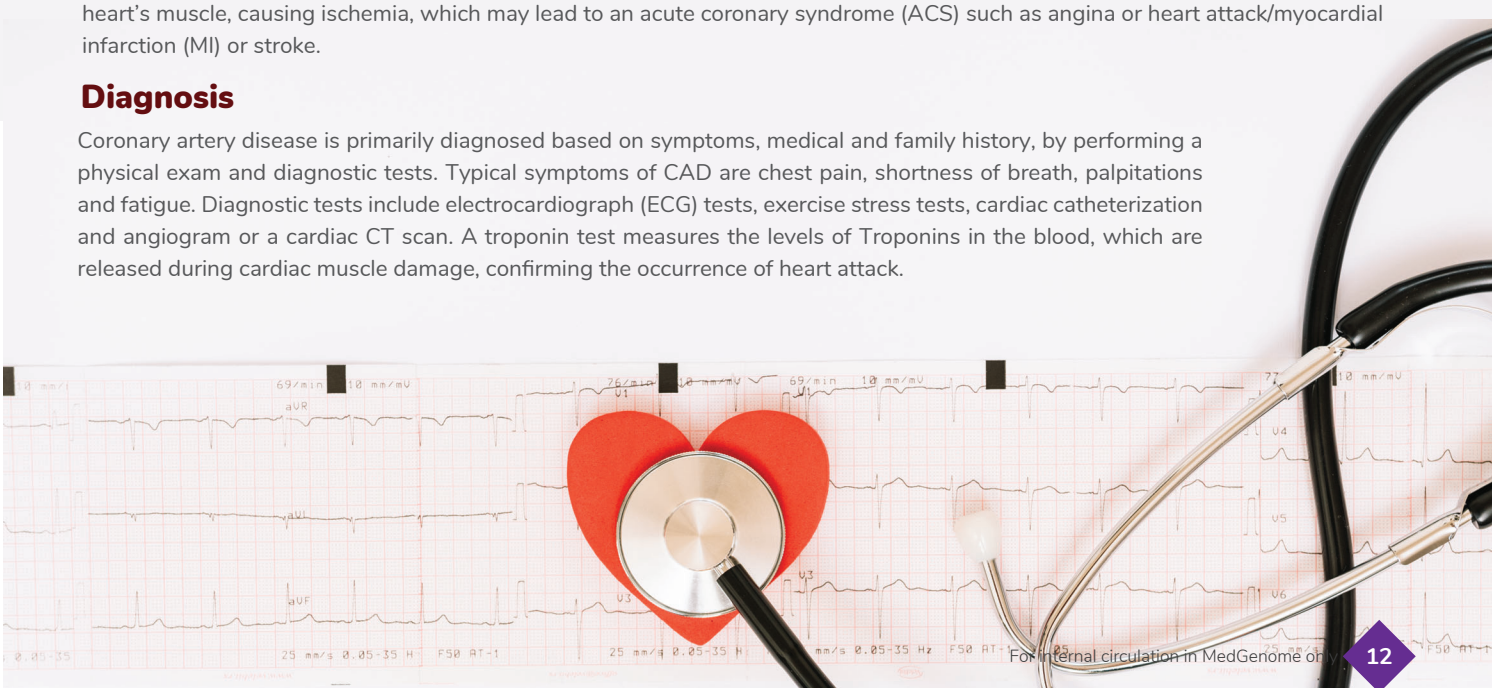
Background

Coronary artery disease (CAD), also commonly known as ischemic heart disease (IHD) is the leading cause of death globally and in India[1]. Epidemiologic studies from various parts of India indicate a prevalence of CAD to be between 7% and 13% in urban and 2% and 7% in rural populations[12]. It is a condition that develops when a waxy deposit with fat, cholesterol, calcium and other substances, known as an atherosclerotic plaque builds up in the walls of the coronary artery, the major blood vessel supplying oxygenated blood to the heart[3]. Cholesterol deposition starts early and fat builds up with age, causing injury to blood vessel walls, attracting inflammatory cells, cellular waste products, proteins and calcium from the bloodstream to form plaque. This causes the lumen of the coronary artery to narrow, limiting blood flow to the heart's muscle, causing ischemia, which may lead to an acute coronary syndrome (ACS) such as angina or heart attack/myocardial infarction (MI) or stroke.



Diagnosis

Coronary artery disease is primarily diagnosed based on symptoms, medical and family history, by performing a physical exam and diagnostic tests. Typical symptoms of CAD are chest pain, shortness of breath, palpitations and fatigue. Diagnostic tests include electrocardiograph (ECG) tests, exercise stress tests, cardiac catheterization and angiogram or a cardiac CT scan. A troponin test measures the levels of Troponins in the blood, which are released during cardiac muscle damage, confirming the occurrence of heart attack.

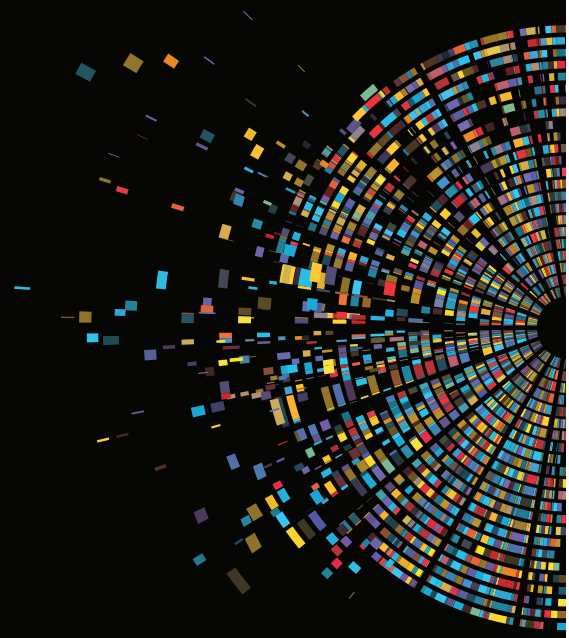


Treatment

Medical management of CAD is available in the form of lifestyle changes and medications to suppress platelet activity (aspirin), reduce cholesterol (Bile Acid Sequestrants, Fibrates, statins), beta receptor blockers, Calcium channel blockers, Angiotensin-converting enzyme, (ACE) inhibitors and angiotensin receptor blockers (ARBs). Cardiac interventions like Percutaneous transluminal coronary angioplasty (PTCA)/stenting and Coronary artery bypass grafting (CABG) are used to increase the lumen of the blocked artery or provide an alternative blood vessel respectively.

Genetics

For long, the known risk factors for coronary artery disease were known to be poor lifestyle choices such as smoking, fatty diet, stress and lack of exercise resulting in high Low density lipoprotein (LDL), low High density lipoprotein (HDL) obesity, high blood pressure and diabetes among others. Presence of a family history of CAD is an established risk factor, indicating underlying genetic causes. More commonly known genetic factors for CAD is familial hypercholesterolemia which is caused by pathogenic mutations in a distinct set of genes resulting in cholesterol metabolism. Such monogenic causes are known to trigger early onset CAD (EOCAD) and have high heritability. However, they only account for a minor fraction of individuals with EOCAD. The Framingham study has established three major variables that contribute to the onset of CAD: constitutional (heredity), and conditioning (environmental) factors, as well as the length of time taken by the conditional factors to act on constitutional factors ultimately resulting in a clinically recognizable condition[12]. The onset of CAD is regulated by the complex interplay for multiple genetic and environmental factors. Now we also know the polygenic risk that regulates this disease and with a PRS scoring model this polygenic risk can be quantified.



Prevention

Preventive measures instituted early are thought to have greater benefits in case of CAD. Healthy lifestyles delay the progression of CAD. Living a healthy lifestyle that includes a healthy diet exercise and well managed weight are known to delay onset of ACS. Statins inhibit 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase, which is responsible for the reduction in the serum LDL levels. Statin and other lipid lowering therapies can prevent cardiovascular events resulting due to high serum lipids[9,12].

Polygenic risk scores and their significance in Coronary Artery Disease

The polygenic nature of complex diseases has gained light recently. Conditions such as diabetes, CAD, obesity arise from multiple small effect genetic factors spread across multiple genes and their interaction with environmental factors. Genome wide association studies have identified disease loci associated with these conditions. This information provides immense opportunity to identify and closely understand the genetic risk factors for effective therapeutic intervention. Nevertheless, most of these studies were done on people of European ancestry. Genome-wide polygenic scores (GPS) integrates information to compute a score by weighing the effect of disease associated makers spanned across the genome Figure 1. These vary with race and ethnicity, and therefore adjustment based on data from ancestry-matched individuals is needed to improve their predictive accuracy.

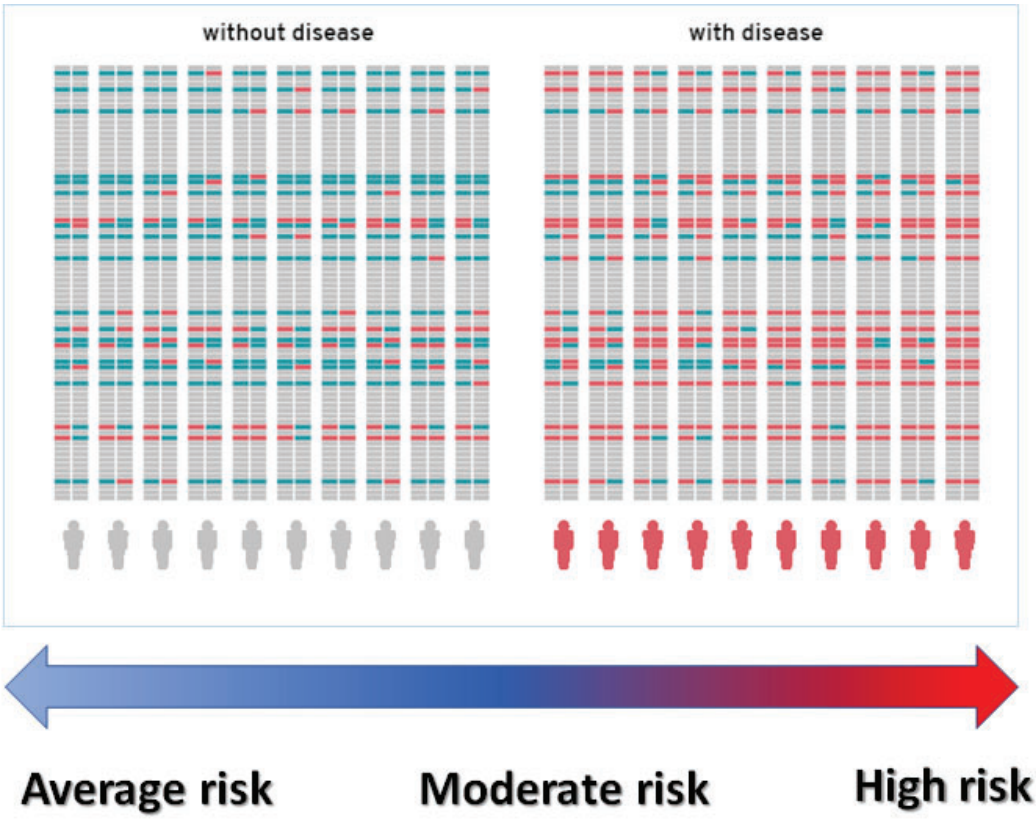


Figure1: Polygenic risk profiling The top panel shows distribution of small effect genetic variants (blue and red) across the genome. Disease risk variants are shown in red. Frequency of these risk variants is higher in people with disease, shown in right. (adapted from http://polygenicscores.org/)

South Asian Genome-Wide Polygenic Score (GPS) for **Coronary Artery Disease**

South Asians show a higher rate of early onset coronary artery disease (CAD) compared to people of European descent[10]. A GPS to identify individuals at high-polygenic risk for CAD is particularly relevant to this population.

