MEDGENOME

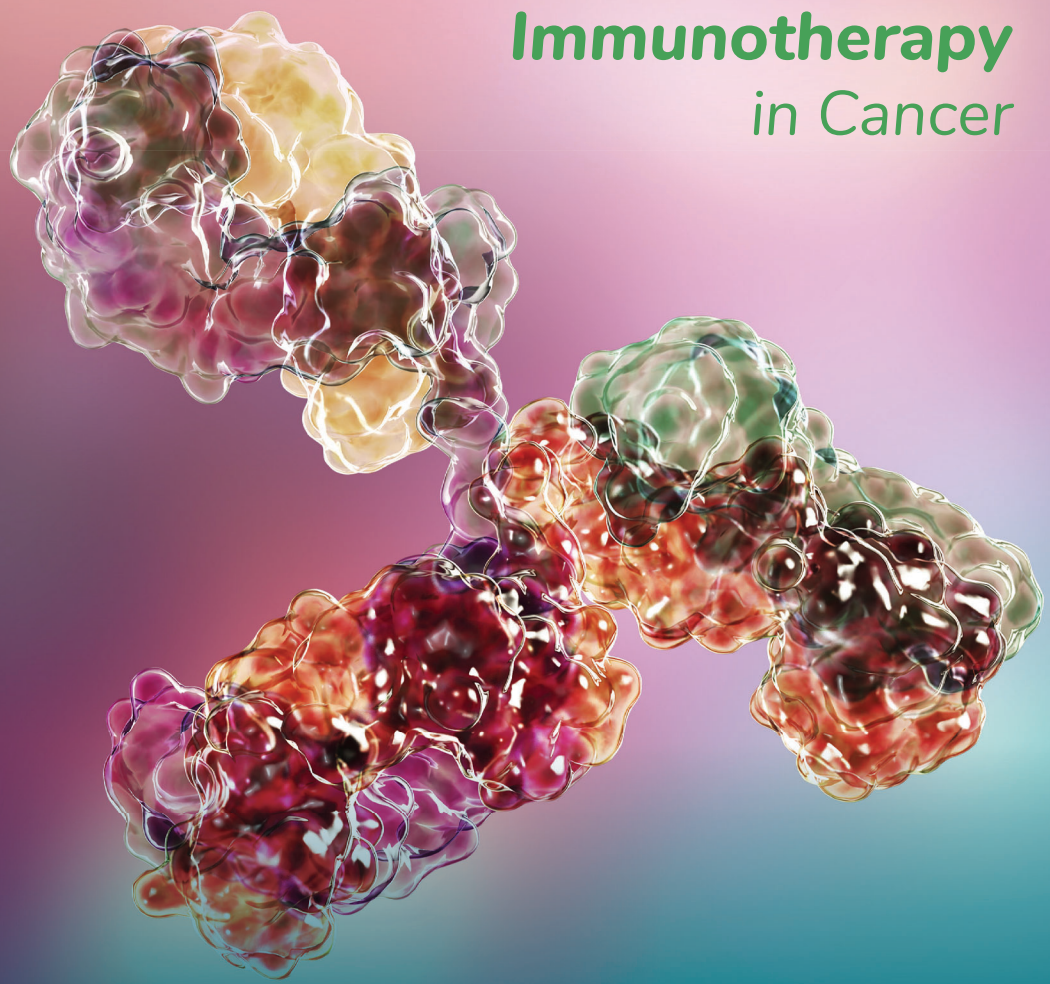
Vol 18 | July 2021

GeKNOWme

Internal Quarterly Newsletter

Cover Story

Immunotherapy in Cancer



Research

Mutations in human ACE2 receptor can alter susceptibility to SARS-CoV-2

Book Review

Man's Search for Meaning

WORDS FROM THE **FRONTLINE**

Dr Avi Nahar,
Director, Sales- Actia, Claria & Micra

> **If You Are Working On Something That You Really Care About, You Don't Have To Be Pushed. The Vision Pulls You.**
>
> **– Steve Jobs**

Dear Colleagues,

Greetings!

As I complete an year with the MedGenome family, I would like to thank everyone here who made me feel welcomed & supported at every step for my better understanding & learning.

I really admire the colleagues who have been around for years, giving their heart & soul to this wonderful organization. The very essence of belongingness sets us apart from other players; no wonder, we indeed are the true market leaders in our space.

Last year & a half has been tough for each one of us & our family members; yet we prevailed & ruled the market with a robust market share, boosting the confidence & faith of our promoters in us. We saw a huge upside in our Claria Sales with increased non-invasive tests, which motivated us to separately draw a strategy around Obstetricians & IVF Centres. MedGenome continues to dominate Actia range of tests with a robust 26% market share as we increase our portfolio & share of Micra range.

As they say, it's easier to achieve the leadership position but it takes an entirely different level of efforts, hard work, sincerity, dedication & belief to maintain the position for years.

For me, it always is an "Extra Mile" that makes all the difference. And we are at the precipice now, where the only option ahead of us is to take off and I'm confident that we will.

I remember, when I joined MedGenome, the team was struggling to find hard grounds due to tough market conditions. But I must congratulate everyone in the organization to have come together when it really mattered to support the Sales and stand besides each other for any Technical, Scientific, Commercial or Management support we needed. Our go to market strategy was & is indeed very simple; increase the breadth & penetrate deeper. We need to continue adding good number of new consultants as regular prescribers & develop new HQs to be as close to the customers as possible. For the same reason, we have started appointing Channel Partners to increase our brand visibility across the country.

We struggled, we adapted, we foresaw, we improvised & we prevailed.

My heart goes out to all who suffered personal loss due to COVID-19, but we are in this together. I plead to every colleague, please do not hesitate to reach out to anyone you feel comfortable with for any assistance you might need: professional or personal. We are all there to hear you, no matter what. I also salute to all our female colleagues who fight a different battle every day & still come out as winner, every single day. You are inspirational.

Everyone working in the Lab Operations & Customer Support deserve kudos. When the world opted to stay in, you stepped out as duty called. Those long hours, those stress calls from Sales, those break downs, those frustrations & the client's fury; you took it all, yet stayed calm, poised & supported us all the way.

Our support verticals, especially Logistic team played a crucial role in their limited capacity to sustain the transits; Genetic Counselling Services, Bio-informatics, IT & Financial teams kept the pace of delivering the objectives for organization's needs which really helped us capture & close many new deals in spite of market challenges.

I would like to congratulate every Sales Team Member for your relentless efforts in strengthening our client relationships which is stronger than ever. You are our foot soldiers on the ground & we are very proud of each one of you. But we need to be cognizant of the fact that we are "Brand Ambassadors" as well; a great responsibility. To live up to the expectations, we need to act smart, professional & keep upgrading our technical selling skills. Educational & Information based selling is a long term game; we need to capitalise on our strength. Sales team is blessed to have our voice heard & our feedback taken positively, which shaped up our performance pretty well in last couple of months. But we have a long way to go; we cannot be complacent about it.

"Knowing Is Not Enough; We Must Apply. Wishing Is Not Enough; We Must Do."
– Johann Wolfgang Von Goethe

We expect our Sales team to continue looking out for opportunities for every level of collaborations, while You would be glad to know that at management level we are entering into new strategic partnerships with premium institutes like Wadia Chldren's Hospital – Mumbai & Ganga Ram Hospital, Delhi which will be one of it's kind.

Although, we all have a lot to introspect in the manner we operate, the processes we set up & vigilance we show to mitigate our business risk; I firmly believe that we are moving in the right direction. With more accountability & ownership at every individual level, I'm confident that we will maintain our market leadership for years to come.

Until we meet again in flesh, we are certainly being tested... but not to show our weaknesses, but to discover our strengths...

Lastly, I extend my gratitude to our management to have brought MedGenome this far & assure on behalf of entire MedGenome family, we will certainly make you all proud.

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A peek into the future - 1

Most Talked About

The News

MEDGENOME NEWS | January to March 2021 | MEDGENOME NEWS

ACTIA • CLARIA • PRIMA • MICRA • Business • Research • Awards • Genetic Counselling • Health Care

July 05, 2021

Outlook
THE FULLY LOADED MAGAZINE

MAGAZINE | INDIA | CRICKET | OPINION | VIDEOS | PHOTOS | WORLD | ENTERTAINMENT
HINDI | BUSINESS | MONEY | TRAVELLER | RESPONSIBLE TOURISM | POSHAN | PLANET OUTLOOK

Home > Website > National > Neanderthal, Extinct 40,000 Years Ago, Have No Role In Covid Severity In South Asia: Indian Scientists

Neanderthal, Extinct 40,000 Years Ago, Have No Role In Covid Severity In South Asia: Indian Scientists

Neanderthal lived about 40,000 years ago in Eurasia and they were supposed to be the closest extinct human relative.

Jeevan Prakash Sharma
11 June 2021, Last Updated at 3:58 pm

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Neanderthals were a different species of archaic human who lived in Europe and Asia.

File photo

A group of Indian scientists has countered a German research paper which showed that South Asians are more vulnerable to the disease Covid-19 than others as they have some genetic similarity with Neanderthal.

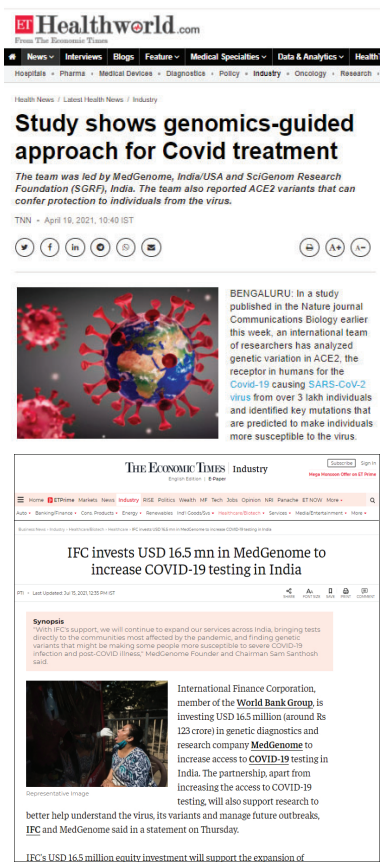
Neanderthal lived about 40,000 years ago in Eurasia and they were supposed to be the closest extinct human relative.

Scientists from Max Planck Institute for Evolutionary Anthropology in Germany wanted to find out why the virus Sars_Cov_2 causes severity and death to some people whereas others get mild or no symptoms.

They believed that besides age and comorbidity, variation in a specific part of people's genes (DNA) might be playing a role in it.

Also read

- Covid Explained: Why Is Oxygen Concentrator In Demand And How Is It Different From Cylinder
- Covid Surge: Prices Of Essential Medical Devices Skyrocket As Govt Fails To Check Black Marketing
- Covid Vaccines Speed Up Production Of Antibodies In Those Who Have Recovered From Infection: BHU Study



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Study shows genomics-guided approach for Covid treatment

The team was led by MedGenome, India/USA and SciGenom Research Foundation (SGRF), India. The team also reported ACE2 variants that can confer protection to individuals from the virus.

TNN • April 19, 2021, 10:40 IST

BENGALURU: In a study published in the Nature journal Communications Biology earlier this week, an international team of researchers has analyzed genetic variation in ACE2, the receptor in humans for the Covid-19 causing SARS-CoV-2 virus from over 3 lakh individuals and identified key mutations that are predicted to make individuals more susceptible to the virus.