We developed 8 candidate GPSs by combining the summary association statistics of 6,630,150 variants contributing to CAD development from the CARDIoGRAMplusC4D Consortium, and LDpred computational algorithm[13,14,15]. The best performing score, p value of 0.003, was chosen considering the discriminative capacity after testing the models on 398 CAD cases and 6,846 controls of South Asian origin from the UK Biobank. Here, the median GPSCAD was in the 66th percentile for CAD cases and in the 49th percentile for control subjects, OR/SD was 1.58 (95% confidence interval CI: 1.42 to 1.76) and a 3.22-fold increase in disease risk was noted in comparing the top versus bottom GPS quintiles (95% CI: 2.25 to 4.70). The performance of the chosen score was tested on 247 cases and 244 control data of the Bangladesh Risk of Acute Vascular Events BRAVE study. The median age of cases here was 34 years, indicating young onset CAD, and those of controls was 33 years. The median GPS was in the 58th and 42nd percentile among CAD cases and controls respectively in this dataset and a 3.90-fold increase in disease risk was noted in comparing the top versus bottom GPS quintiles (95% CI: 2.14 to 7.26). In both the datasets, odds ratio progressively increased from the middle to top percentiles and adjusting for traditional risk factors such as diabetes, hypertension, hypercholesterolemia, family history of heart disease/heart attack, current smoking, and family history of myocardial infarction led to a modest decrease in OR/SD.

Subsequently, we developed a new scalable South ancestry-specific framework for GPS assessment. Whole genome sequencing data from 1522 Indian individuals from Phase 2 of the GenomeAsia 100K project was used to generate a static ancestry-specific genetic ancestry space and generate a fixed GPS reference distribution for GPSCAD. The 5 principal components were computed for this set then raw PRS was calculated for each of the 1522 based on the 6.6 million variants. To calculate ancestry adjusted PRS, individual PRS were projected to the ancestry space. This framework was tested using 1,800 CAD cases and 1,163 control individuals recruited in India through 5 collaborating centres as part of MedGenome's CAD study. Ancestry adjusted PRS was calculated for these CAD cases (median age 54 years) and control (median age 55 years) by projecting onto the principal components of ancestry derived from the reference population. The median percentile for cases in this set was in the 64th percentile compared to controls, individuals who did not have CAD until middle age, for which the median was 48th percentile. We observed a 3.22-fold (95% CI: 2.23 to 4.74) increased risk when compared with those in the middle quintile Figure 2. Adjustment for diabetes, hypertension, hypercholesterolemia, smoking, and body mass index led to minimal effect attenuation, OR/SD decreased from 1.66 to 1.58 (95% CI: 1.42 to 1.75). We have validated a scalable polygenic score framework in India and developed a GPSCAD for South Asians that can be used for CAD risk stratification in this vulnerable population[15].

FIGURE 5 Evaluating the Performance of the Framework for Calculating Genome-Wide Polygenic Scores

DATA/CUT-OFF	Top Percentile CASE/CONTROL	Middle Quintile CASE/CONTROL	P VALUE	OR [95 CI]
MedGenome South Asian				
2.5%	145/26	381/240	3.79e−07	3.30 [2.11–5.33]
5%	225/43	381/240	1.09e−09	3.22 [2.23–4.74]
10%	348/95	381/240	3.43e−08	2.26 [1.70–3.03]
20%	598/209	381/240	1.27e−06	1.79 [1.42–2.28]

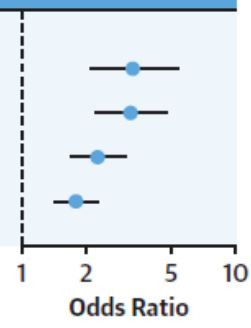
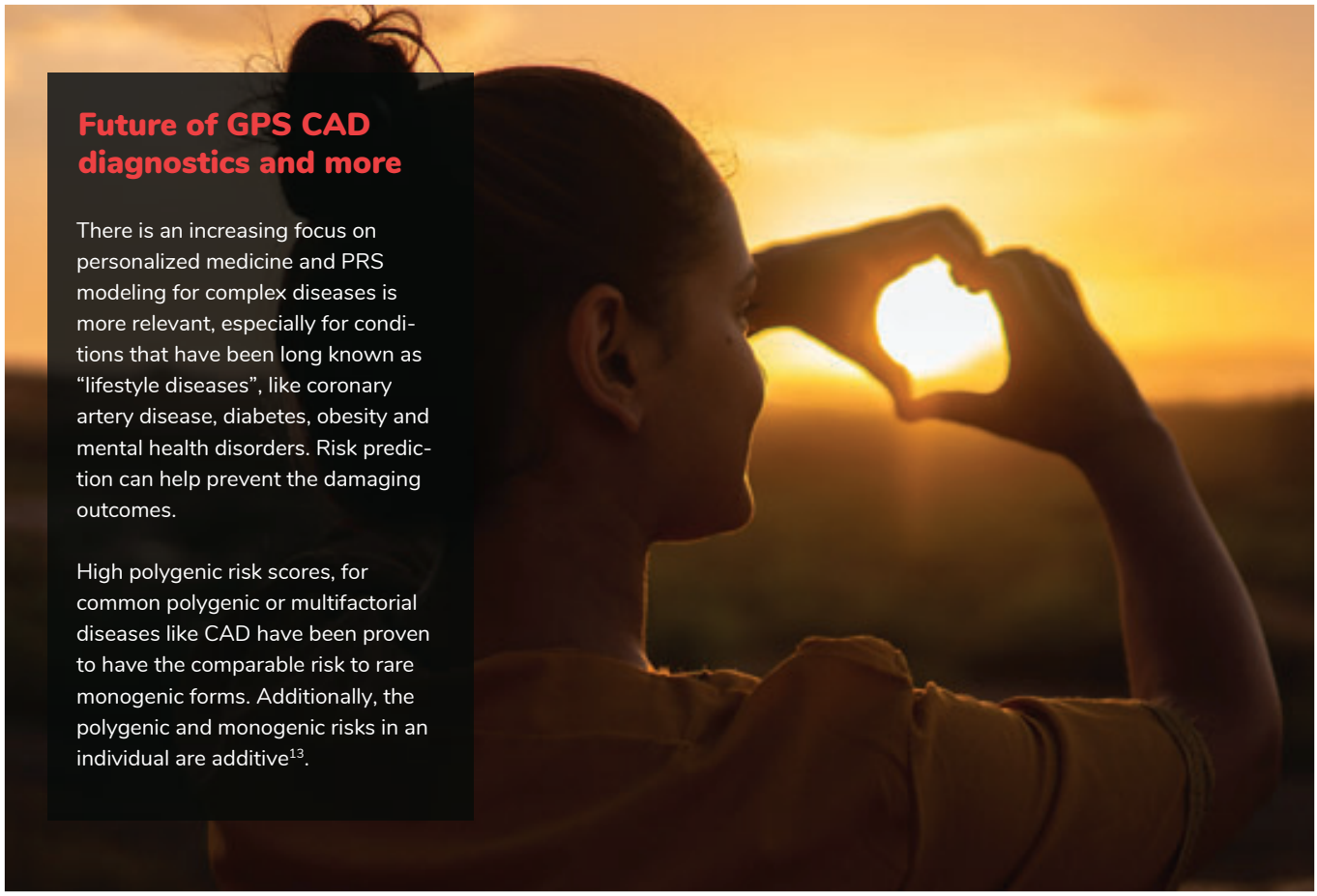


Figure 2: Performance of GPSCAD Table shows comparison between the number of CAD cases in top high percentile and middle quintile in the MedGenome evaluation dataset. Graph shows increase in Odds ratio at each data cut off (top 2.5% shows highest risk with OR of 3.3 while top 20% shows OR of 1.79). (Wang M, et.al., Validation of a Genome-Wide Polygenic Score for Coronary Artery Disease in South Asians. *J Am Coll Cardiol*. 2020 Aug 11;76(6):703-714.)



Future of GPS CAD diagnostics and more

There is an increasing focus on personalized medicine and PRS modeling for complex diseases is more relevant, especially for conditions that have been long known as "lifestyle diseases", like coronary artery disease, diabetes, obesity and mental health disorders. Risk prediction can help prevent the damaging outcomes.

High polygenic risk scores, for common polygenic or multifactorial diseases like CAD have been proven to have the comparable risk to rare monogenic forms. Additionally, the polygenic and monogenic risks in an individual are additive[13].

Ethnicity plays a major role in interpreting PRS. There are significant differences in genetic variation frequencies and linkage disequilibrium patterns between various ethnic groups. Therefore, it is imperative to systematically evaluate polygenic score performance in applicable populations[1]. In India, CAD is one of the leading causes of mortality with twice the risk compared to Europeans and has a younger onset of coronary events. Clinical factors alone do not capture the total risk for CAD. Therefore, a risk stratification protocol based on genetics, considering both, monogenic and polygenic risk factors will make a comprehensive tool along with traditional risk factor estimations (serum lipid levels and lifestyle risks). We have developed a method to estimate one's genetic risk for CAD with GPSCAD. The CADPRS calculated using this model is one's lifelong CAD polygenic risk. It is available as a simple low-cost saliva/blood test categorising one to be at a population average, moderate or high risk of acquiring CAD. Together, with genetic tests available for familial hypercholesterolemia, which eventually leads to CAD, it provides a comprehensive package for one's risk to have an acute coronary event such as a heart attack. The next step will be is to improvise the tool to clearly identify individuals at high risk of EOCAD (below 45 years).

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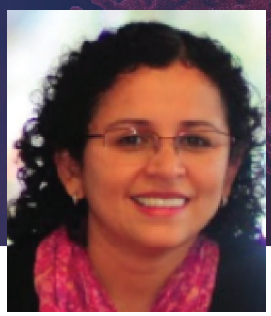
Approaches to **Fighting COVID-19** and **New Emerging Infectious Diseases**



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RACE FOR DEVELOPING COVID-19 VACCINES

COVID-19 pandemic has infected over 23 million individuals and claimed over 800,000 lives globally as of August 2020. SARS-CoV-2, the organism causing COVID-19 belongs to the family of coronaviruses and shares 79% genome sequence identity with SARS-CoV. The spike antigen used by the virus to enter host cells became the prime target for immediate vaccine development efforts because of prior work on SARS-CoV that showed neutralizing antibodies against the spike antigen protected mice and chimps against new infection[1, 2]. Currently, over 166 vaccines are in development against SARS-CoV-2, which can be divided into two major categories – nucleic acid (DNA/RNA) and protein-based (antibodies, viral proteins, inactivated/attenuated viruses and virus-like particles[3,4] vaccines. Four vaccine candidates – RNA-based delivery of spike protein (Moderna), RNA-based delivery of receptor-binding domain (RBD) of spike protein (Pfizer/Biontech), DNA-based delivery of spike protein (Inovio) non-replicating adenovirus-based delivery of spike protein (Oxford/Astra Zeneca and CanSino Biologics) and inactivated virus (Sinovac) are in Phase-I or have completed Phase-I/II trials[5-9]. Preliminary data from some of these trials show the induction of neutralizing antibodies against the spike antigen. T-cell immunity is relatively less robust in treated individuals. At present, efficacy data are lacking to support whether the induction of neutralizing antibodies alone will be sufficient to protect individuals from new infections.

Several features of SARS-CoV-2 infection are unique and do not follow the path of other respiratory viruses. For example, infected individuals remain asymptomatic carrying high viral load thereby becoming a potent source of viral transmission. Further, the immune response against SARS-CoV-2 is skewed towards a T_H1/T_H2 CD4 T-cell response, which results in severe immune toxicity in 15-20% of infected individuals[12,13]. Based on studies in other respiratory viruses, the development of protective immunity against SARS-CoV-2 in vaccinated individuals may face certain challenges. First, the mucosal antibody response is short-lived against respiratory viruses and shows a similar trend in SARS-CoV-2 raising the concern about whether an antibody response is sufficient for long-term protection[10]. Second, some vaccinated individuals can experience life-threatening immune toxicity when exposed to the virus[11]. Our understanding of how the immune system interacts with the vaccine and how this interaction will translate to a response during active infection remains rudimentary and therefore a source of concern especially in older individuals who are both susceptible to infection and also to immune toxicity, but need the vaccine most urgently. A good vaccine will engage both T-cell and B-cell immunity to provide immediate pathogen clearance and induce memory for long-term protection.

B AND T-CELLS IN ADAPTIVE IMMUNITY

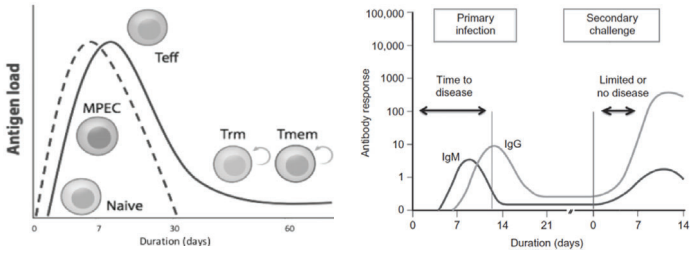


Figure 1. Shows that B cells (left) and T cells (right) elicit a very similar activation profile post-infection. Both cell types get activated and generate IgM/IgG or effector cells aiding in antigen clearance and then maintain low levels of IgG or memory cells for long term immunity. Image sources: Introductory Immunology, 2nd Edition, Modified from CD8 T Cell Exhaustion During Chronic Viral Infection and Cancer, Annual Reviews of Immunology 2019.

Historically, the B-cell memory arm responsible for pathogen-specific neutralizing antibodies is characterized in greater detail in vaccine development studies. Figure 1 (left) demonstrates how B-cells secreting IgM molecules provide short-term clearance of pathogens and pathogen-infected cells, while concurrently maturing into IgG secreting plasma cells that confer long-term protection. The kinetics of the T-cell arm Figure 1 (right) follows a similar profile where antigen-experienced T-cells expand in number, differentiates into a killer phenotype, and clears infected cells. Following clearance of the infection, T-cells persist as resident memory cells in the tissues and as effector memory cells in circulation becoming sentinels to prevent future infections[1]. While the B-cell arm of adaptive immunity has been widely emphasized in vaccine development, the T-cell mediated immunity has remained underexplored primarily due to lack of the right technologies. However, significant technological advancements in the past decade have galvanized the study of T-cell mediated immunity in human diseases.

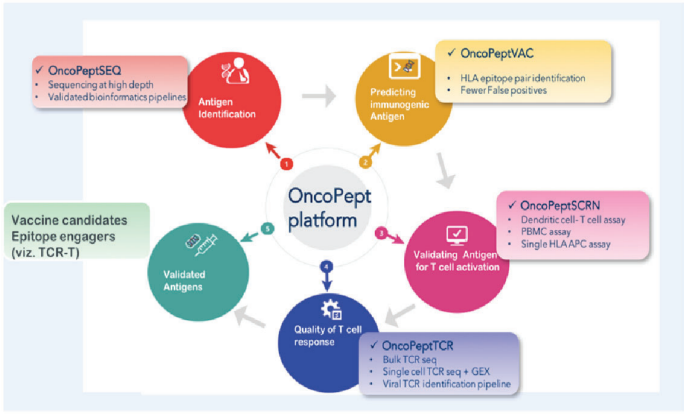


Figure 2. OncoPept platform developed at MedGenome is an integrated Immuno-informatics platform that aids the identification of personalized CD8 immunomodulatory epitopes. Post sequencing peptides are analyzed by the patented OPVAC2 (OncoPeptVAC2.2) algorithm that prioritizes CD8 T-cell-activating epitopes. These epitopes are further validated for a robust CD8 T-cell functional response and the quality of the T-cell response is assessed by T-cell receptor sequencing.

The activation of T-cells is MHC-peptide dependent. T-cell receptors (TCR) on CD8+ cytotoxic T-cells and CD4+ helper T-cells bind 9-15-mer peptide fragments in complex with MHC (referred to as HLA for humans). These peptides are recognized as foreign (non-self) and activate T-cells to generate protective immunity. A large diversity of MHC genes and their polymorphic variants bind millions of peptide fragments from proteins and non-protein antigens and present them to a large diversity of T-cells expressing ~ 10^6 - 10^9 unique TCRs. A single peptide can mobilize and activate many T-cells each expressing a unique TCR. Identifying a good TCR-MHC-peptide pair that can clear pathogens is the holy grail of cellular immunology. Figure 2 is a schematic of MedGenome's OncoPept platform that identifies potent MHC-peptide-TCR combinations for efficient pathogen clearance and protective immunity.

T-CELLS AND COVID-19

In early April, the OncoPept team conducted their very first immune assays with peptide pools from the spike antigen of SARS-CoV 2 and were surprised to observe pre-existing T-cell immunity in healthy donors who were unexposed to the virus. Sequence alignment analysis revealed the possibility that a part of the global population may be protected against the current pandemic as a result of pre-existing immunity against other "common cold viruses'' in the Corona virus family. In fact a recent study in Cell reports that many healthy individuals have both CD4+ and CD8+-T cells that elicit an antigenic response to the new coronavirus even though they have never been exposed to SARS-CoV or MERS[2].

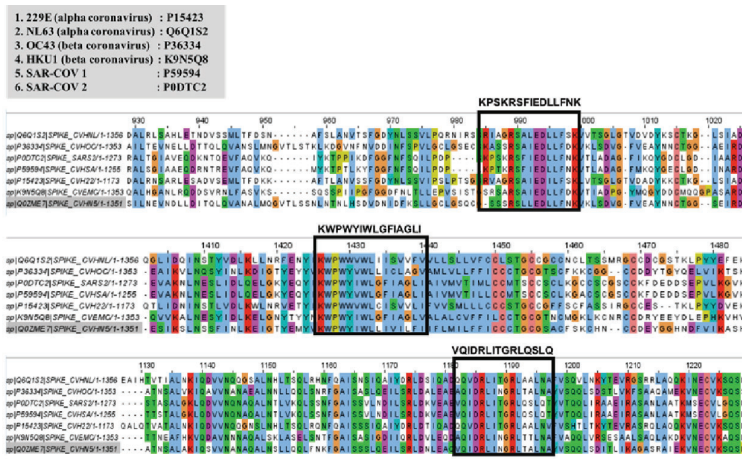


Figure 3. Globally dominant common cold Coronavirus strains (1, 2, 3, 4) are listed in the grey box. The bottom panel shows conserved antigenic regions of SARS-COV2 with common cold viruses that may confer some degree of immune resistance in humans.

Going back to clues on de novo CD8 immunity against SARS-CoV-2, earlier infection by SARS-CoV can perhaps shed some key insights since it is one of the closest homologs in the phylogenetic tree. Patients who had recovered from SARS-CoV back in 2003 had indeed presented an antibody response that faded within two or three years. Interestingly, these patients also elicited detectable virus-specific robust T cell response 10-17 years after the infection had disappeared[3, 4]. These startling pieces of evidence support the notion that perhaps targeting T-cell driven immunity may be a key to a robust long-term immune protection against the COVID-19 pandemic in the population[5].

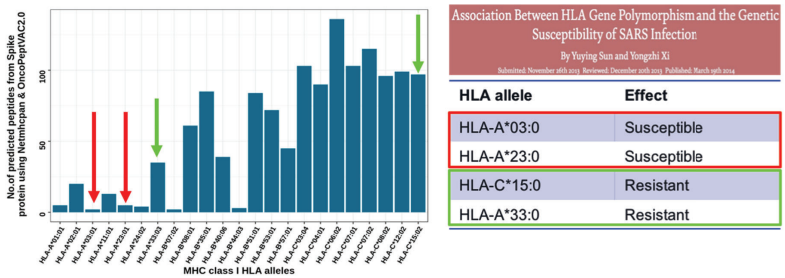
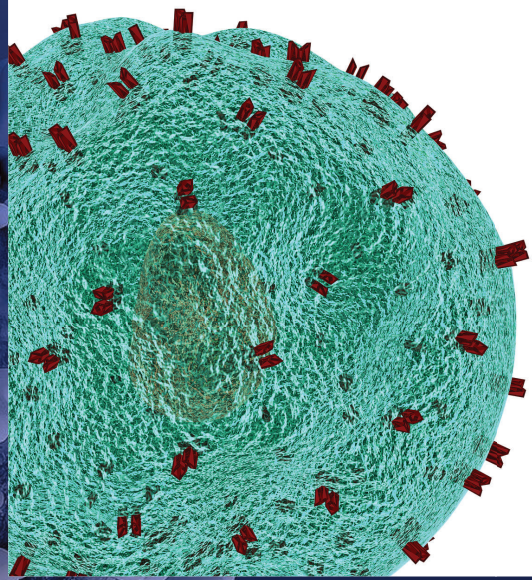


Figure 4. Bar plot depicting HLA-wise prediction of immunogenic SARS-CoV2 CD8 epitopes by OPVAC2. HLAs predicted to present fewer epitopes (red arrows) appear to be reported as susceptible alleles in the highly homologous SARS-CoV infections highlighting the importance of CD8 T cell immunity.

The OncoPept platform was used to assess CD8 T-cell-targeted immunity to the spike protein demonstrated to be highly immunogenic in SARS-CoV studies[6]. The algorithm identified CD8 T-cell epitopes restricted to 23 HLAs. Figure 4 shows certain HLAs were restricted to a small number of peptides, whereas other HLAs presented many peptides. If an HLA presents a few peptides from a pathogenic organism the immune system may not register its presence and will fail to mount a protective response. Our prediction analysis indicated that individuals harboring HLA-A:03 or A:23 will present fewer peptides for immune recognition and individuals carrying these HLAs may be more susceptible to infection. Interestingly, a study showed that individuals carrying HLA-A*03 and A*23 were indeed more susceptible to SARS-CoV than individuals carrying HLA-C*15 and HLA-A*33, which bound many more peptides (Figure 4). The data is purely correlational but supports the idea that CD8 T-cell immunity is critical for developing a robust protective SARS-CoV-2-specific immune response.



POSSIBLE CHALLENGES IN DESIGNING COVID-19 VACCINES

Published studies from Phase-I/II vaccine clinical trials by different groups have indicated a milder CD8 T-cell response against the spike antigen[8, 9]. It is possible that potent T-cell response may lie in regions outside the spike protein as shown by the presence of memory T-cell responses against nucleocapsid protein and the non-structural proteins NSP7 and NSP13 gene products from the ORF-1 region in convalescent individuals[4]. Identification and characterization of these epitopes and their inclusion in a selected vaccine cocktail may yield a more robust and targeted T-cell protective effect.

Another important consideration while using full-length Spike antigen over "selected epitopes" with immunogenic potential is the phenomenon of epitope dominance. The use of a full-length antigen may result in immuno-dominant T-cell responses outcompeting sub-dominant ones. In many scenarios, these immuno-dominant epitopes saturate MHC molecules on cells and mobilize large families of TCRs with reduced cytotoxic potential. This is a common mechanism employed by viruses as a means of evading the immune system. The response can be made broader and potent by utilizing a rational selection of sub-dominant T-cell epitopes or immuno-dominant epitopes that mobilize a productive and robust cytotoxic response for a well-rounded T-cell immunity[13, 14].

An important hallmark of SARS-CoV-2 infection is viral pneumonia accompanied by pulmonary inflammation and edema characterized by eosinophilic infiltrates. A current study highlights the critical role of host T_H17 inflammatory responses in mediating this process. Elevated T_H17 responses were also observed previously in MERS-CoV and SARS-CoV patients. Also, studies in experimental animals using vectored vaccines have reported substantial immune enhancement in both the lungs and liver of experimental animals characterized by eosinophilic infiltrates[15, 16]. Therefore, careful parsing of T-cell epitopes is much needed to prevent the presentation of T_H17-inducing epitope elements increasing the chances of immune toxicity and disease susceptibility.

CONCLUSION

To conclude, a wide array of respiratory viruses induces severe pneumonia, bronchitis, and even death following infection. Despite this immense clinical burden, there is a lack of efficacious vaccines with long-term therapeutic benefit. Most current vaccination strategies employ the generation of broadly neutralizing antibodies, however, the mucosal antibody response to many respiratory viruses is short-lived and declines with age. In contrast, several studies on respiratory viruses have shown the presence of robust virus-specific CD8-T cell responses which has been shown to last for decades. Therefore, vaccine designs for emerging respiratory viruses need consideration and rational inclusion of CD8 epitopes to confer long term resistance. The OncoPept platform developed at MedGenome combines computational and experimental methods to mine strong CD8 immunomodulatory antigens with therapeutic utility across disease areas spanning respiratory and other infectious diseases, cancer, and autoimmunity.