THE ECONOMIC TIMES | Industry
English Edition | E-Paper

IFC invests USD 16.5 mn in MedGenome to increase COVID-19 testing in India

PTI • Last Updated: Jul 15, 2021, 12:35 PM IST

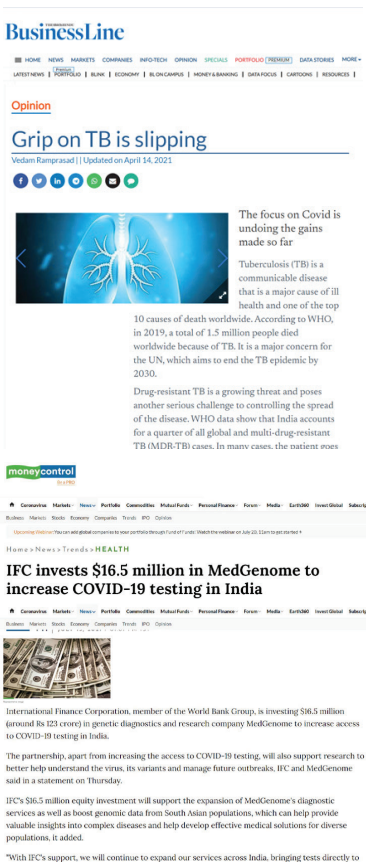
Synopsis

"With IFC's support, we will continue to expand our services across India, bringing tests directly to the communities most affected by the pandemic, and finding genetic variants that might be making some people more susceptible to severe COVID-19 infection and post-COVID illness," MedGenome Founder and Chairman Sam Santhosh said.

Representative Image

International Finance Corporation, member of the World Bank Group, is investing USD 16.5 million (around Rs 123 crore) in genetic diagnostics and research company MedGenome to increase access to COVID-19 testing in India. The partnership, apart from increasing the access to COVID-19 testing, will also support research to better help understand the virus, its variants and manage future outbreaks, IFC and MedGenome said in a statement on Thursday.

IFC's USD 16.5 million equity investment will support the expansion of



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Opinion

Grip on TB is slipping

Vedam Ramprasad | | Updated on April 14, 2021

The focus on Covid is undoing the gains made so far

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the top 10 causes of death worldwide. According to WHO, in 2019, a total of 1.5 million people died worldwide because of TB. It is a major concern for the UN, which aims to end the TB epidemic by 2030.

Drug-resistant TB is a growing threat and poses another serious challenge to controlling the spread of the disease. WHO data show that India accounts for a quarter of all global and multi-drug-resistant TB (MDR-TB) cases. In many cases, the patient goes

moneycontrol
by e4m

Home > News > Trends > HEALTH

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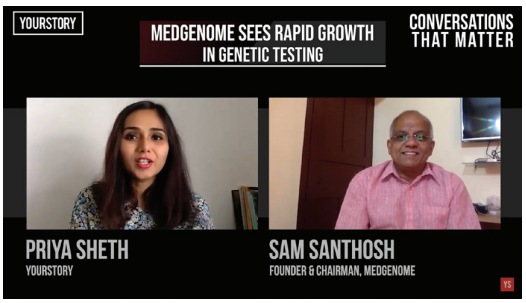
IFC's $16.5 million equity investment will support the expansion of MedGenome's diagnostic services as well as boost genomic data from South Asian populations, which can help provide valuable insights into complex diseases and help develop effective medical solutions for diverse populations, it added.

"With IFC's support, we will continue to expand our services across India, bringing tests directly to

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

Please click below to play video
https://www.youtube.com/watch?v=SfYDzXWJM0U



Please click below to play video
https://yourstory.com/video/daily-dispatch-yourstory-monday-14th-june-2021/amp

MedGenome Connect

Claria
Reproductive Genetics

The pandemic continued and the 2nd wave hit us hard in this quarter but unlike last time, we at MedGenome, were better prepared. We ramped up our digital engagement especially for NIPT as we had observed an uptick in NIPT numbers during last year's lockdown. Our advertisement campaign and creatives were targeted at positioning NIPT as a better alternative to traditional screening methods during the lockdown since it offers superior accuracy and convenience of minimal hospital visit. This helped push our NIPT numbers despite the lockdown. But unlike the previous year, this year affected doctors in large numbers and due to this we could not conduct any events or webinars due their unavailability. However, the lockdown period has shown NIPT to be a reliable and sought-after test for first trimester screening and we hope to continue the momentum as the lockdowns are lifted.

ACTIA
Inherited Genetics

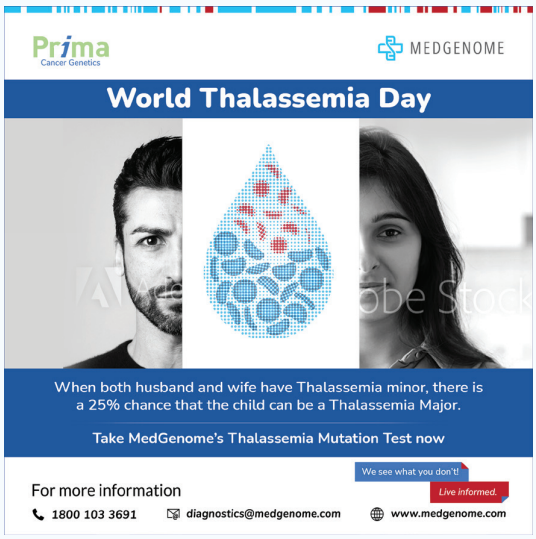
The past quarter for Actia was moderate as the OPDs were either curtailed or cancelled. Due to this, we also limited our digital engagements and redeployed our resources towards Covid testing and NIPT. But we did get a publication out on DMD in a renowned journal- Molecular Genetics and Genomic Medicine. With the situation improving and lockdowns being lifted, we are looking forward to a more engaging next quarter particularly with advancements in our exome tests in the pipeline.

MedGenome Connect

Prima Cancer Genetics

We continued to focus on digital platform and leveraged the various digital campaigns. National Cancer Survivor's Day was on 6th June 2021 and we initiated a social media campaign to create awareness to appreciate the warriors of cancer.

For World Thalassemia Day on 8th May, we did a campaign focussing on the importance of carrier screening in Thalassemia. The idea was to emphasize that two Thalassemia minor parents can give birth to Thalassemia major child.



micra Infectious Disease Genetics

The last quarter has been very busy for Micra as we ramped up the RT-PCR testing for COVID diagnosis to meet the demands of our customers in the second wave of COVID-19 in India. We also initiated our inhouse COVID antibody kit which is currently in the final stage of approvals. We leveraged our digital campaigns for RT-PCR testing and utilised them to the full capacity. We offered various schemes such as discounts for healthcare workers, senior citizens and media professionals. Dr. Vedam Ramprasad had an exclusive interview with NDTV on the new variant of concern i.e Delta variant of SARS COV2.

What's new

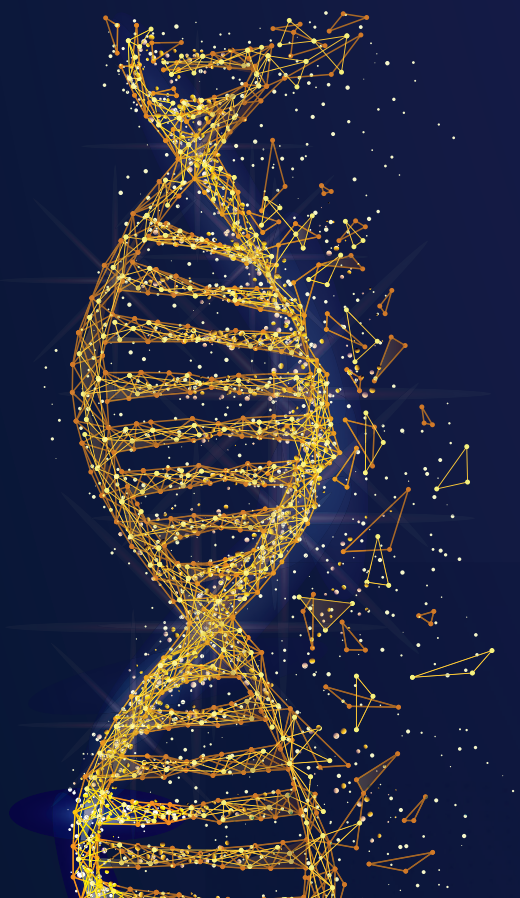
Publications

1. ***Human ACE2 receptor polymorphisms and altered susceptibility to SARS-CoV-2 published in Nature***

   To read, click- https://www.nature.com/articles/s42003-021-02030-3

2. ***Matrilineal analysis of mutations in the DMD gene in a multigenerational South Indian cohort using DMD gene panel sequencing published in Molecular Genetics and Genomic Medicine***

   To read, click- https://onlinelibrary.wiley.com/doi/10.1002/mgg3.1633



Accreditation Announcement

MedGenome has been awarded the prestigious European Federation for Immunogenetics (EFI) accreditation for our NGS based Class I and II, low- and high-resolution HLA typing, Chimaerism and Engraft Monitoring.

About the EFI

EFI is a European organisation that focuses on immunogenetics, tissue typing and transplantation.

The EFI Accreditation Programme provides an internationally recognised accreditation scheme for laboratories providing Histocompatibility & Immunogenetics (H&I) testing services in support of solid organ and haematopoietic stem cell transplantation, blood transfusion, disease diagnosis and drug hypersensitivity reactions.

MedGenome is proud to be a recipient of this accreditation

New Launch

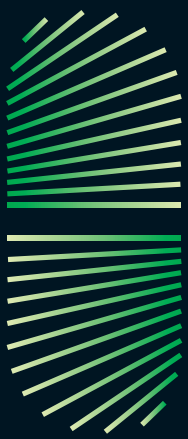
GENESSENSE

Powered by MEDGENOME

We have some exciting news to share with you! MedGenome, is launching 'Genessense', a new division that makes the power of predictive genetics accessible to individuals in India. Genessense will leverage MedGenome's extensive database of Indian genetic information to offer high quality predictive genetic tests to help individuals plan and manage their health better. To begin with, we are introducing two tests,

KARDIOGEN

Analyses
over 6 million genetic markers to create a Polygenic Risk Score (PRS) which outlines the risk of an individual developing coronary artery disease due to genetic factors



CUREGEN

outlines an
individual's response to medication
based on their genetic makeup

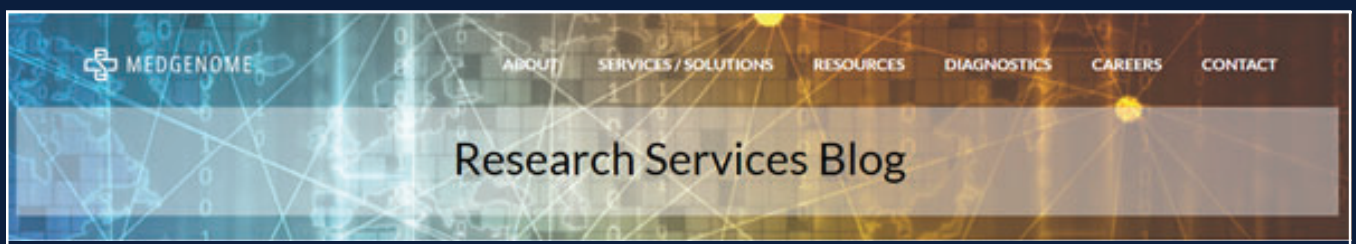
Let's share with our friends and family!

www.genessense.com

From our US office

We added a second ***NovaSeq 6000 Sequencing Machine*** to double our sequencing capability and to provide fast turnarounds to our existing and future customers.