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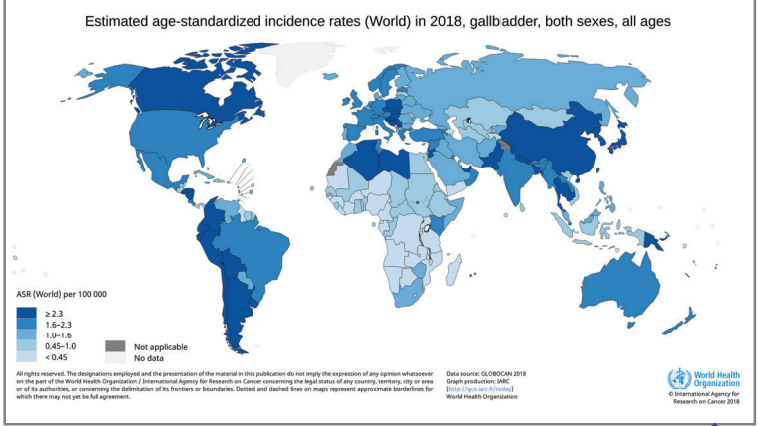
Identification of actionable targets and potential immunotherapy strategies to treat gallbladder cancers

Dr Kushal Suryamohan,
Bioinformatics Scientist,
MedGenome (USA)

Gall bladder cancer (GBC) is an aggressive gastrointestinal malignancy with a poor prognosis. It is the 20th most common type of cancer worldwide and its incidence is particularly high in specific regions of the world including Bolivia, Chile, Ecuador, Peru, Korea, Japan and India and is currently rising in Western populations (https://bit.ly/3kSLDMw) (Figure 1). In the United States, it is a more common malignancy in Southwestern Native Americans and Mexican Americans. There is also a gender disparity with GBC more prevalent in females than males. The median survival of patients with GBC is typically <1 year. This is mainly due to the fact that it is difficult to diagnose in the early stages and most patients are asymptomatic until the disease reaches an advanced or metastatic stage. Furthermore, the anatomical location of the gallbladder under the liver makes it easier for GBC to grow undetected. Radical surgery, chemo and radiation therapy remain the current mainstay for treating GBC. However, only about 10-15% patients are amenable to surgery and the 5-year overall survival rate of less than 5%. Currently, it's not clear what causes gallbladder cancer. Likely causative factors include gallstones, female hormone estrogen, lifestyle, food and feeding habits, etc.

While most cancer genome sequencing studies to date have focused on highly prevalent cancers, few large-scale studies have been performed on rarer forms of cancer such as GBC. Thus, we decided to focus on GBC and created a global consortium involving researchers from India, USA, Korea and Chile. This collaborative effort allowed us to obtain 167 GBC primary samples as well as 39 non-GBC samples and the corresponding matched normal tissue. This unprecedented dataset enabled us to map genomic alterations frequently observed in GBC and to determine if there were differences among tumors from different geographic regions. In our study published in Nature Communications, we carried out exome, whole genome and transcriptome sequencing of GBCs from these ethno-geographically diverse populations and identified several significantly mutated genes that were not previously linked to GBC. This included ELF3, a frequently mutated gene in GBC with genomic alterations in 21% of the sequenced tumors. We integrated somatic mutation, copy number variation and gene fusion data to identify affected pathways in GBC. TP53/RB1 pathway was most commonly altered in GBC. We also found WNT pathway and KEAP1/NFE2L2 pathway activation in GBC. WNT pathway activation was primarily driven through activating mutations in CTNNB1 and RSPO3 fusion. We observed frequent inactivating mutations in SWI/SNF pathway genes including SMARCA4, ARID1A and ARID2. We also found several therapeutically actionable mutations in RAS/PI3K pathway involving frequent alterations in ERBB2. ERBB3, BRAF and PIK3CA.

Figure 1. Worldwide prevalence of GBC.



The advent of immunotherapy has revolutionized cancer treatment with significant survival benefits observed in various cancers including melanoma and lung cancer. In order to determine potential opportunities for immunotherapy in GBC, we evaluated neoantigens arising from somatic mutations. We predicted high-affinity MHC class I binding neoantigen peptides for each tumor. This resulted in the identification of roughly 15 neoantigens per tumor. Most predicted neoantigens were derived from frequently mutated genes in GBC which included TP53, ELF3, CTNNB1, ERBB2, ARID1A and CDKN2A. Using peripheral blood mononuclear cells (PBMCs) from HLA-matched healthy donors, we were able to determine the ability of mutant peptides to activate T-cells. Three mutant ELF3 peptides, two mutant ERBB2 peptides and one mutant TP53 peptide were indeed found to activate T-cells and can be used as potential cancer vaccines. We also identified several actionable targets in GBC based on comprehensive characterization of genomic alterations. Up to 20% of all tumors in our study were found to have actionable targets based on available approved targeted therapies (OncoKB). We also identified neoantigens that can be pursued for developing immunotherapy strategies to treat gall bladder cancers (Figure 2).

By studying a diverse set of GBC samples across geographically diverse populations, our study has identified novel and potential cancer vaccine candidate genes for treating GBC. This is an important milestone in the ongoing global effort for finding biomarkers of translational significance. By selecting ethnically (and genetically) diverse population groups, this study further underscores the importance and need for incorporating genomic data analysis to identify candidate marker genes for diagnostic as well as therapeutic applications. This will result in better patient outcomes in the clinic through use of approved targeted therapies.

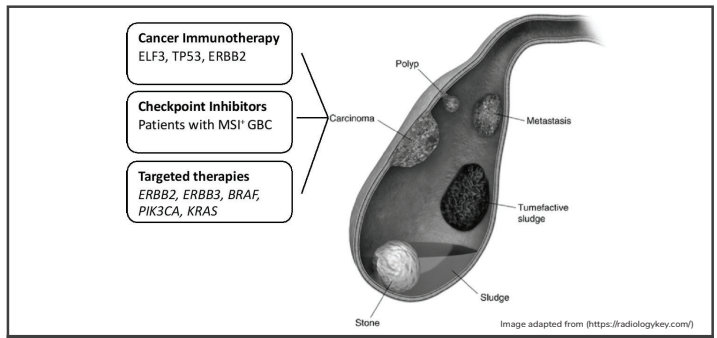


Figure 2. Actionable targets and potential immunotherapy strategies to treat GBC.

Link to manuscript: https://www.nature.com/articles/s41467-020-17880-4

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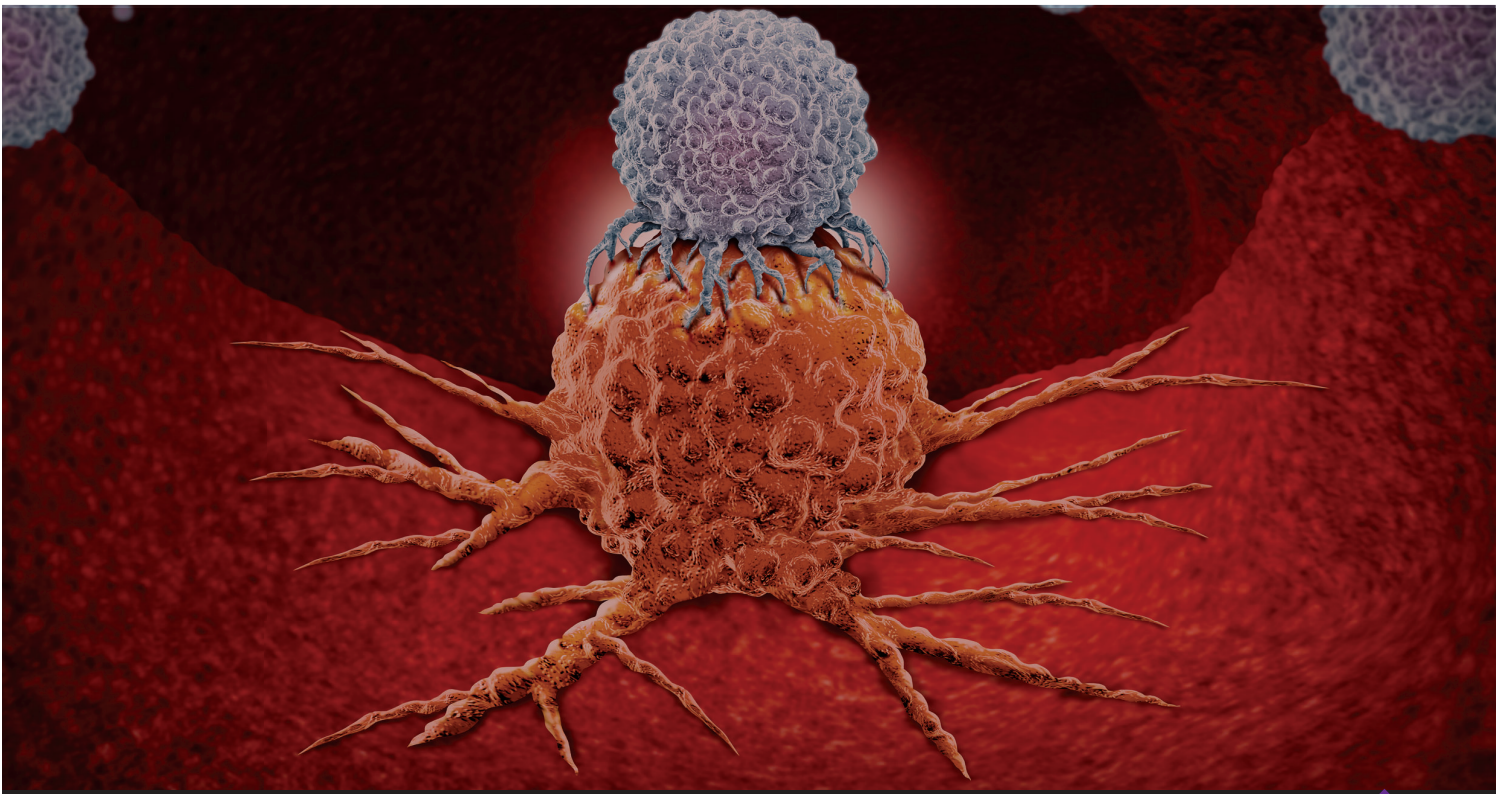


Special feature

Heart to Heart with Dr Ajit Mullasari

Director of Cardiology at the Institute of Cardio-Vascular Diseases at Madras Medical Mission, Chennai, India.

Dr Ajit has been part of a recent study on Coronary Artery Disease based on the upcoming Polygenic Risk Score (PRS) Technique. This study received recognition and has been published in the Journal of the American College of Cardiology.

We had a candid chat with Dr Ajit on issues related to CAD in Indian context, latest technology in CAD diagnosis, relevance of this new technique in CAD management and many more. Some excerpts below:

Why is the Indian population so vulnerable to CAD- Is it our lifestyle, food, genetics, or any other factors?

We always considered that there is a genetic issue with Indians with respect to CAD as South Asians no matter where they stay – in India or any other country always had higher cases of CAD than any Caucasian. Even if our body structure is much leaner, smaller and thus comparatively lower food consumption than the Caucasian, still we end up showcasing higher accounts of CAD.

> *"it is evident that Indians have higher accounts of CAD and we often arbitrarily blame it on either lifestyle or genetics."*

It can be said that the environmental issues such as blood pressure, diabetes, smoking, etc. affects every population and importance to that is paramount as these are lifestyle problems and affect our health irrespective of our genetic predisposition. And hence, a major focus has always been, very rightfully on keeping lower weight, quit smoking, keeping cholesterol down and other such environmental factors. But despite all these measures, it is evident that Indians have higher accounts of CAD and we often arbitrarily blame it on either lifestyle or genetics. We have found that certain cases of heart diseases such as high cholesterol also known as familial hypercholesterolemia runs in a family and is caused by a single gene i.e. it is a monogenic disorder. Thus, once identified, such groups of people can be given appropriate medication to manage this problem as they tend to suffer with severe diseases. However, these are very infrequent, around 1 in 200 as compared to the accounts of CAD we have in the country. So, it can be considered that South Asians have some genetic issue that is causing high CAD cases and hence, it is evident that a genetic factor is playing a major role apart from the monogenic factors, the genetic risk for South Asians was a bit abstract until now while all the focus was on the environmental factors.

> *"South Asians have some genetic issue that is causing high CAD cases and hence, it is evident that a genetic factor is playing a major role apart from the monogenic factors"*

Do you think it is critical to have a strong system to tackle Coronary Artery Disease in India?

Yes, and it can be done in two parts:

- Follow primary preventive health programs such as exercise, eat healthy, eat less, manage blood sugar, fats, reduce stress, get the pollution level down, etc. and take appropriate medication if you already have been diagnosed with cholesterol or diabetes, etc. This is of primary importance.
- Now with the scoring (PRS) available, we can identify a small population who are at a higher risk and in need of aggressive treatment and a stricter management of sugar and aggressively manage lifestyle factors- strictly no smoking, regular exercise, etc. As we cannot apply general or uniform treatment for all South Asian and hence, the scoring technique (Polygenic Risk Score technique) will help us to identify and give the much-needed focused treatment to those at high risk.