In terms of new platforms, we on-boarded Miltenyi gentleMACS tissue dissociation platform and Promega Maxwell(R) RSC 48 System for extraction of automation. These platforms enable MedGenome to expand its scope of services within the single cell space as well as improve our turn-around time on projects requiring extraction in large volumes.



We continue to add more articles on our Research Blog. MedGenome colleagues are encouraged to take initiative and contribute towards the blog. You can share your viewpoints and articles with Vinay and Hiran at **mgus-blog@medgenome.com**

To read our interesting articles on the cutting-edge research please visit us at: **https://research.medgenome.com/blog/**

We also recently conducted a webinar on our Bioinformatics capabilities titled “Elevate your research with advanced analysis of bulk and single cell transcriptomics data.”

Further details are available on our Scientific Sessions Portal: **https://research.medgenome.com/videos/**

Making the difference

NIPT Offers Superior First Trimester Screening

Patient information

Mrs. X, a 38-year-old woman at a gestational age of 13 weeks and 2 days came to us with first trimester screening as low risk at 1: 1610. Her ultrasound showed no abnormalities with NT measurement 2.1 mm and CRL 74 mm. She was keen to evaluate further and decided to go in for an NIPT test.

Previous History

This was Mrs. X's third pregnancy, and she had no previous history of genetic disease in her family or earlier pregnancies.

Genetic testing at MedGenome

Non-Invasive Prenatal testing was done at MedGenome

Results

The NIPT result showed high risk for Trisomy 21. Confirmatory Amniocentesis was done and the QF PCR result confirmed Trisomy of chromosome 21, thus confirming the NIPT result.

Case Discussion

NIPT can detect Trisomy 21 with >99.9% sensitivity and specificity. In a general population cell-free DNA screening can have a Positive Predictive Value (PPV) of 80.9% and a False-Positive Rate (FPR) of 0.06% which is much higher than standard screening.

All existing international guidelines including ACMG, ACOG and ISPD recommend confirmatory diagnostic testing with invasive procedure in case of high-risk report on screening tests.

In this case, the fact that the ultrasound and the conventional screening did not pick up the Trisomy 21 needs to be noted. Due to higher accuracy and predictive nature of the NIPT test, the patient was able to get the right diagnosis that helped her with further management.

PPV

Conditions	Standard Screening	cfDNA testing
Trisomy 21	3.4%	80.9%
Trisomy 18	14.0%	90.0%
Trisomy 13	3.4%	50.0%

FPR

Conditions	Standard Screening	cfDNA testing
Trisomy 21	5.4%	0.06%
Trisomy 18	0.3%	0.01%
Trisomy 13	0.3%	0.02%

Source: Norton, Mary et al. (2015). Cell-Free DNA Analysis for Noninvasive Examination of Trisomy. The New England journal of medicine. 372. 10.1056/NEJMoa1407349.

Conclusion

NIPT is an effective screening test with higher sensitivity and accuracy compared to first trimester screening.

All high-risk screening tests must be followed with a confirmatory testing.

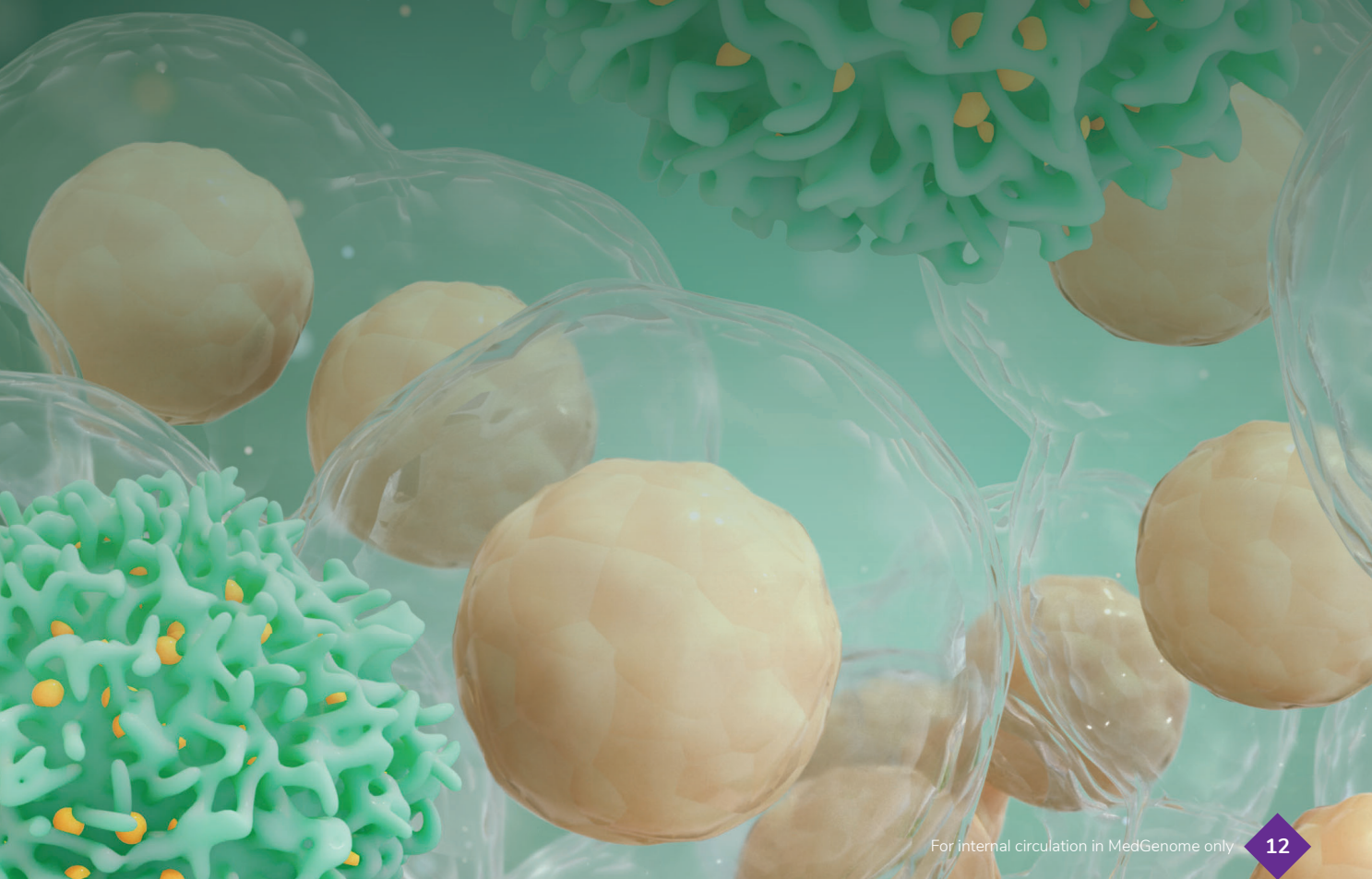
Genetic Counselling must be case specific and involve guidance that will benefit the patient with their decision.

Immunotherapy in cancer

Immunotherapy is an upcoming treatment that has seen some great advancements in recent times. Immune checkpoint inhibitors bind to specific cell surface molecules that result in activation of immune cells activation against the tumor cell. Immune checkpoint inhibitors have transformed the treatment algorithms of solid tumors and are approved for the treatment of multiple malignancies, including but not limited to melanoma, RCC, lung cancer (small cell and non–small cell), head and neck squamous cell carcinoma, gastric cancer, ovarian cancer, Hodgkin lymphoma, and tumors with DNA mismatch repair defect [1].

By Charu Bahl, *PhD*
Manager, Scientific Affairs

By G. Arun Kumar, *PhD*
Head, Technical Support

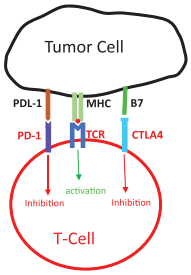


Science behind the Immunotherapy:

The human immune system dynamically monitors the development of any tumor cell in the system and elicits a cytolytic response mediated by T-cells, specifically CD8+ T cytotoxic cells. In a healthy individual, at an early tumorigenesis setting, the tumor cell generates many altered self-proteins called neoantigens. These neoantigens are presented to the CD8+ T-cells by the tumor cell via Class-I MHC molecules. The CD8+ T-cells in turn recognise the neoantigens and elicit a cytotoxic response on the tumor cell, thus curtailing the tumor. The activation of T cells requires 2 conditions: (i) activation signal: presentation of neoantigens by MHC and recognition of this by T-cell receptor (ii) absence of inhibitory signals: PD1-PDL1 binding and CTLA4-B7 binding (Figure-1)[2].

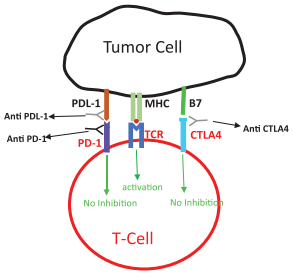
Inhibitory signals are interactions between the tumor cells and the T cells that result in T cell anergy. Interaction of PD-1 molecule expressed on the T-cell with PDL-1 molecule expressed on the tumor cell leads to inhibition of T-cell activation. Likewise, interaction of CTLA4 molecule expressed on the T-cell with B7 molecule expressed on the tumor cell also sends an inhibitiory signal to the cell. These two interactions are exploited in the immune checkpoint inhibitor therapy, where monoclonal antibodies against PD-1 or PDL-1 or CTLA4 prevent the interaction with their corresponding ligands, thus preventing the inhibitory signal to the T-cell, ultimately leading to T-cell activation and anti-tumor response[3].

(Figure-1)



Interaction of MHC-neoantigen complex with T cell receptor leads to T-cell activation

Interaction of PL-1 with PD-1 and B7 with CTLA4 generates inhibitory signal for T-Cell



Immune checkpoint inhibitor drugs such as anti- PD1, anti-PL1 or anti-CTLA4 antibodies present the interaction of these molecules with their receptors thus suppressing the inhibitory signal

Currently available Immune checkpoint inhibitors:

In 2011, ipilimumab, the first antibody blocking an immune checkpoint (CTLA4) was authorized. This was rapidly followed by the development of monoclonal antibodies targeting PD1 (pembrolizumab and nivolumab) and PDL1 (atezolizumab and durvalumab). T-cell-targeted immunomodulators are now used as single agents or in combination with chemotherapy as first or second lines of treatment for about 50 cancer types. However, some of these tested in phase 3 trials, as a single agent for early line therapy resulted in sub-optimal response in some patient populations[4]. There are more than 3000 active clinical trials evaluating T cells modulators, representing about 2/3 of all oncology trials[5]. Table-1 lists the immune checkpoint inhibitors approved by FDA[6].