> *"Now with the scoring (PRS) available, we can identify a small population who are at a higher risk and in need of aggressive treatment and a stricter management"*

What role do you think that a genetic testing would play in treating CAD?

The moment we say South Asians are at higher risk than Caucasians or east Asians, we need to understand what are the factors behind it . **No single gene is responsible for CAD**. Most people suffer from a mixture of "bad" genes in various proportions. It is not one gene but a precise mix of the mutations together causing the phenotype /CAD.

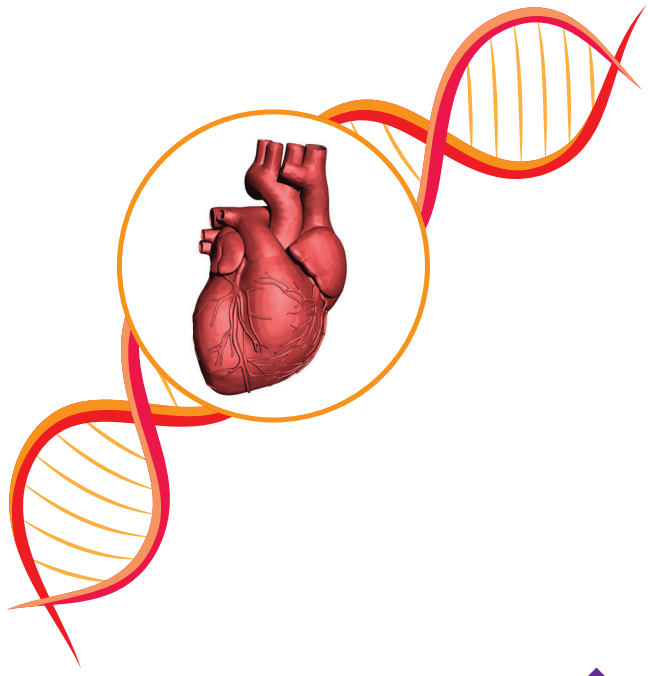
> *"Polygenic Risk Score technique is a way that will help us to use the data to stratify your risk and help in diagnosis and treatment."*

Hence, it is important to know the genetic correct traits. Earlier, it was very difficult to get the genetic traits as getting the whole genome sequencing was extremely expensive 10 years back and people also lacked the understanding of what to do with the information obtained from this sequencing i.e. how to analyse the data and what to seek from it. Polygenic Risk Score technique is a way that will help us to use the data to stratify your risk and help in diagnosis and treatment.

How do you anticipate the acceptance of this approach by people and do you expect any scepticism in the community?

Scepticism is warranted. That is how science improves and that is why nothing in science is taken on a face value. People were sceptical when Down's syndrome was first considered to be a chromosomal disorder and there will be many more such examples. With PRS, we are now taking a grip on the issue and it may get improvised further as we move along. What we have now with us is a validated science that was published in a prestigious and well-known journal. Now our focus is its application on a larger population. With this, a patient with PRS can be given a personalised treatment depending on his risk even if he may not have any immediate symptoms or issues. Thus, it promises a better management and prevention of possible heart problems. However, acceptance will also be affected by affordability of the tests.

> *"patient with PRS can be given a personalised treatment depending on his risk even if he may not have any immediate symptoms or issues"*



Talking about PRS, i.e. Polygenic Risk Score technique, you said that this technique is going to help in CAD diagnosis. But how exactly is it going to sync with the existing technique or system in place, what more can it add to the current diagnosis system?

This (PRS) is a completely new way of thinking. It is not like the other cases, where for example, a person is suffering from downs syndrome and you get the chromosomal analysis done or do one gene or one chromosome test and identify the root cause.

> *"60 genes that showcased as predisposing to the heart problem, but the absolute risk was approx. 1.6 times more among the South Asians compared to Europeans"*

What we are proposing now is that we are looking at a person's whole genome. To put it simply, no one gene determines that you will get a heart disease. It is always a result of the polygenic mix. More than 60 genes have been identified that seem to predispose heart disease at least in the European ancestry group. So, now we are taking a whole genome and looking at these 60 genes and analysing the frequency in which it comes out. Then, taking a set of diseased and healthy people, we see what is different in these 60 genes of these people. With a very sophisticated technology and based on the frequencies, it was clear that these 60 genes played a significant role in causing heart diseases in European population. This is also known as the GWAS (Genome Wide Association) study. With this result, we knew that these genes were important. But we did not have any information on the South Asian data. Hence, we targeted to analyse these genes among the South Asian population. Interestingly, it was the same 60 genes that showcased as predisposing to the heart problem, but the absolute risk was approx. 1.6 times more among the South Asians compared to Europeans in the same dataset. So, the same genes are not only the problem but also posing a higher risk to South Asians. This was validated in case control studies in South Asians from the UK Biobank, Bangladeshi cohort and MedGenome's data set of Indians/South Asians.

> *"Being a South Asian we already have a 1.6 times higher risk and for an individual the risk maybe 4 times higher"*

PRS code is a number, just like a score- so those people in top 5% -high risk scores will have risk similar to monogenic risk - even if they may look normal, may not have any family history, could be a non-smoker, physically fit, etc. PRS- Is a polygenic risk score of an individual calculated by using blood to determine a person's risk. Being a South Asian we already have a 1.6 times higher risk and for an individual the risk maybe 4 times higher. Hence, PRS can be a very important technique to diagnose a potential fatality and thus help in prevention by taking appropriate personalised treatment.

Where do you place this test in order of sequence for diagnosis and treatment- a preliminary or subsequent tests?

As someone with a significant background in the field of genetics of CAD, I would take it as a first step and consider PRS to be included within the very first few tests. So, along with the usual questions about one's habits, family history, I would like to know the PRS as well during the initial consultation. But for this to happen,

> *"consider PRS to be included within the very first few tests."*

- we need to first educate the people. It is important for people to understand that we now have a way to evaluate your genetic risk and we can guide you better.
- Another important deciding factor would be the cost. It needs to be affordable enough for people to go for it.
- Availability and accessibility to this test is also an important factor for people.

However, It's application should be validated in a large population, based on which the scores will be modified.

Is the young onset of CAD seen more in India than other countries?

People suffering from heart disease in their 30s and 40s do not always have the traditional factors. A Caucasian getting a heart attack would mostly attribute it to his/her lifestyle or habits such as smoking and high cholesterol. In India, about one third of smokers under 40 years of age get a heart attack but about 67% of them will have no associated disorders such as high cholesterol, sugar, or BP. In such cases, people end up associating the cause of the heart attack to other external factors such as stress, pollution, etc.

However, it is a matter of thought why a healthy person falls prey to a sudden heart attack or an active, lean, physically fit person running a marathon suddenly drops dead.

> *"matter of thought why a healthy person falls prey to a sudden heart attack or an active, lean, physically fit person running a marathon suddenly drops dead."*

If we analyse such cases, we may not find any classic family history or related to second degree relatives. In such a situation, one can assume that perhaps the entire family has the risk factor, but the disease has not been expressed due to low impact from any possible environmental trigger factors.

For example, if a parent has lived up to 80 years despite carrying the risk, it does not mean that their children will not get a heart attack in their 40s. As even with risks, perhaps the parents may have been a little more vigilant about their health as compared to the children and this would have been helpful in suppressing the trigger factors, which may not be the case for the children. So, if we do a PRS test for these people, we will be able to guide them that though their parents had a high-risk score, but with certain lifestyle practices they were able to manage their health well. Hence, we can give proper guidance along with medication to manage their heart health and avoid potential damage.

At what age should one get tested?

This is a one-time test unlike many other tests that we do yearly or at a certain interval. However, the idea is not to make everyone go for this test and create a panic. Some situations where I would recommend this test would be

> *"This is a one-time test unlike many other tests that we do yearly or at a certain interval"*

- If a person has witnessed sudden deaths or angioplasty or bypass surgery in the family due to cardiac problem with no apparent history known or despite following a balanced lifestyle, then the genetic factor could be evaluated.
- If there is a history of heart disease in a family and a person wants to take a precautionary step. Taking PRS, would help them understand their risk and manage their health better. Like the case of a known actress -Ms. Angelina Jolie, who has a family history of breast cancer, on testing found herself to be a carrier of the same BRCA gene which put her in 100% risk of developing cancer. The test gave her the choice to opt for double mastectomy, though an extreme but well informed and lifesaving decision. Likewise, PRS will also give people the choice to decide what they want to do for their well-being. Hence, a person showing a high-risk score, but no immediate symptoms of any disease can be guided to take required medication and precaution to avoid a severe illness in future.
- Someone who had angioplasty or bypass in their 40s.

This is a future of personalised medication like administering lipid lowering therapies to bring down total cholesterol to lower than 50, as risk score may vary person to person and no fixed treatment can be applied to all. Based on risks, the treatment will be personalised to suit each case.

Is the young onset of CAD seen more in India than other countries?

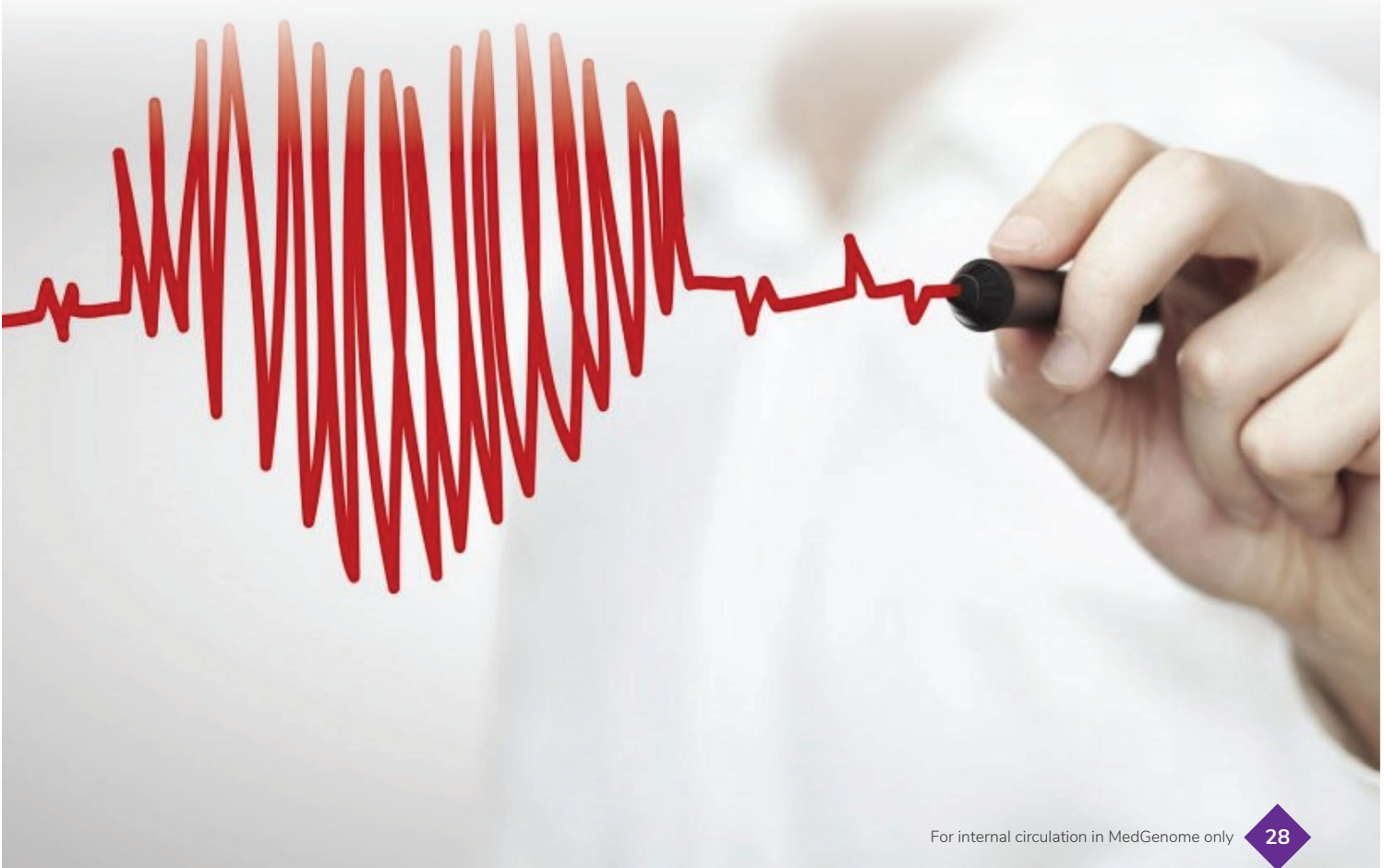
Yes, it will surely be used in diseases such as diabetes, cancer, and so on. We need to understand one fact that even if environmental factors play a role in causing diseases, the issue often lies within our own system. Even generations back these diseases existed. In current times, it may have only got worse due to additional players like the environmental problems or lifestyle changes and cases are more visible as people are living longer, dying less due to other reasons such as infectious diseases.