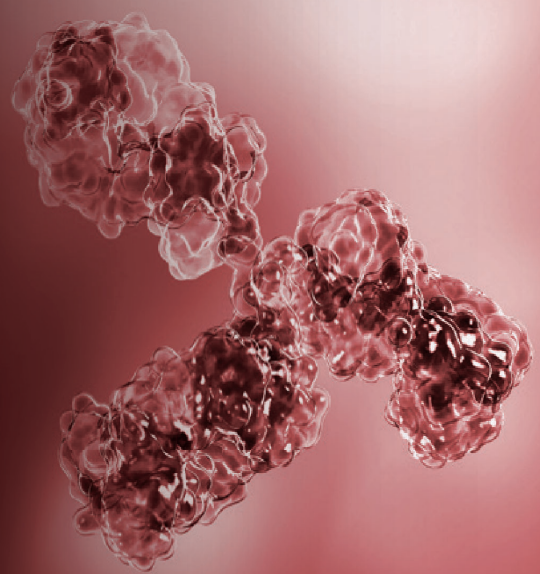


Table-1: List if immune checkpoint inhibitors approved by FDA [6]

Immune checkpoint Inhibitor	Target	Mechanism of Action	Indications
Ipilimumab	CTL-4	Inhibits CTLA-4 and allows T cell activation	CRC (in combination with nivolumab) HCC (in combination with nivolumab) Melanoma (alone or in combination with nivolumab) Mesothelioma (in combination with nivolumab) NSCLC (in combination with nivolumab), RCC (in combination with nivolumab)
Cemiplimab	PD-1	Inhibits PD-1 and allows T cell activation	BCC, CSCC, NSCLC
Nivolumab	CTL-4	Inhibits CTLA-4 and allows T cell activation	CRC (alone or in combination with ipilimumab), Esophageal SCC, HCC (alone or in combination with ipilimumab) Hodgkin's Lymphoma HNSCC Melanoma (alone or in combination with ipilimumab) Mesothelioma (in combination with ipilimumab) NSCLC (alone or in combination with ipilimumab) RCC (alone or in combination with ipilimumab) Urothelial carcinoma
Pembrolizumab	CTL-4	Inhibits PD-1 and allows T cell activation	Breast cancer, Cervical cancer,CRC, CSCC, Endometrial carcinoma, Esophageal carcinoma, Gastric carcinoma, HCC, HL, HNSCC, melanoma, mesothelioma, MCC, MSI-High/MMR-deficient/TMB-high cancers, NSCLC, large B cell lymphoma, RCC, SCLC, urothelial carcinoma
Atezolizumab	PD-1	Inhibits PD-L1 and allows T cell activation	BC, HCC, melanoma, NSCLC, SCLC, urothelial carcinoma
Avelumab	PD-1	Inhibits PD-L1 and allows T cell activation	MCC, RCC, urothelial carcinoma
Durvalumab	PD-1	Inhibits PD-L1 and allows T cell activation	NSCLC, SCLC, urothelial carcinoma

Biomarkers for prediction of response towards Immune checkpoint inhibitors

Immunotherapy is found to be useful in all solid tumors. However, it is observed that even patients with similar clinical characteristics do not respond in the same manner and survival rates vary greatly[7]. Currently, three major biomarkers are included in clinical practice: PD-L1, microsatellite instability (MSI), mismatch repair (MMR) deficiency and tumour mutational burden (TMB).

PD-1/PDL-1

PD-1 is usually expressed on activated T cells, and it has two ligands PD-L1 and PD-L2 which are expressed on the surface of antigen presenting cells and play a role in activating the T-cells. PD-1 also plays a role in keeping T cell responses within the range thus preventing autoimmune responses and tissue damage. Tumor cells producing PD-L1 thus bind to PD-1 and suppress the T cells responses leading to inhibition which helps the tumor cells grow and progress. Higher expression of PD-L1 in the tumor tissue corresponds to better response to PDL-1/PD1 inhibitors.[8].

Expression of PDL-1 has been identified to be a prognostic marker for good response to immune therapy[9].

Table-2 list the currently approved anti PDL-1 clones used during IHC and their attributes[10].

Cancer Type	*Clone of anti-PDL1*	*NCCN approval (line of therapy)*	*Scoring system*
NSCLC	22C3 pharmDx	Pembrolizumab+Cisplatin/carboplatin+Pemtrexed: 1st Line	CD, TPS
Gastric	22C3 pharmDx	Pembrolizumab: 2nd line	CD, CPS
Cervical	22C3 pharmDx	Pembrolizumab	CD, CPS
Esophageal SQCC	22C3 pharmDx	Pembrolizumab	CD, CPS
Urothelial	22C3 pharmDx	Pembrolizumab	CD, CPS
NSCLC	SP142	Atezolizumab+chemo	COPD, TPS
NSCLC	SP142	Atezolizumab: 1st line	COPD, TPS
TNBC	22C3 pharmDx	Pembrolizumab: 2nd line	
Urothelial	SP142	Atezolizumab: 1st line for cisplatin ineligible	CD, IC
Head and Neck SQCC	22C3 pharmDx	Pembrolizumab: subsequent therapy	CD, CPS
NSCLC	SP263	Nivolumab+Ipilumtab+Pemtrexed: 1st line	COPD, TPS
Urothelial	SP263	Durvalumab: 2nd line	COPD, TC/UC
TNBC	SP142	Atezolizumab (Tecentriq) plus nab-paclitaxel (Abraxane): 2nd line	CD, IC
Head and Neck SQCC	28-8 pharmDx	Nivolumab	COPD, TPS
NSCLC	SP263	Durvalumab	COPD, TC/IC
Urothelial	28-8phax	Nivolumab	
Gastric, Gastroesophageal junction and Esophageal ADCC	28-8 pharmDx	Nivolumab+ Chemo: 1st line in HER2 negative metastatic tumors	COPD, CPS

Legend: COPD – Complementary diagnostics, CD – companion diagnostics, CPS – combined positive score, IC - tumor infiltrating immune cells, TC – Tumor cell

Tumor Mutation Burden:

Tumor Mutation Burden (TMB) estimates the number of somatic mutations in a given genomic region in a tumor tissue. More the mutations in the tumor cell (high TMB), more will be the number of neo-antigens in the cell and hence stronger will be the immune response against the tumor. TMB estimate is expressed as number of mutations per megabase pair of DNA.

TMB varies among cancers and can range from 0.01 to greater than 1000 somatic mutations per megabase of interrogated genomic space. Melanoma and NSCLC have historically demonstrated higher levels of TMB, whereas breast, kidney, and ovarian cancers typically have low expression[11]. The current consensus on scoring of TMB is that tumors with <10 mutations/Mb is low TMB, while those with >10 mutations/Mb is high TMB. High TMB is associated with improved response to Immune checkpoint inhibitor[12].

A recent study concluded that TMB may at best be a limited surrogate marker for response to immunotherapy and will be more valuable in combination with other markers. Although it may be considered a "reasonable" predictive biomarker in NSCLC, its predictive value in melanoma is weak, and it is not predictive in isolation for renal cell carcinoma.[13].

Microsatellite Instability and Mismatch Repair Deficiency:

Microsatellites are short, tandemly repeated DNA sequences of 1 to 6 bases scattered throughout the human genome. These sequences may be in both the gene and intergenic regions[14]. Microsatellite Instability (MSI) is an alteration in length of a microsatellite allele due to either deletion or insertion of the repeating unit during DNA replication and failure of the DNA mismatch repair (MMR) system to rectify these errors. There are 7 major MMR genes (MLH1, MLH3, MSH2, MSH3, MSH6, PMS1 and PMS2) whose proteins repair errors taking place during DNA replication. MMR deficiency can be determined by estimating the expression of MMR genes in the tumor tissue by IHC. One can predict the effect of MMR deficiency by measuring MSI by fragment analysis technique that measures the variation in microsatellite allele count in the tumor tissue[15], [16]. Defective MMR and pathogenic mutations in MMR genes leads to genomic instability and hence increase in neoantigens in the tumor tissue that can lead to effective T cell response upon immune checkpoint inhibitor therapy[17].

For the first time, in its latest announcement, FDA has approved pembrolizumab with a tumor-agnostic indication for MSI-H or mismatch repair deficient solid tumor, in paediatric and adult patients, which is the first biomarker-based chemotherapy rather than organ-based approaches. In colorectal and non-colorectal carcinoma, subsets show MSI-H, either due to inherited germline mutations of mismatch repair genes or epigenetic inactivation and are reported to have increased sensitivity to checkpoint inhibitors[18].

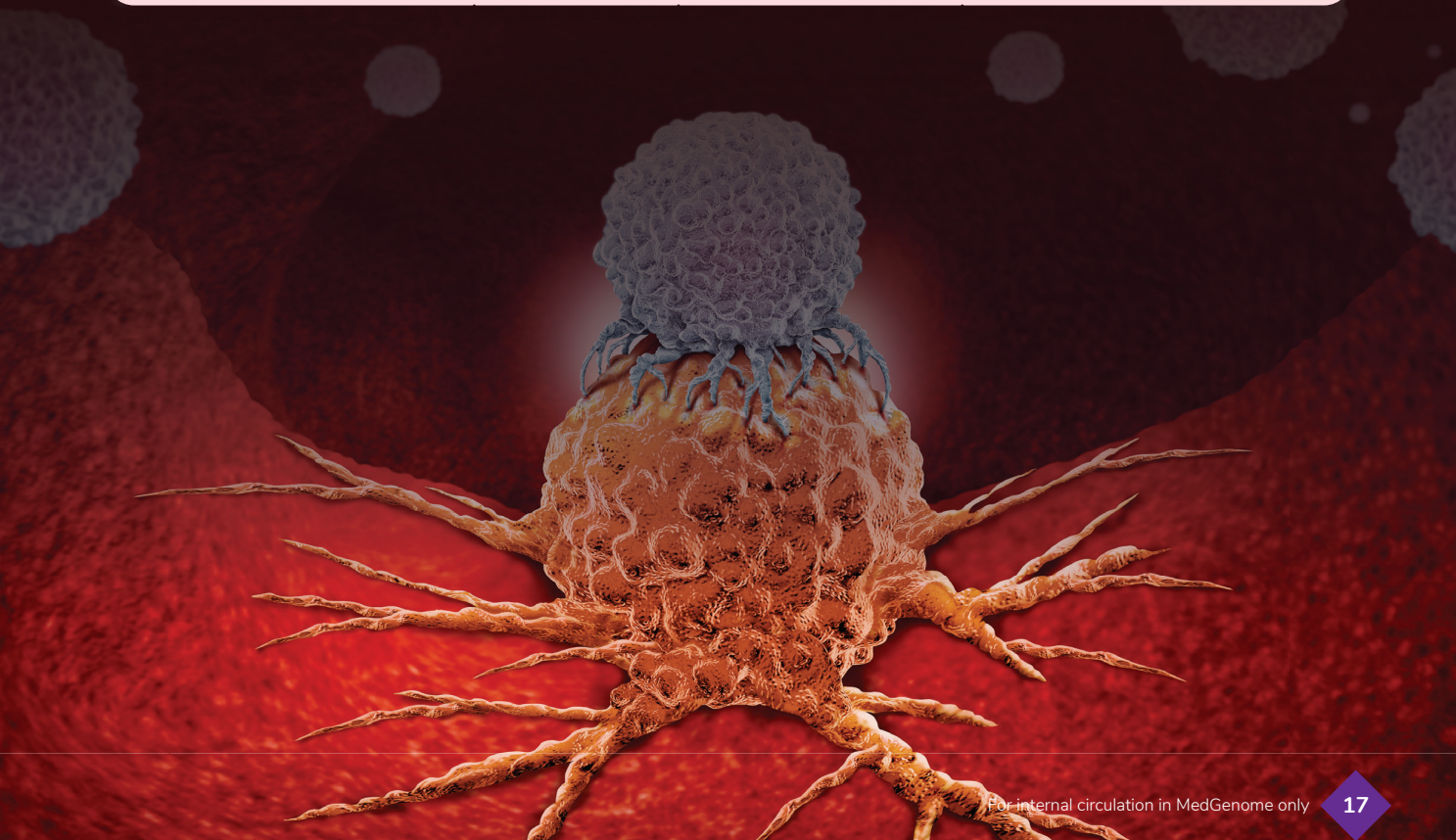
FDA has granted approval to administer the PD-1 inhibitor pembrolizumab for the treatment of patients with unresectable or metastatic, MSI-H or MMR-deficient (dMMR) solid tumors (site-agnostic). Presently, the approval is for patients with tumors that have progressed after preceding treatment, who have no satisfactory substitute treatment options, and for MSI-H or dMMR colorectal cancer (CRC) patients, considered after progression on a fluoropyrimidine, oxaliplatin, and irinotecan, and in the first line for non–small cell lung cancer (NSCLC). In 2017, the FDA granted accelerated approval of single-agent nivolumab, another PD-1 inhibitor, for the treatment of MSI-H or dMMR CRC, in adult and older than 12 years pediatric patients. Eventually, in 2018, the FDA granted accelerated approval to a combination of nivolumab plus ipilimumab for treatment of the same set of patients[19].

Other upcoming markers for prediction of response towards checkpoint inhibitors:

The use of serum biomarkers as predictive markers for Immune Checkpoint Inhibitor therapy, is yet to be established, although several serum markers, such as c-reactive protein (CRP), lactate dehydrogenase (LDH), vascular endothelial growth factor (VEGF) and soluble CD25 are considered to be associated with anti-CTLA-4 and PD-1/PD-L1 blockade response in advanced melanoma[20-24]. Table-3 lists some biomarkers under evaluation.

Immune checkpoint inhibitor therapy is thus a tumor type agnostic approach that has encouraging results both in first line and subsequent line of therapy in various cancers. Both mono therapy and combination therapy modes have been evaluated and responses have been encouraging. Scientifically driven predictive biomarkers of response to this therapy are being evaluated that promise a tectonic shift in the landscape of cancer therapy.

Biomarker	*Association with better clinical response*	*Tumor type*	*Platform used for assessing*
HLA class I diversity	Positive	Melanoma and NSCLC	Targeted sequencing
Copy number variations	Negative	Various solid tumor types	Whole genome/exome sequencing
T cell-inflamed microenvironment	Positive	Various solid tumor types	RNA-seq by NGS or immunostaining
TGF-β expression	Negative	Urothelial and colon	Microarray/RNA Seq
Mutations in β-catenin pathway	Negative	Melanoma	Targeted sequencing
STK11 mutations	Negative	NSCLC	Targeted sequencing
POLE and POLD1 mutations	Negative	Various solid tumor types	Targeted sequencing
ARID1A mutations	Negative	Various solid tumor types	Targeted sequencing



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Mutations in human ACE2 receptor can alter susceptibility to SARS-CoV-2

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By Devi Santhosh,
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The COVID-19 pandemic is an ongoing global crisis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus was first identified in December 2019 in the province of Wuhan in China. As of 9th June 2021, more than 174 million cases have been confirmed, with more than 3.75 million confirmed COVID-19-related deaths, making it one of the deadliest pandemics in history. Since the outbreak and subsequent rapid, global spread of COVID-19, numerous scientists and research groups turned their efforts to find ways to track and prevent this deadly disease. Viral genome sequencing identified this novel coronavirus (CoV), SARS-CoV-2, and found that it shared many traits with the coronaviruses (SARS-CoV-1 and MERS - Middle East Respiratory Syndrome) linked to previous outbreaks of SARS and MERS from the early 2000's. Like the SARS-CoV-1 and MERS viruses, SARS-CoV-2 uses a protein on its surface, called a spike glycoprotein (S protein), to bind to a specific receptor on our cells, called angiotensin-converting enzyme 2 (ACE2). ACE2 is an important protein that regulates blood pressure, wound healing, and several other vital functions. The interaction between the viral S protein with ACE2 is necessary for the virus to enter our cells, so that it can replicate and spread further (Figure 1). Biochemical studies showed that this new SARS-CoV-2 was much more infectious because it was able to bind to our cells better, with a ~10 – 15-fold higher affinity. This explained the greater infection rates doctors were witnessing.

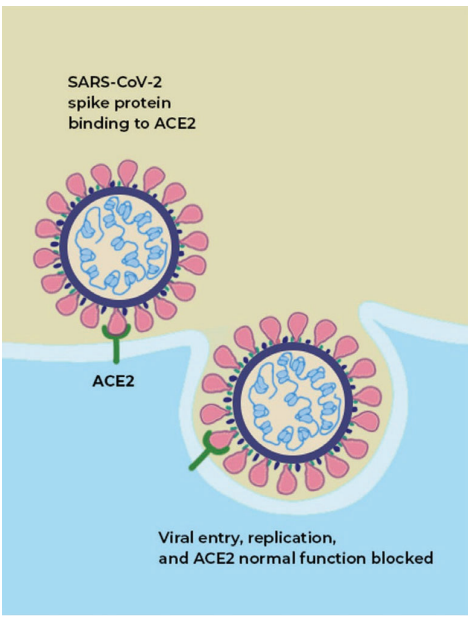


Figure 1: ACE2 acts as the main receptor for SARS-CoV-2 virus entry into cells (source: theconversation.com)

Elegant structural biology studies that studied the interaction between the virus and ACE2, showed that a specific region on the virus S-protein, called the receptor binding domain (RBD), is responsible for recognizing the human ACE2 receptor. Analogous to a key fitting a lock, the RBD fits into the ACE2 receptor to enter the cell where it can then replicate and cause infection. In fact, evolutionary studies revealed that the region in ACE2 is highly conserved in many other animals, including the region recognized by the virus. The high conservation in this receptor means that it is very easy for viruses to jump, not only from animals to us (zoonosis), but also from us to animals (reverse zoonosis). Both scenarios pose significant problems as they increase the chances for viruses to evolve, or change sufficiently enough, to spread widely and cause severe health problems (see here and here). Given the critical role of ACE2 in SARS-CoV-2 infection, many researchers began to investigate how this relationship could dictate susceptibility to COVID-19. This was especially important given the wide range of symptoms in infected patients.

We decided to investigate the genetic basis of susceptibility to COVID-19 by investigating the following hypothesis: are there any natural variations in the ACE2 receptor that could alter our susceptibility to infection? To this end, we used genomic data from over 290,000 samples representing >400 population groups from public genomic datasets and identified genetic changes (polymorphisms) that could potentially affect this virus–host interaction (Suryamohan et al., 2021) (Figure 2). These changes in turn are likely to either protect or render individuals more susceptible to the virus. By combining large population datasets with published protein structures, we were then able to test key variants in the lab and successfully confirm our predictions through various biochemical assays.

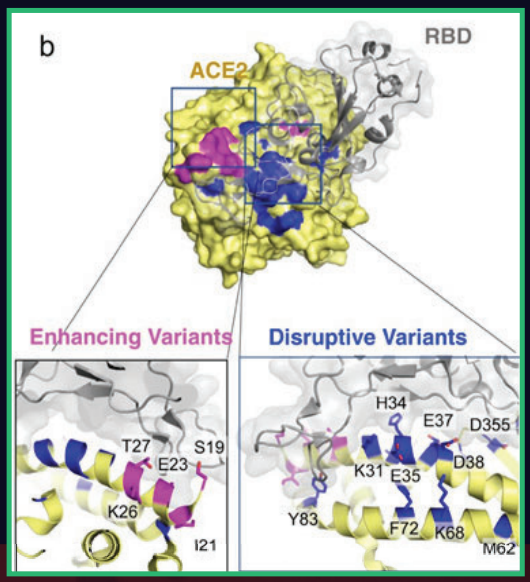


Figure 2: Residues on ACE2 that are predicted to effect binding to S-protein RBD

Overall, we found 9 variants that increase susceptibility, and 17 variants that were predicted to be protective, as they reduced susceptibility to infection. To continue with the lock and key analogy, alterations in the ACE2 receptor would change the shape of the 'lock', thus affecting whether the 'key', i.e., the RBD, would fit or not (Figure 3). It is important to note though that these ACE2 variants are rare in the human population. This is consistent with the fact that CoV infections are relatively recent and we have not yet seen the effects of the kind of evolutionary pressure that would lead to the selection of pathogenic or protective variants. Thus, while genetic variation in ACE2 alone is unlikely to explain the vast variability in infection susceptibility and severity of COVID-19, these studies contribute to developing targeted therapeutics. One possible therapy would be a soluble ACE2 protein that would act as a decoy receptor for SARS-CoV-2. By creating a synthetic, recombinant form of ACE2 protein carrying variants that have higher affinity for the virus than the receptors found in most human cells, it is possible to block viral entry into cells. We tested this prediction in a lab experiment, where an altered ACE2, with increased affinity for the S protein, did in fact block the virus from infecting the cell.

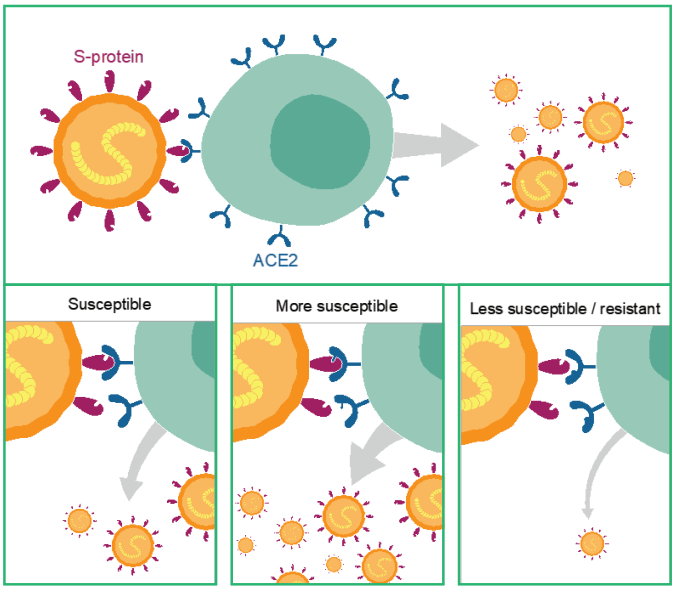
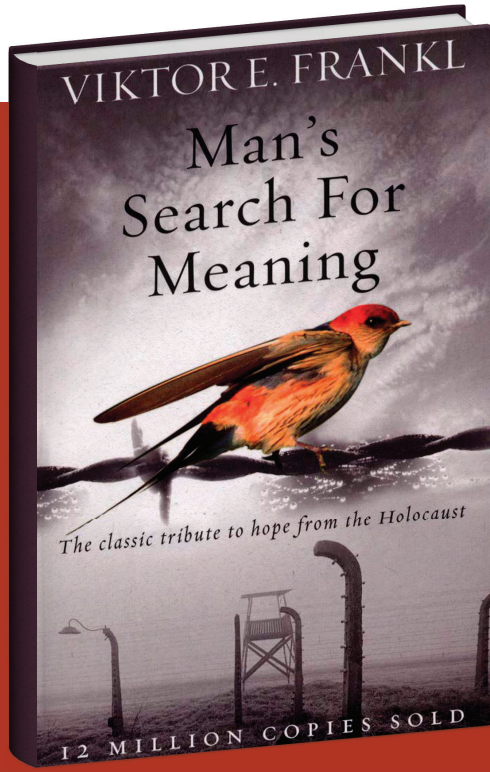


Figure 3: ACE2 receptor variation may alter susceptibility to SARS-CoV-2

Developing drugs against CoVs is an imperative goal since only a small handful of drugs have been repurposed or received emergency authorization, though vaccines have, of course, been critical in managing the spread of COVID-19 (https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-therapeutics-tracker). In fact, as the number of SARS-CoV-2 variants increase, the fear of another pandemic is becoming less of a future scenario, and more of an immediate problem. Currently, the WHO recognizes 4 variants, the Alpha, Beta, Gamma and Delta, previously known as the UK variant, the South African variant, the Brazilian variant and the Indian variant, as being the most concerning (https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Concern). These variants are considered especially troubling because they have shown some evidence of an increase in transmissibility, increase in virulence, or decrease in prevention effectiveness. Despite these worrying developments, improving our understanding of the interaction between the viral S protein and our ACE2 receptor could provide information on the origins of COVID-19, how it turned into a global pandemic, and more importantly, ways to combat it and diseases like it going forward. Through continued monitoring and concentrated research efforts, we can stay ahead of the ever-evolving dangers present in the numerous microbial and viral strains found around the world.