> *"surely be used in diseases such as diabetes, cancer, and so on"*

Are there any limitations for this technique?

Currently it is still undergoing validation so I cannot announce it as the pinnacle of all solutions for CAD diagnosis. We need to fine-tune it as this is just the beginning. We need to validate it among a larger audience in India, especially younger folks with heart diseases. This will help us to refine the score.

This is a very important publication as we always suspected that SA are predisposed to heart disease. This is also the first time that the study on this topic, even if the group was small, has been commendable and that too getting published in a big journal- American Journal of Cardiology, one of the top three journals in cardiology. This assures that the study has a lot of value and scope. MedGenome has helped us with the research in India, and we hope this association continues.



Featured article

My Journey through the Art and Science of **Genetic Counselling**

Dr GK Madhavilatha

Associate Scientist, MedGenome Labs Ltd;
Certified Genetic Counsellor (BGC-I, Level II)

I discovered the wonderful world of genetics during my graduation days, all thanks to my botany teacher, Mrs. Devaki Devi. The subject later became intriguing during my post-graduation in Applied Microbiology and is one of the reasons I went on to do a PhD in Biotechnology. The program at RGCB, Trivandrum gave me an opportunity to work on the genetic aspects of host-pathogen interaction of the most successful and highly adaptive human pathogen, Mycobacterium tuberculosis. From Sanger sequencing and analysis of 1000s of DNA fragments of mycobacterium, we went on to do WGS and published the first Tb Genome from India. This opened a door to the world of Genomics and Bioinformatics for me.

The call from MedGenome for the post of Bioinformatics Scientist, was more of a blessing than an opportunity, after my maternity break. And when I learned coding, I realised that learning to code is learning to create. I was part of the team curating variants deposited in various databases and also in our own reports. But I remember the day when I first saw an NGS Test report, and thought to myself that,

> *"How in the world a parent or a patient is going to understand this? how and why is a C greater than A (C>A) in a genetic test report? And thus, began my journey from Genetics to Genetic Counselling."*

So the questions many people ask is that 'what makes a genetic test report difficult to understand? Why do we need genetic counselling?' What we all need to realize here is that the clinician, the diagnostic company or the counsellor sees numerous reports a day, but for a patient and their family it is the one and only report which is the most important document related to their diagnosis, and this is going to be a permanent lifelong report card!!

We all know that there are over 6,000 genetic disorders (with known genotype-phenotype disorders....many are still unknown!!), many of which are fatal or severely debilitating. These disorders can be single-gene disorders, chromosomal disorders, mitochondrial disorders and complex/multifactorial disorders. And the variations themselves are again either whole chromosome changes (aneuploidies), portions of a chromosome (micro-deletions/duplications), exonic deletions/duplications, or single nucleotide variations, leading to different genetic testing methodologies for each of these different kinds of variations.

Thus, genetic testing raises a broad range of questions.

How will we choose the appropriate test? How reliable is the test? How many times should I do a genetic test? Does genetic testing hurt? What are our chances to have healthy children? What will the information mean for me and my family? What is the nature of the disorder and its severity? What options and resources are available? Will this affect my health, longevity, quality of life? What does this information mean for future insurability, employability, personal and social stigma, and discrimination?

Genetic counselling (GC) addresses such issues. The term "genetic counselling" was first introduced in 1947 by Sheldon Reed. It is now defined as a "process of helping people to understand and adapt to the medical, psychological and familial implications of genetic contributions to disease". Thus, GC is a communication process by which patients and their families are (i) informed about the inheritance pattern, genetic and genomic basis of genetic disorders, (ii) guided through the testing options available, and (iii) explained in a simple way, the complex technical and scientific information.

"But that is just the Scientific Part!"

Genetic counselling is not only about explaining the technical and scientific jargon in simple words. There is much more to it. It also includes the Art of Communication!

The issues are different in different scenarios. For instance, a negative or normal Chromosomal microarray (CMA) report is 'good news' for pregnant parents, but the same negative report for parents of an affected child need not be an answer they were expecting. A null report or a VUS is not good news for parents who have lost two neonates to cardiomyopathy, the situation is all the more distressing. The psychological impact of a genetic diagnosis in any disorder varies with its severity, treatability, and with the unique responses of different individuals and families.

A genetic counsellor tries to understand why the person wants the genetic testing and then provides information regarding the risk status, the benefits and limitations of the testing, the limitations of available testing methods, and the implications of the test results, including the psychosocial consequences of such testing. In this context the counsellor needs to be sensitive to the feelings of the affected family while delivering ground realities to them and be careful with the choice of words. For instance words like condition and variation are routinely used instead of disorder and defect.

Though the GC sessions include a pre-test and a post-test session, multiple sessions are the norm. It's a PROCESS. During the initial GC session, the counsellor will determine why the patient/family is seeking genetic counselling, followed by pedigree construction, discussion regarding the pattern of inheritance of the condition, risk of recurrence, available testing procedures and test limitations and reproductive options. A post-test session not only involves providing relevant information and but also focusses on psychosocial issues and referrals for other affected or unaffected family members.

Diagnosis and treatment do not come under the purview of genetic counselling. But at the same time, the family history and the clinical history received from the family or the patient during counselling goes a long way to provide an accurate diagnosis by the lab. We have quite a few number of cases where a revised report was sent after information from counselling was included.

The major ethical principles which govern the attitudes and actions of genetic counsellors are: 1) respect for patient autonomy, 2) non-maleficence 3) beneficence, and 4) justice. This requires that GC services be distributed fairly to those in need. Nondirective counselling, a hallmark of this profession, is in accordance with the principle of individual autonomy. This enables the patients to make educated and informed decisions regarding genetic testing.

Genetic counselling differs for different types of genetic testing like Diagnostic testing, Predictive testing, Carrier testing, Prenatal testing, Pre-implantation Genetic testing, Cancer testing Pharmacogenetic testing, etc. Counselling could be for a paediatric case or an adult onset disorder, could be for a 20 year old or 43 year old with breast cancer. The counsellor faces unique challenges in each of these contexts. So the language, the terminology, the tone, the setting are all different and unique for each case.

“This is the ART of Communication!”

A genetic counsellor faces ethical, moral and emotional challenges during counselling, and has to consider the socio-economic and cultural background of the patients. I remember my first case which was a rare condition, called recurrent hydatidiform mole, referred by the oncologist where the wife had six miscarriages. The ‘husband decided’ not to go for any genetic testing to even try to rule out a genetic cause, which could help in further reproductive decisions. In another case, the mother, a doctor herself, did not want to go for genetic testing for ‘fear of diagnosis’ of skeletal dysplasia in her daughter who had presented with short stature. But after repeated sessions over a period of 6 months, the genetic testing was done, and the child was diagnosed with Growth Hormone deficiency that is an absolutely treatable endocrinal disorder. I vividly remember a post-test counselling case where the parents, in a ‘phase of denial’ tried to persuade me to talk to the hospital authorities, convinced that their baby has been switched at the hospital.

There are both UPs and DOWNs in genetic counselling, as in any profession. The UPs are the THANK YOUs and gratitude shown by the parents, patients, mothers, grandparents and even the doctors. There is a satisfaction and contentment experienced at the end of each day. We give hope to a cancer patient, reassurance to parents who have lost their child, a dream to a pregnant couple, or a wish to a grandparent. At this juncture, I would like to thank all the teams at MedGenome Labs, because we are all part of THE BIG TEAM that makes this happen. Every sample that comes to our lab, and every report that goes out, matters to one family and can change their lives. Especially, in prenatal cases there have been many late-night messages conveyed to the couple (when reports are released late evening) saying that their foetus’s report is normal and the sigh of relief heard from the other side is a silent thanks to all of you.

But of course, all is not rosy, because we are dealing with pain, death and morbid conditions. The DOWN side of counselling is the emotional drain, anxiety and a feeling of helplessness on many days. The cases remain with us. It is not easy to talk to parents of an 18-year-old boy with suspected Alport syndrome, who have lost one 20-year-old with the same disorder two years ago; or a 20-year-old girl who has been diagnosed with breast cancer and has had a mastectomy; or a 36-year-old man with a progressive neurological condition. Peer support and team discussion play an important role to overcome these situations.

The GC team at MedGenome Labs is very special, in the sense that we are team of nine counsellors who can talk to families and patients in 7 different Indian languages other than Hindi and English. This helps us in building rapport with the patient quickly from any part of India. Genetic counselling is changing in this era of telemedicine. It is true that in telephonic counselling we cannot see the body language of a patient, but we are more tuned to understand the mood and tone of the patient over the telephone. As a counselling session goes anywhere from 30 minutes to an hour, we have not had any person simply disconnect the phone call.

So personally, for me the journey that started out as concern, led to curiosity, developed into a growing desire, and quickly turned into a vivid career aspiration. And when I brought my passion into it, I knew I want to be there when new milestones are reached in genetics and genomics, I want to continue helping people, train young aspiring counsellors and contribute in my own way to what we all term as personalised and precision medicine.

Science Meets Art

ASM Agar Art Contest 2018, 1st Place.
"The battle of winter and spring," Ana Tsitsishvili

Genetic counselling is a vast field where Science meets Art.....
And my journey through this wonderful field continues.....

From our Colleagues

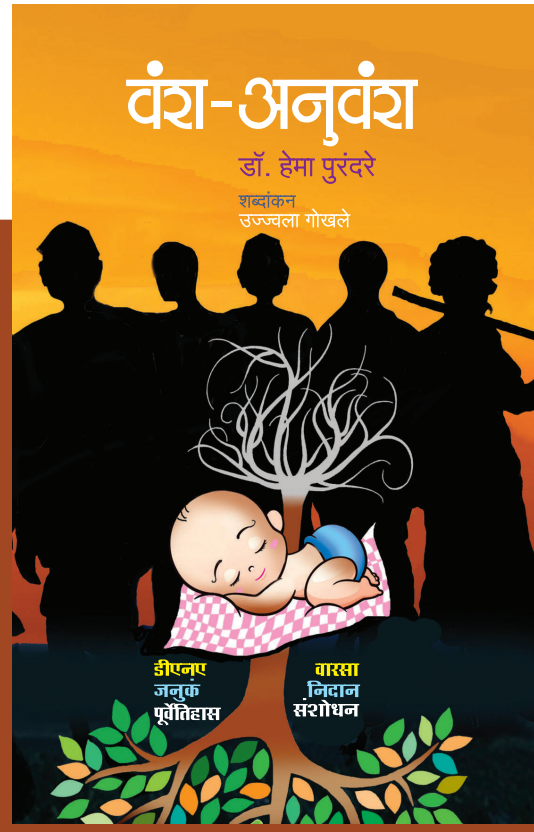
Verbum

Book

Vansh Anuvansh

Book review by Author

Dr Hema Purandarey,
MedGenome-CGHC, Mumbai



Dr Hema Purandarey is a well-known doctor and geneticist with over 40 years of experience. She has written several books, with the recent being 'Vansh Anuvansh'. The book is a memoir of Dr Hema's discovery of love for genetics, her journey to expand her knowledge and her experience with which she has touched numerous lives.

We are presenting a summary of Dr Hema's book, in her own words.

Spending almost over four decades in the field of Medical Genetics in India, I find my journey quite exhilarating. It includes the sight of evolution in this field as I wrinkled my skin, every prospect that seized me and each door I custom made for opportunities to knock. After writing more than five books on Genetics and clinical aspects of it, I was rather amused and fascinated to find myself still intrigued about all the learnings I was taught in between those moments. For the last couple of years, my best friend for more than half a century Dr. Nalini Inamdar who had witnessed my struggle to lay the foundation of private genetic services in India was urging me to write about my story and that's how in 2019 'Vansh-Anuvansh' gave itself birth and Ujjwala Gokhale transformed it with her beautiful words. My mother tongue, Marathi, that I hold so close to my own voice, decided to be the medium of my expression.