From our Colleagues



Book Review

Book

Man's Search For Meaning

Book review by

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Genomics Medicine, MG India

Any language dictionary in the world with all its vocabulary combined will not be able to picturise to the reader the gruesome nature inside a Nazi concentration camp must have been like. Author of this book, Viktor Frankl was one of those holocaust survivors, he survived for more than three years in three different concentration camps. On any given day in those concentration camps, odds of being alive were slimmer than the obvious stanching smell of death all around the camp. The celebrated survivor Viktor Frankl spent the remaining part of his life teaching what he had learned during his hardships in Nazi concentration camp. That teaching is today known as 'Logotherapy' and that people can, and must, find meaning in their lives against all odds.

This book is not a scientific journal; however, this book is of paramount significance to each one of us in this Covid-19 pandemic crisis. The year that went by was more challenging than any seen so far in our lives. A year in which we felt so helpless, with staff pay cuts, job losses, school closures and the endless uncertainty, left us all thinking what else could we do. This book is the best thing that could happen to anyone in this period, and I hope many of us and the others in the world too will agree to this fact. There are many lessons that we can learn from this world famous 1946 book.

The three key lessons from the book are:

1	Sometimes the only way to survive is to surrender to death (get over that fear – then the only option left is to survive and fight another day)
2	Your life has its own meaning, and it is up to you to find it (when the purpose becomes clear, any journey is tolerable and achievable)
3	Use paradoxical intention to make your fears go away (when you face your worst fear, there will not be any obstacles to overcome)

Being indifferent to death allowed Viktor Frankl and some of his surviving peers to be alive, sounds quite paradoxical, isn't it? This sort of indifference to death shielded them and made them immune to the horrible terror surrounding them. They were not worried about any standard of living, but merely to exist and surrender to the present.

There is no general meaning of life, it depends on one's own decisions and situations, only unique to that individual. Finding one's own purpose in life - the reasons we get up in the morning, eases everything. Purpose can guide life decisions, influence behaviour, shape goals, offer a sense of direction, and create meaning. But we become so captured by our daily activities, engagements, goals and so forth, that our awareness of our own unique life purpose gets blurred.

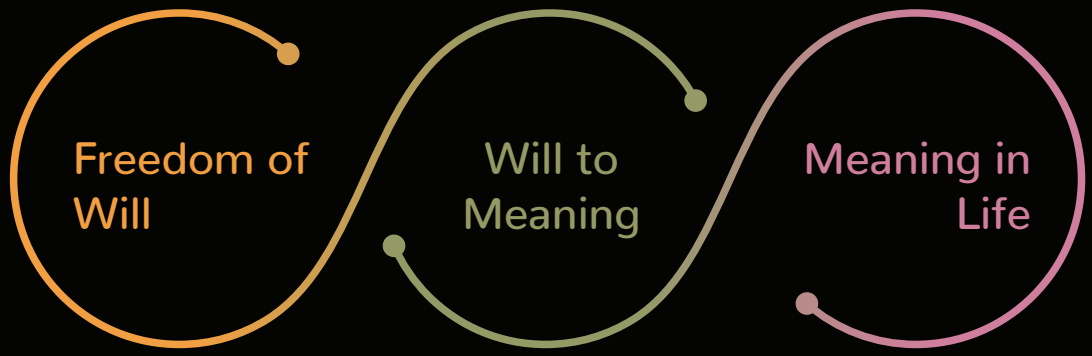
One key factor to abide by in today's COVID chaotic crisis is just to focus on SURVIVAL. In my opinion, no other book can explain it better than 'Man's search for Meaning'. The way Viktor Frankl endured the holocaust and survived the unimaginable, and yet bounced back to teach the world, the ways to overcome such challenges in life through his mastery of paradoxical intention. On several occasions in the book, Frankl approvingly quotes the words of Nietzsche, "He who has a Why to live for can bear almost any How." Frankl's doctrine of logotherapy, curing the soul by leading it to find meaning in life, gains credibility against the background of his anguish in Auschwitz.

In this book, Frankl poignantly describes the fellow prisoners who gave up on life who had lost all hope for a future and were inevitably the first to die. They died less from lack of food or lack of medicine than from lack of hope, lack of something to live for. By contrast, Frankl kept himself alive and kept hope alive by summoning up thoughts of his wife and the prospect of seeing her again after the war and dreaming at one point of time lecturing after the war about the psychological lessons to be learned from the Auschwitz experience. Clearly many prisoners who desperately wanted to live did die, some of disease, some in crematoria, but Frankl's concern is less with the question of why most died than it is with the question why anyone at all survived.

We, as in health care professionals get to witness similar stories in ICU, Cancer wards and many such end stage disease conditions. Some of the patients who were given better prognosis succumb early as compared to some who had no chance, however time and again the medical science gets pleasantly surprised. Beyond medicine, there is hope for everyone to cling on to and that hope is not just limited to recovery from debilitating diseases, it transgresses to other spheres of life too, be it one's own love story, that dream vacation and many other breakthroughs in life. For many of us the life in lockdown was depressing and curtailing one's own freedom clubbed with some loss of life in our near and dear circles, was all the more debilitating. The logotherapy explained in this book which focuses on the future, on the meanings to be fulfilled by the patient/person in his/her future, can help in overcoming such odds.

Logos is Greek word which denotes "meaning." Logotherapy focuses on the meaning of human existence as well as on man's search for such a meaning. This is also known as "The Third Viennese School of Psychotherapy," speaks of a will to meaning in contrast to the pleasure principle, the will to pleasure on which Freudian psychoanalysis is centered, as well as in contrast to the will to power on which Adlerian psychology, using the term "striving for superiority," is focused. Life is not primarily a quest for pleasure, as Freud believed, or a quest for power, as Alfred Adler taught, but a quest for meaning.

The great task for any person is to find meaning in his or her life. Frankl saw three possible sources for meaning: in work (doing something significant), in love (caring for another person) and in courage in difficult times (facing the odds). In Logotherapy/Existential Analysis (LTEA) the search for a meaning in life is identified as the primary motivational force in human beings. Frankl's approach is based on three philosophical and psychological concepts:



The therapeutic techniques used in LTA: Paradoxical Intention, Dereflexion and Socratic dialogue/modification of attitudes. I will not go into details; each one is a textbook by itself.

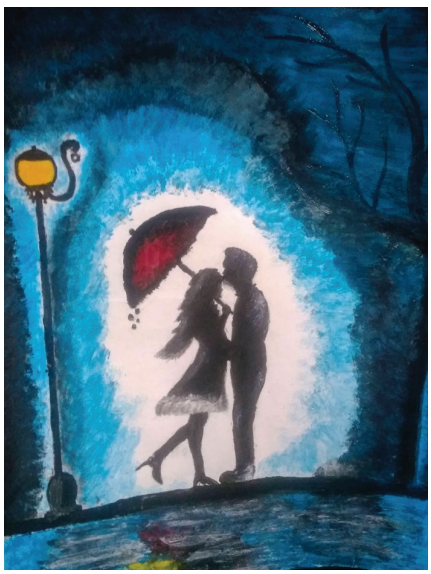
One of the drawbacks of the book is, it really tests your patience and your understanding of the philosophy explained, some have even concluded that this is a profoundly religious book. It insists that life is meaningful and that we must learn to see life is meaningful despite our circumstances. This is not an easy thing to realize let alone understand for many. In various walks of our life, this ability to understand the nuances that Frankl has explained in his book can only come from our prior experiences. Likewise, in the book Frankl has spaced his teaching of Logotherapy only after explaining in detail the ordeal that he went through in the concentration camp. If you read the section on 'Logotherapy in a nutshell' without reading Frankl's 'Experiences in a Concentration Camp', you will see Alice in the wonderland. One must relate to their own struggles of the past in their own created concentration camps before validating their learnings through Logotherapy. This book takes a different meaning to different age groups of people, and for the same individual every five years, the meaning derived changes. That is the beauty and the challenge posed by this book. I cannot say 'Happy Reading!' however I will always say, 'Have a meaningful Read!!'

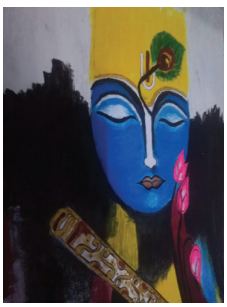
From our Colleagues

Art meets Science

Art and science have their meeting point in method. — Earl Edward George Bulwer-Lytton

By: Keerthana
Research Trainee





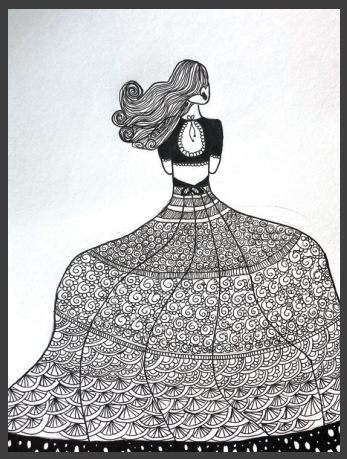
By: Roopa Shanmugham
HR Dept.

By: Sravanthi Parchuru
Senior Research Associate

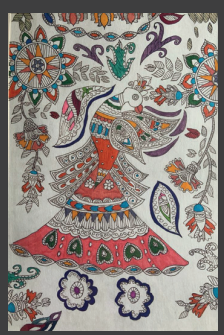
From our Colleagues

Our employee's little Picasso :)



By
Trisha Chakrabartty (12 years)
DNA of Surajit Chakravartty, CFO, MG India



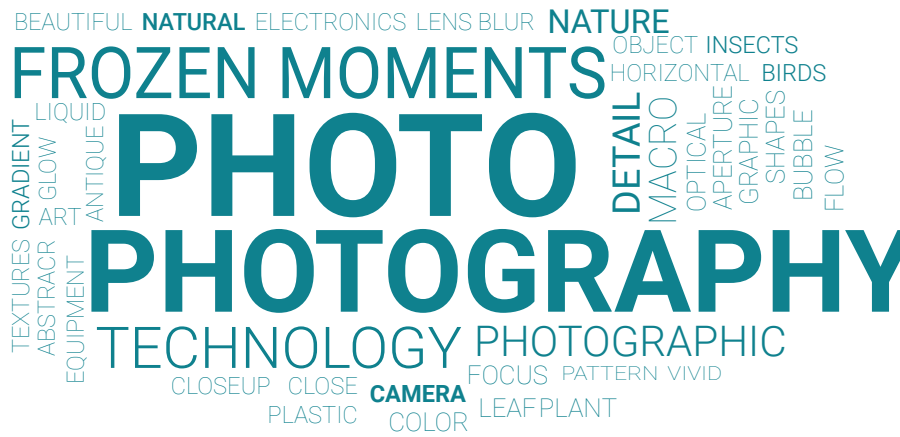

By
Perie Nitin Pai, (17yrs)

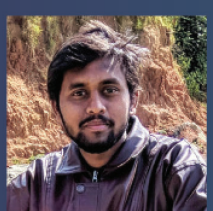
By
Ada Nitin Pai, (14yrs)

DNA of Priya Kadam, Asso. Director, Operation Dept., MG India

By
Kirthana Warrier (11 years)
DNA of Hiranjith Vice President, MedGenome US

From our Colleagues





By: Kalmesh Vyaparagi,
Analyst, Bioinformatics Dept.

Pandemic

Few months ago, we could find people
on the streets, kids on ground.
A peaceful life they lead, with a fun
place around.

People gled, their faces irradiated,
But human wasn't gratified.
Persistently, he undermined.

After several intervals,
An assailant took birth
Who flickered the earth
Human's discourtesy lead
to his growth.

No! He wasn't a disaster
He was the pivot of existence
He striked back the gesture of human,
who was the main circumstance.

Our hysterical actions
Caused this pandemic
This was a lesson
And it remains mystic.....

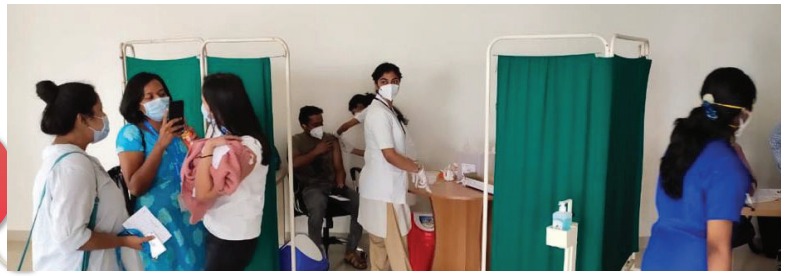
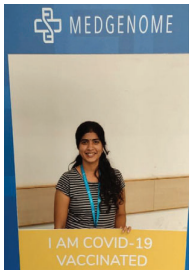
Written by
Deepanwitha Chandra Shekar (15 Years)

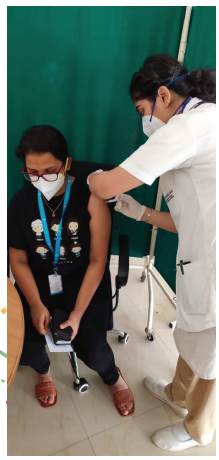
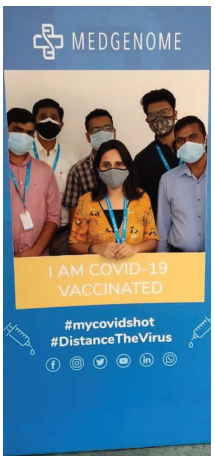
DNA of & photo courtesy
Chandra Shekar Shamanna

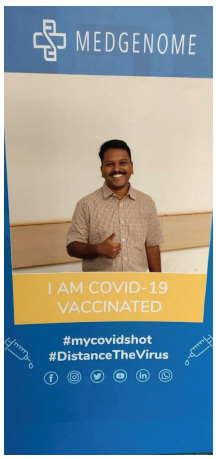
Photo Feature

Events and Activities

MG initiated covid-19 vaccine drive.

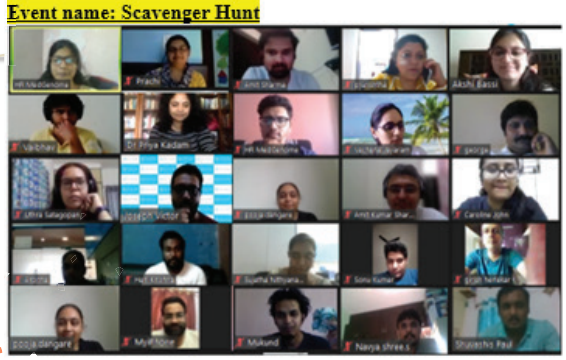



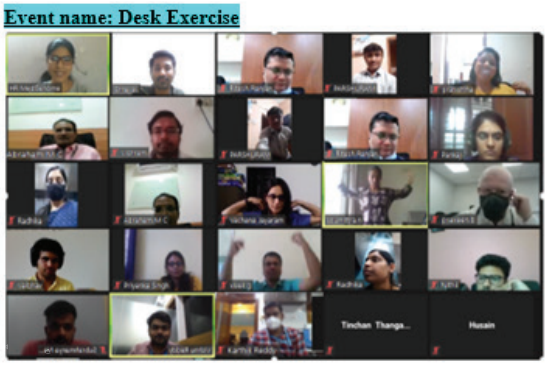
Thank God It's Thursday (TGIT)

A weekly fun filled activity -Thank God It's Thursday! has been introduced by our HR department. With interesting games and activities to refresh our minds and to give us a good laugh, it is surely an event you wouldn't want to miss. See some glimpses from the crazzzy moments!!

Event name: Scavenger Hunt



Event name: Desk Exercise



Employee Connect

WELCOME

Our New-Joiners


Aarti


Ajay P R


AJITH


Mansukhbhai


Amit


Anakha K


Anitha R

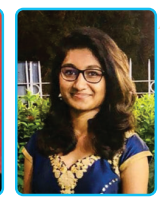

Ankit


Ashok


Yashaswini


Ayyappan


Basit


Bhavana N


Bhupendra


Bhupinder Pal


Bikkad Ganesh


Caroline


CH Parshuram


Charu Bhagl


Chhavi Dawar


Deepak Bhattacharya


Divyashree Hedge


Dr Krishnaveni


Eswari

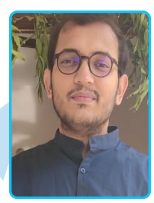

Geeta


Girish Herlekar


Gowni


Hari Krishnan S


Harish Kumar


Harsha


Vishram


Kalwad Piyusha


Karthik


Kummara Hriprasad


Lahari


Lavina


Madhuri


Mahesh


Mathivanan


Meenakshi


Mohib


Naveen Nagaraju


Neeraja


Nilesh


Parimala


Pinakshi


Pooja


Praksh J R


Pranjal


Prerna Das


Prerna Priya


priya dadlani


Priyanka


Pushpanjali


Rachit


Yaseen


Rahul


Rajesh Jha


Rajesh M


RANPAL SINGH


Sahrath M B


Vishram


Santosh RajaramIngle


Satish Kumar


Chandra Shekar


Shilpa


Shiva Shankar


Shreyas


Shrikant


Shubam


Shuvashis


Sonu


Sreejesh


Sreya


Subrahmanya N


Sudhakar

Sunil Kumar

Supraja

Sushma

Syed massem

Tavisha

Thasmia

Tuhin

V Bhooma

Vaishnavi Patil

Vennila

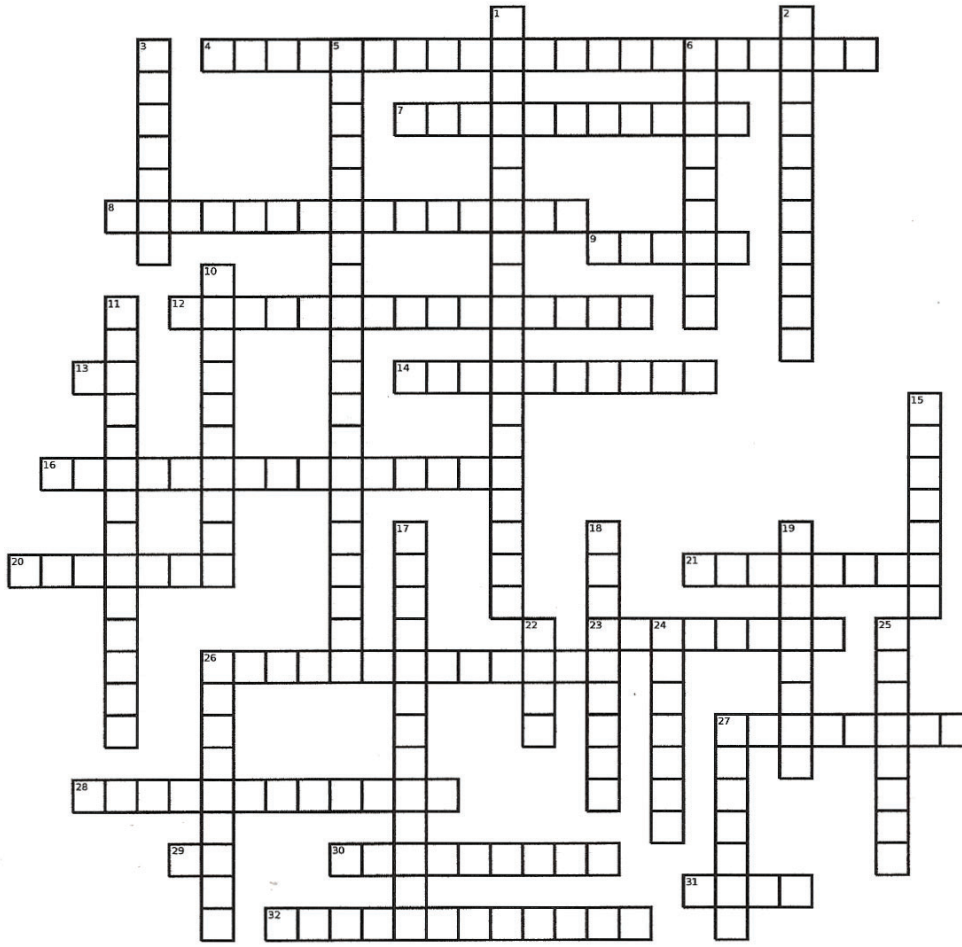
Vijay Nagampalli

Vijayraj

vipul singh

Vishnu

Employee Connect



Across

4 When the alleles for one trait segregate, they have no effect on other segregating alleles. This is known as?
7 In some cases, two or more alleles may be dominant and both dominant alleles may show up in the offspring
8 Genes that have two or more alleles are called?
9 The characteristics that an organism has such as hair color, eye color, etc.
12 When working genetics problems, how does one represent a recessive gene?
13 The sex chromosomes found in females.
14 The type of genetic cross that involves only one trait.
16 What is meant by the symbol F1?
20 By what process does a parent pass one allele for each gene to the offspring?
21 The genetic makeup of an organism.
23 The type of genetic cross that involves two traits.
26 A diagram used to show the allele combinations that an offspring might receive.
27 The science that studies how genes are transmitted from one generation to the next.
28 The Father of Genetics.
29 The sex chromosomes found in males.
30 The chromosomes that are the same in males and females.
31 A segment of DNA that controls one hereditary trait.
32 Term meaning that both alleles are different.

Down

1 In some cases, alleles blend or mix together. This is known as:
2 Every individual carries two alleles for each trait. These alleles are separated during meiosis. This is known as the Principle of ___?
3 In what part of the cell would chromosomes be found?
5 In this type of genetics, the determination of a given trait is the result of the interaction of many genes.
6 The type of allele that can be masked by another allele.
10 Term meaning that both alleles are the same.
11 The pair of chromosomes that are different in males and females.
15 The different forms of a gene are called?
17 When working genetics problems, how does one represent a dominant gene?
18 The vegetable used for early experiments in genetics.
19 The type of allele that has the ability to mask or cover up another allele.
22 When Mendel crossed true breeding tall plants with true breeding dwarf plants, all of the offspring were?
24 The offspring of two different parents are known as?
25 This type of chart shows relationships within a family.
26 The physical characteristics of an organism.
27 Name given to sex cells.