Dr Hema Purandarey (left) with Ujjwala Gokhale (right)

It is a memoir based on my life and my chronicles. The book depicts the journey of both me, and the field, since the 1980s to its current day. I borrowed the emotions of various events from my life, encompassing the people who molded me and remained as the echo of my life-learnings, still reverberating. The book revolves around the sweet unforgettable summer stories of my childhood, the gracious ever learning adulthood, and the dogma of a genetic clinic in a nation during the era that saw the field rise.

Setting a climatic tone in the book with my initial chapters about my own lineage – anuvansh. Beginning with the family I was born into and then the family I was married to, the book describes all the strong characters that shaped me. Parented by Dr. Shridhar. R Lele., who belonged to a remote village Mutat', in Sindhudurg district in Konkan region of Maharashtra and obtained his doctorate from London, the founder of Borosil Glassware and Mrs. Geeta Lele, M.A. (Sanskrit), the family tradition of high qualifications had set its tone in the early 1900s. I was named after the golden creeper (Hemlata), who was defined so, to achieve great heights. But identifying myself in the carefree summer days in 'Mutat', I wanted nothing more in life, than the mangoes and creeks that I cling on to as one of the most treasurable parts of my life. Medical life is not something I chose for myself, yet with all the ambition and challenges it came with, it is something I pursued with the perseverant principles, that I have inherited from my parents.

My husband Mr.Madhav Purandarey, B.E.(electrical) with IBM came along as a life partner who understood those principles and advised me to chase my dreams. I started as a lecturer in Anatomy at Grant Medical College, J.J Hospital, Mumbai. Since my family was my priority then, I pursued post-graduation nine years into my career as the associate professor, yet when I found Genetics and Embryology in my textbooks and lectures, that was when I fell in love with the subject. I never stopped at any degree or examination, which is why I think it was not at all surprising when I did seek my PhD in Genetics at the young age of late 60s. Seeing my passion for the subject Dr. Sanjay Deshmukh, Professor of Life Sciences and Head University Department of Life Sciences, University of Mumbai was kind enough to accept me as his student. When I ventured in the field of Genetics, there was no formal education or a degree or a diploma in medical genetics. But like drops adding to the ocean, one by one I did more than 25 self-sponsored courses across the field of Cytogenetics, FISH, IVF, Genetic counselling and Reproductive Sciences from the hospitals of U.S.A., U.K. and Singapore and other such countries, for learning every worldly course possible surviving the harshest of winters and maintaining the precarious work life balance single handedly.

Dr. Victor McKusick – Father of Genetics

Innovator of Mendalian Inheritance in Man

Seeking the mentorship from 'the father of medical genetics' Dr. Victor McKusick to Nobel Laureate Sir Robert Edwards, a pioneer in reproductive medicine and one of the brains behind in-vitro fertilization, to the renowned geneticist Dr. Raju Chaganti of Sloan Kettering Institute who specializes in the study of genomic instability in cancer cells, all the courses and fellowships and experience in the foreign land, most of the time alone made me yearn for my own country. Dr. Victor McKusick also believed only a native can best understand their culture and beliefs and gifted me an inscribed copy of his Mendelian Inheritance in Man. In the following years, I visited many renowned foreign institutions to upgrade my knowledge and to keep abreast of the new technology. When I returned, I was allowed to start a genetic lab at the Grant Medical College itself by my then superior Dr. Lata Mehta head of Anatomy Department. However, when I wished to expand it, every door that I knocked for permission, every official I met and tried to explain the benefits of genetic testing and counselling, I was turned down and found myself to meet a never-ending series of challenges but with each test my resolve became firmer.

While I was trying my best to build a foundation for the genetic services in India, my husband passed away in his early 40s and with two daughters Smita and Shilpa to look out for, provide for and educate while also dealing with bureaucracy and struggle of explaining the healthcare professionals – the unheard, sometimes I myself wonder that where did I get the energy to deal with that daunting situation. I believe I got every ounce of that strength from the legacy of my parents' principle of 'never ever giving up' and the support of a few of my colleagues and the Leles and Purandares.

In 1981, with the blessings of my guru, Padmabhushan Dr.R.D.Lele, I founded my own clinic namely 'Birth Defects Centre'. However, in a few days realizing that the patients were apprehensive of the name of the clinic, it was changed to Centre for Genetic Healthcare (CGHC). To include all prenatal diagnostic care under one roof, I reached out to fetal experts, sonologists, technicians who I trained myself and managed the clinic independently for nearly 25 years.

To expand the scope of tests I collaborated with Dr. Avinash Phadke's Lab - Piramal Diagnostics now SRL. CGHC participated and contributed to a lot of medical camps. This enriched the status of genetics in the remote areas of Maharashtra and elsewhere in the country. Later for further upgradation in molecular testing CGHC became a part of 'MedGenome Labs Ltd.' founded by Mr. Sam Santhosh, with an envisioned dream to help thousands of people and their future generations.

I pursued courses on Plant and Animal Genetics, Poultry Science, Ayurveda, Graphology and Painting. Many of these courses were also to entice students towards genetics, which I loved the most. As my own career progressed, to my immense satisfaction my daughters qualified in the fields of Pediatrics, Obstetrics and Genetics and though settled in U.S. and U.K. are my pillars of strength. Despite my busy schedule, I offer support to the local government recognized school started by my father at Mutat. and do take care of my certified export quality mango orchards and guide other farmers too.

जनुकीय प्रयोगशाळा

समाज ऋण, मुटाट, माझी स्वप्न नगरी

हेमँगो

Encompassing my life journey along with different stories that I came across during my clinical experience, I tried to portray in my book the inspirations of my life. We see people coming for premarital counselling, conceptional, prenatal and even predictive counselling and testing. This book is about more than dozens of those case studies which will in turn help the people to understand the role of genetics in healthcare.

A few years ago, I encountered an urbanite couple who had a family history of an adult onset disorder which made the person deteriorate both mentally and physically. Realizing something was amiss, they consulted me to make sure it was not passed on to the next generation. With detailed history and testing, we had a confirmed diagnosis of the Huntington disease. The patient was wise enough to create awareness in his family. This was one of the whole new shifts in the perspective I observed during my journey.

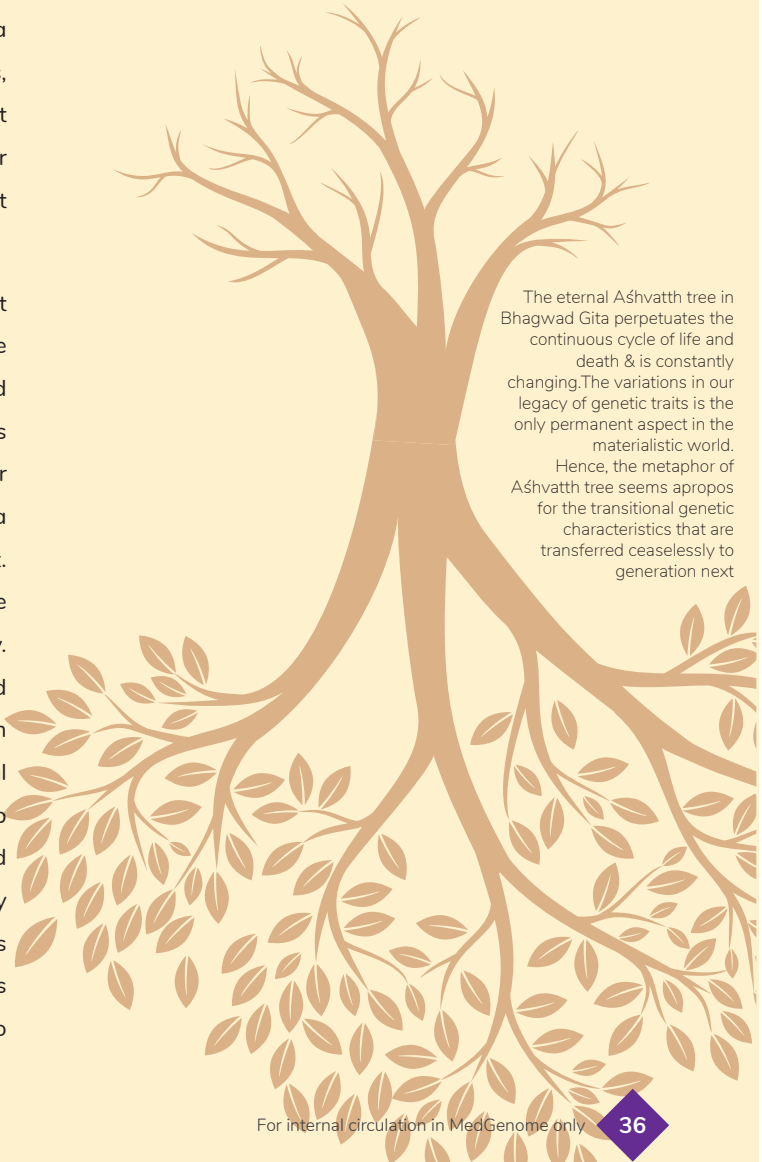
One of the most astounding cases I did come across is of a lady with Marfan syndrome. The lab test confirmed the gene for the Marfan and her inheritance pattern. Considering the syndrome, she was advised a timely motherhood. But she chose to take advantages of prenatal diagnosis or IVF with PGD and even surrogacy so that she can pursue her career goals. A determined millennial kid indeed!

As the generations pass and technologies come up, I have seen my passion grow as said, 'now we have moved from cadaveric dissection to molecular dissection.' What started as a detection of chromosomal errors has reached the study of gene mutations and nearly editing the genes.

Even though the blood reports indicate something is wrong, due to lack of genetic advice some patients may overlook it. Such was a case of this patient with sickle cell trait. Hence, when the duo mentioned their great difficulty in breathing during their trip to Ladakh which they had to forgo halfway through, it was used as evidence they demanded for their condition. Genetic Counselling sessions are not limited to diagnosing the patient himself but the repercussions and serious risk to the progeny is also predicted on the basis of the inheritance pattern of the particular disease.

Some stories even enrich you with humanity and grace that as a species we have for each other. Stories of Muscular disorders, severe immune deficiency disorders and many more that do not affect a person's cognition, makes it difficult to convey their diagnosis and to be the spokesperson of the life sentence that biology intended to pronounce.

The medical camps that I had collaborated with, set a different experience. It unveiled people a little more for me. I remember one of the patients I met during the 'Chromosomal Abnormalities and Club Foot' camp, which was conducted by the collaborative efforts of Dr. R.S Kulkarni, the Civil Surgeon of Oras Hospital and our CGHC team. The old farmer accompanying the patient, a soon-to-be grandfather had an isolated unilateral clubfoot. Obviously, working in the fields had proved bothersome for him. He had a hunch that what he had had something to do with heredity. Unfortunately, his daughter in law's sonography report had indicated similar defect in the fetus. However, this illiterate person was very observant. He had not only noticed many such physical deformities in his neighborhood but was aware of the mental sub normalcy associated with a few of them. Obviously, he was worried about the mental health of the unborn. The survival of the progeny may be an animal instinct, but every species adapts its own heights to do so. Thus, when a counselling was done to explain, his instincts were taken right, and prenatal diagnosis was offered to the family.



The eternal Aśhvatth tree in Bhagwad Gita perpetuates the continuous cycle of life and death & is constantly changing.The variations in our legacy of genetic traits is the only permanent aspect in the materialistic world. Hence, the metaphor of Aśhvatth tree seems apropos for the transitional genetic characteristics that are transferred ceaselessly to generation next

डॉ. हेमा पुरंदरे, उमा कालेकर, डॉ. संतोष करमरकर, गो फोलिक, मेयर विटाबायोटिक्स, सी. एम. ई., सिंधुदु

टॉग कॉनक्लेव्ह, विशाखापट्टनम

सी. एम. ई., रत्नागिरी

Similarly, another unforgettable memory is of the patients I met during the 'Pediatric ECHO camp and Janukiya Samupadeshan Shibir' conducted at Dr.Redkar Hospital at Redi, Sindhudurg. I remember the 12 years old girl who was bullied for being lethargic in her physical training classes. At her age, usually children find all excuses to play. However, this grievance struck me odd. Her evaluation suggested that her breathlessness and fatigue were related to her heart condition. Thus, they were suggested to inform the school about her condition and to visit a pediatric cardiologist for management.

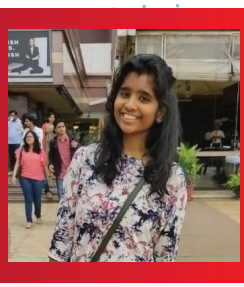
We perceive our world through our senses, and this becomes the key understanding of our outlook. Although over the years, I have realized how patients of congenital eye and hearing disorders adapt and combat with life. However, if they have a family history, genetic counselling becomes imperative. I have practiced reproductive counselling for the longest and it gives a very close look up to all the family dynamics and nature of people. The case of Fragile X that I have mentioned in the book is the experience that has enriched me to the soul. We have to send out the message that the genetic diagnosis is neither a bad affair or a stigma. With ever changing face of technology such as CRISPR Gene Editing among others, we will find a way to even manage / treat such diseases someday in future.

All genetic disorders are in perpetuity however, the people who live with the patients and care for them are highly overlooked in our society. Right from survivors' guilt to disgrace that society casts on such families, all stir a need to unburden the load. Hence, awareness should be spread to help people who are suffering – both aloud and silently. Thus, I have translated all my clinical and laboratory experience in the simplest way possible, making this book for non-physicians and physicians. For this journey, I thank from the bottom of my heart, all my patients for trusting me, my staff for supporting me, Ujjwala Gokhale and Ms. Shweta Mahalingam for their assistance in writing Vansh Anuvansh and Granthali respectively, my publishers & above all Mr. Sam Santhosh for letting me reach out to the entire MedGenome team.

From our Colleagues

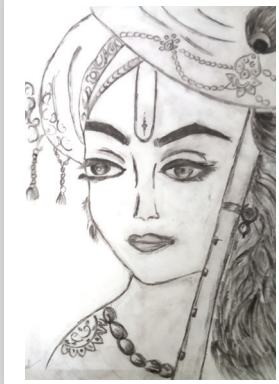
Art meets Science

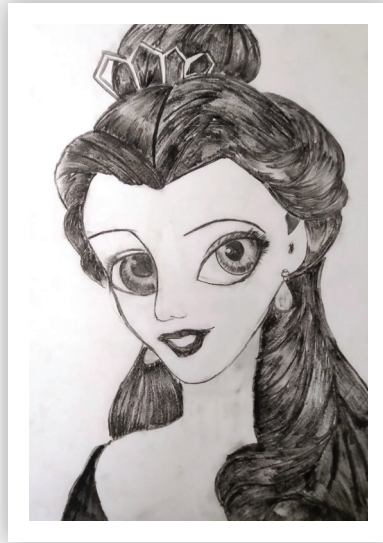
"Art and science have so much in common, the process of trial and error, finding something new and innovative, and to experiment and succeed in a breakthrough." - Peter M. Brant



By: Ms. Rojashree J

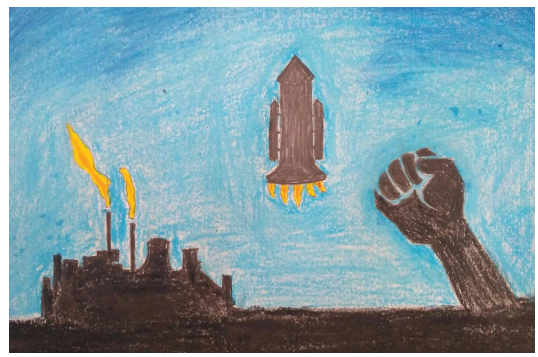
Genome Analyst, Ops Dept





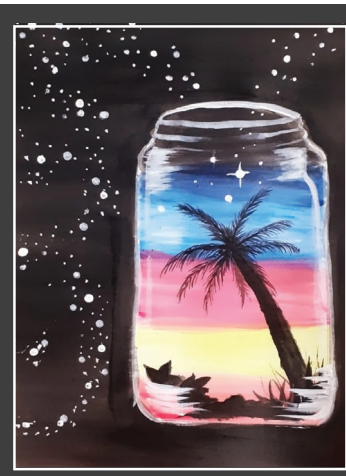
By: Dr Priyanka Shrivastava

Associate Scientist, Ops Dept

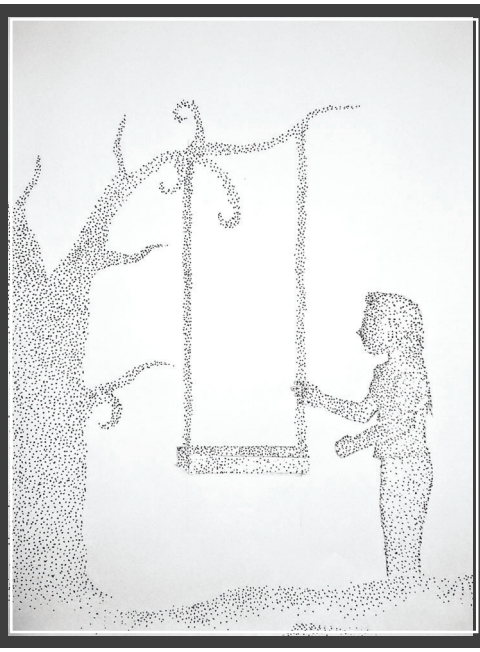


Our employee's little Picasso :)

By: Aayushi saha (7 years)
DNA of Ujjwal Saha,
Sales Dept



By: Nithyashri Lokesh (12 years)
DNA of Sujatha,
Finance Dept



"Stippling is the creation of a pattern simulating varying degrees of solidity or shading by using small dots"

By: Kirthana Warrier (11 years)
DNA of Hiranjith G H,
Corp Marketing, MedGenome- USA

From our Colleagues

By : Sanjay nayak

Hide and seek, Old airport road, Blore

Hide and seek, Old airport road, Blore

Splash of colors, Lalbagh Botanical Garden, Blore

Serenity, Nandi Hills

Celebrations

MedGenome celebrated the **74th Independence Day** with fun filled activities and entertainment. Our very dear Mr. Malaichamy was the commentator of the evening who with his wit, kept the audience engaged throughout the event.

An online Independence Day Quiz related to the Indian Independence Movement and Constitutional Law was organised. Ms. Sandhya Nair won the competition followed by Amit Sharma and Abhishek Khandelwal in 2nd and 3rd position respectively

Some of our very talented teammates performed for the event.

Kudos to the HR & Administration department for organising it !!

Employee connect

EDIFY-Healthshots

Corporate communications now has a new identity – Edify! All company-wide announcements are being shared through this mailbox to ensure the key messaging is not lost in the bunch of mails our employees may receive on regular basis.

On another important note, Edify launched HealthShots, MedGenome's wellness brand for the employees. It focuses on holistic wellness of our employees, covering physical, emotional, and social wellbeing. We started the initiative with an objective of promoting healthier lifestyles and encouraging our employees to achieve a sustained wellbeing.

The brand has been kicked off with a series of weekly wellness related mailers covering topics on importance of hydration, sleep, laughter etc. Watch out for more such informative mailers and wellness related activities under this brand!

Be Healthy! Stay Happy!

Employee connect

WELCOME

Our New-Joiners


Amulya Prasad Muduli


Devi Sooryanarayana S


Gunjan Satvir Tanwar


Indrajit Dey


Jetti Purushotham


Keerthana K


Navjot Singh Aulakh


Raj Vignesh Murugan


Ravichandran


S Sameeruddin

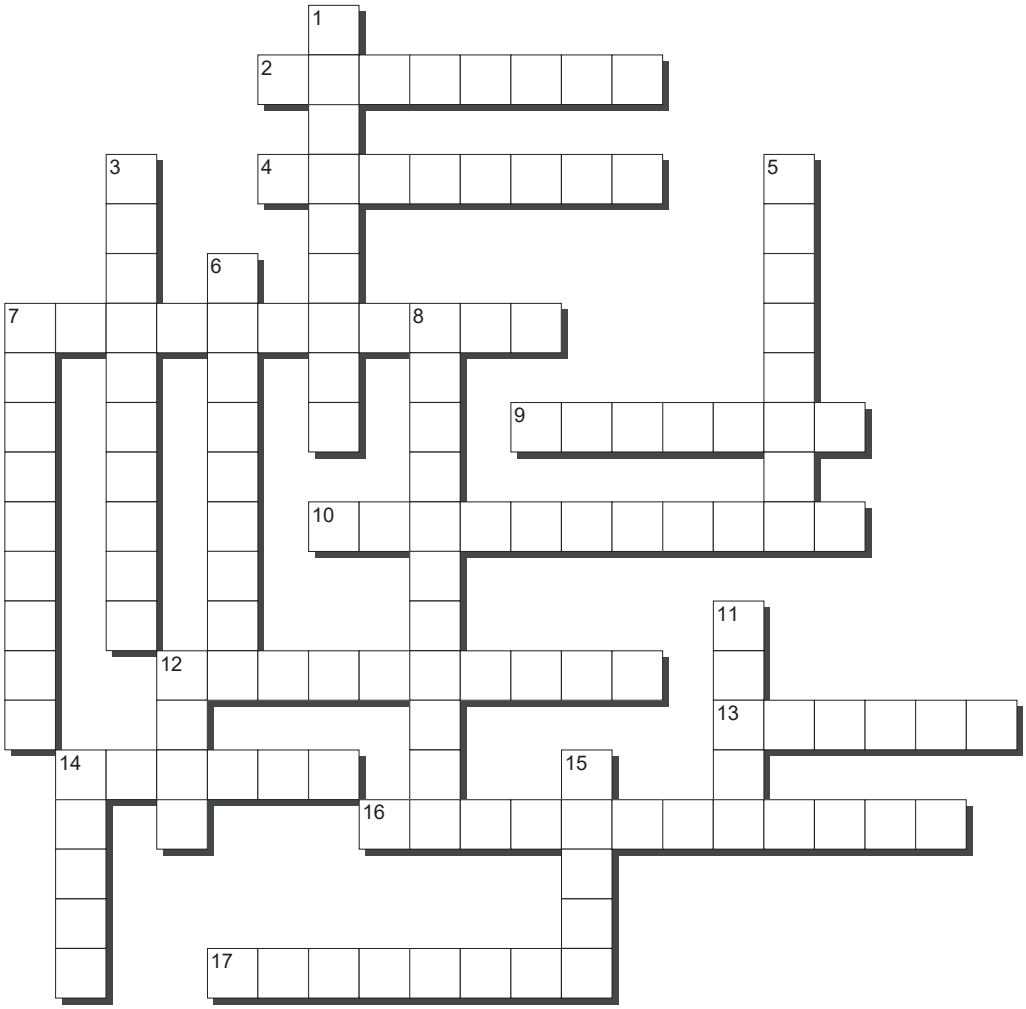

Sunmathy K


Tijimol Chandy


Venkatesan


Yash Dadhich

MedGenome connect



[Across]

2. The genetic makup of a living thing.
4. The field of biology that studies how genes control appearance.
7. The likelihood that an event will happen.
9. Different versions of a gene.
10. Long molecules made of DNA that hold genes.
12. All the individuals born at the same time.
13. The part of the flower that creates pollen.
14. A monk who experimented with pea plants.
16. Two different alleles for a trait.
17. The trait that is visible when other traits are present.

[Down]

1. The trait that is hidden when other traits are preset.
3. Two copies of the same allele.
5. Separate units.
6. An image of chromosomes.
7. The physical appearance of a living thing.
8. Genetic traits are _____ from a parent.
11. Stores female reproductive cells.
12. Region of DNA where instructions for one trait are kept.
14. Paired male and female cells for reproductive purposes.
15. Characteristic like hair freckles or dimples.

Previous Winner

Lakshmi Soundarya

Anurag Gupta

Kindly mail your answers by 31st Oct 2020 to editor@medgenome.com. The first two people to answer the puzzles correct will be featured in the next edition of our newsletter.

Wishing you and your family,
a very Happy Dussera & Happy Diwali!

MEDGENOME

The market leader in Genomics-based Diagnostics and Research

One-stop solution for all your Diagnostics and Research needs

Flow Cytometry | Microarray | Sanger | FISH | NGS | PCR | IHC | Fluidigm

NGS: X10 | HiSeq | MiSeq

INDIA

Bangalore
Chennai
Delhi
Kochi
Mumbai

US

Foster City

SINGAPORE