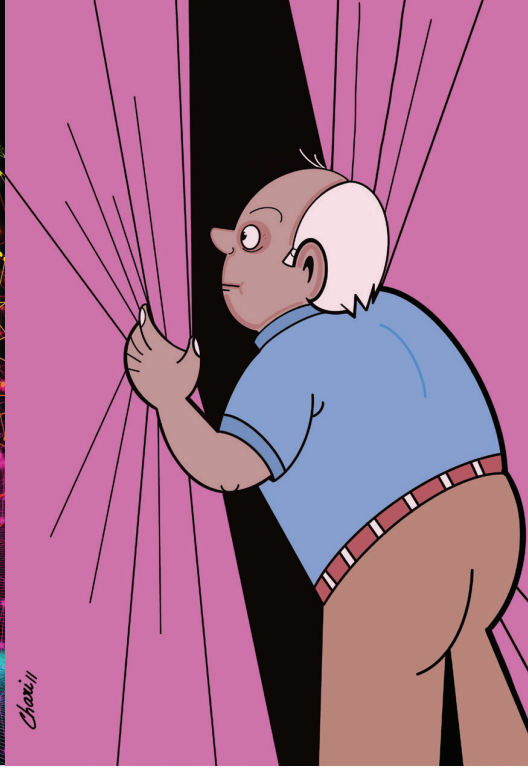
*Kindly mail your answers by 15th August 2021 to **editor@medgenome.com**. The first two people to answer the puzzles correct will be featured in the next edition of our newsletter.*

Solve the Puzzle & WIN Voucher

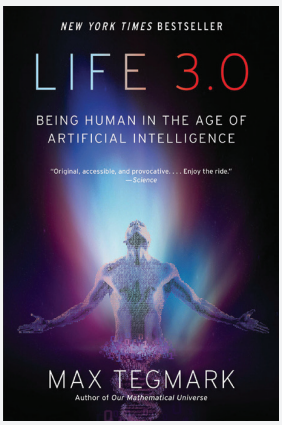
Finishing Touch

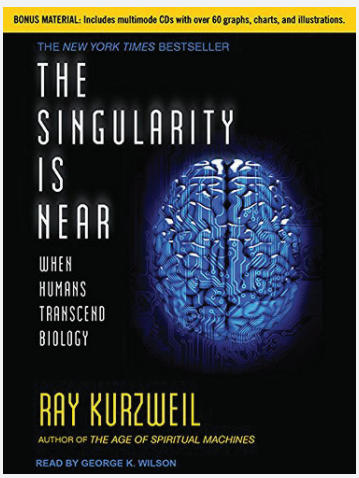
A Peek into the Future - 1

SAM SANTHOSH
Founder Chairman and Global CEO



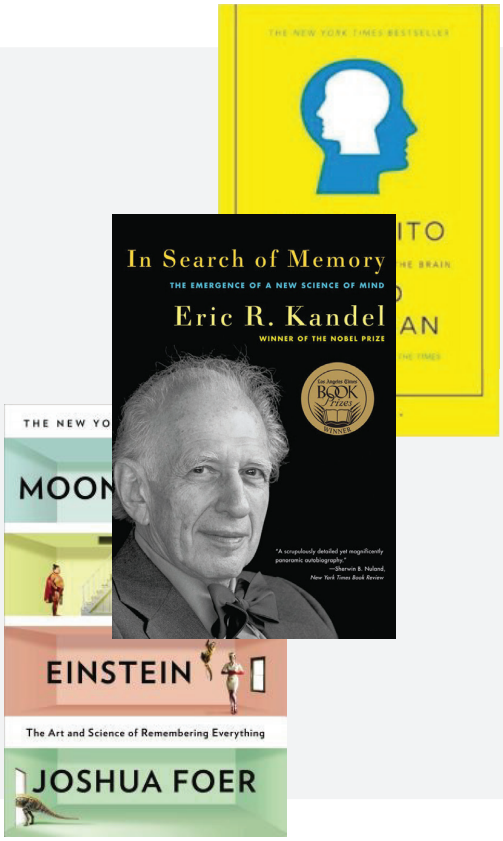
In his book '*Life 3.0 : Being Human in the Age of Artificial Intelligence*' Max Tegmark ponders about the future of humanity. If we manage not to go extinct with our nuclear weapons or biowarfare, will we spread across the universe with the help of artificial intelligence (AI), robotics, nanotechnology and genetics? Will we change our genetic code and become immortal or will we end up becoming slaves of AI powered robots who would have taken over the world? I guess we can appreciate it when Yogi Berrera says "The Future ain't what it used to be". But before I go more into Tegmark's book, let me give you some background of how I got interested in this.





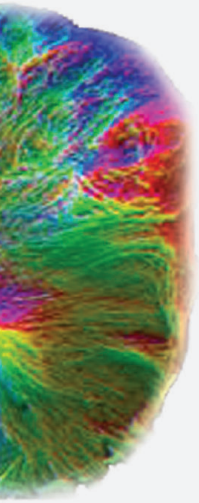
One of the books that influenced me considerably was '*The Singularity is Near: When Humans Transcend Biology*' by Ray Kurzweil in 2005. In life, timing is everything and I was in an exploring state of mind when I read this book. After more than 15 years in the software industry, I was looking for something different. The sequencing of the human genome that had been announced the previous year had caught my interest and I had started reading up on that subject. Now, I was excited to see that Kurzweil had mentioned genetics as one of the three revolutions, along with nanotechnology and robotics, that would take humanity to the point of singularity. He defined singularity as the time when humans can defeat natural death; and he was brave enough to predict that we will reach it by 2045. I was neither interested in immortality, nor was I convinced we could reach that point by 2045; but the book was very interesting and Kurzweil's points about industries that go through periods of exponential growth and his articulation of genetics being the intersection of information science and biology were fascinating. Coming from the IT sector, this gave me comfort in my decision to move into genetics. Additionally, the book also got me interested in the brain and neuroscience – reverse engineering the brain and being able to upload it into a computer was an important step in Kurzweil's path to singularity.

One good thing leads to another and as I was continuing to learn more about genetics, I picked up a book on the brain at the San Francisco airport – it was '*In Search of Memory: The Emergence of a New Science of Mind*' by Nobel Prize winner Eric Kandel. It is one of the most fascinating books that I have ever read! I got hooked and set out to learn as much as possible, as a layman can, about the brain. A friend pointed me to V.S. Ramachandran's '*Phantoms in the Brain*' – an older book, but a great one. The timing, once again, turned out to be serendipitous, as newer imaging techniques and other technologies started throwing more light on how the brain works resulting in a slew of books in the last 10 years from the writers I mentioned above, as well as many others, on memory, the mind and the brain. The most illuminating among them were '*Moonwalking with Einstein*' by Joshua Foerr (focusing on memory) and '*Incognito*' by David Eagleman (focusing on the self and consciousness). These books demonstrate one of the holy grails of neuroscience, which is to understand what 'consciousness' is. Is it just an outcome of increased computational power as Kurzweil says? Many scientists like Kurzweil believe robots will soon become 'self-aware' as their computational ability crosses a threshold. If that is so, we will have a hard time explaining what 'being human' is. An immediate answer would be to say that – only 'living' things can be human. Well, then we would have to define what is life? And surprisingly that is not as simple as it looks.

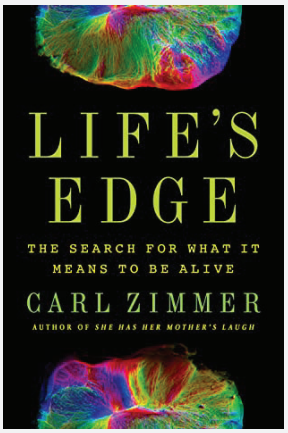


What is Life?

In 1944, an essay by Physicist Dr. Erwin Schrodinger with this header started a revolution in the field of biology. He predicted inheritable units in the cell that can mutate. This was before the structure of DNA had been discovered. Schrodinger's piece inspired many scientists, including Watson, Crick & Franklin, who finally solved the structure of the DNA molecule. The subsequent revolution in biology, due to the progress in genomics, led many to believe that we had solved the definition of life. But it was not to be. Biology seems to be full of exceptions to every 'rule' it finds. Life also seems to follow this, throwing up new puzzles as we explore more.



Carl Zimmer in his recent book (March 2021), 'Life's Edge: What it means to be Alive' explores the definition of life. To quote him:



> ***"We all assume we know what life is, but the more scientists learn about the living world – from protocells to brains, from zygotes to pandemic viruses – the harder they find it is to locate the edges of life, where it begins and ends. What exactly does it mean to be alive? Is a virus alive? Is a fetus?"***

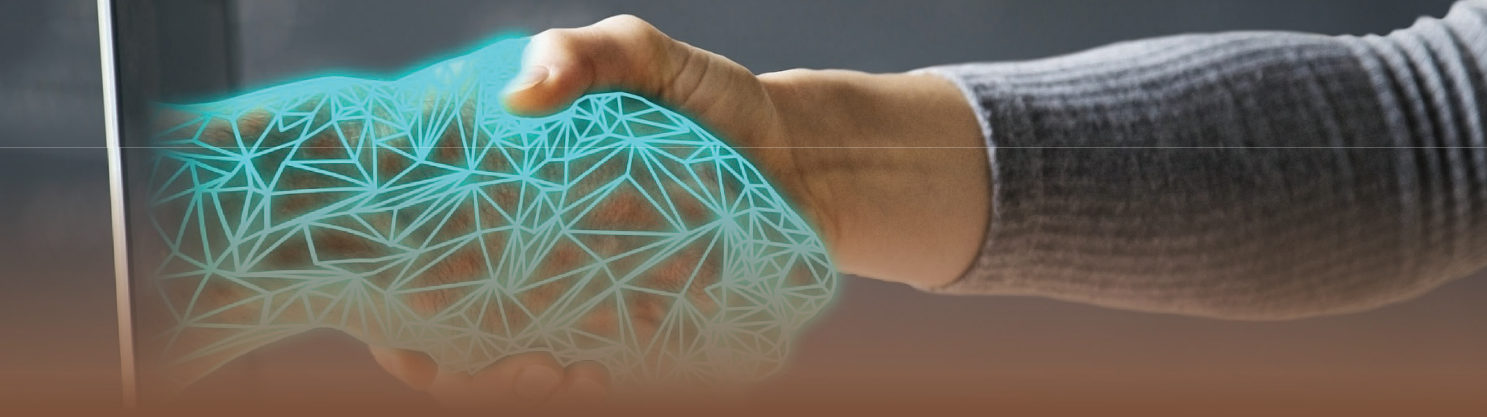
> ***"What is life? The answer seems obvious until you try to seriously answer it. Is the apple sitting on your kitchen counter alive, or is only the apple tree it came from deserving of the word? If we can't answer that question here on earth, how will we know when and if we discover alien life on other worlds? The question hangs over some of society's most charged conflicts – whether a fertilized egg is a living person, for example, and when we ought to declare a person legally dead."***

As you read Carl's book, the impact of these questions strikes you. How will society handle the developments in science? After more than 50 years of legal wrangling, America has still not been able to resolve the 'abortion dispute'. With these debates ongoing, it begs the question as to how new issues will be handled – for example will organoids be considered alive? Will a brain organoid become 'conscious'? Will a brain uploaded to a computer have the legal rights of the 'dead person'?

The Future is in the Brain

These complicated questions make me believe that one of the most important topics for humanity to focus on is the brain. All of us carry this critical organ – maybe one of the most complex things in the universe and sadly we still don't really know how it works. Now, understanding the brain is important, not just from a scientific curiosity point of view, but for the well-being and progress of our society. As we increase our life spans, neurological illnesses, like Alzheimer's and Parkinson's, are becoming more pervasive and we hardly made any progress in solving them. Many new brain related illnesses, like ADD in children and depression and compulsive disorders in adults, most probably created by a combination of many factors like stress, artificial food, environmental pollution, social media etc., are taking a heavy toll on our well-being. Pharmaceutical companies prefer more medications instead of cures, but efforts so far have made it clear that they are chasing up the wrong tree. All our efforts should be focused on understanding how the brain works, which will then not only solve the above problems, but also help us in developing AI tools better.

Additionally, a clear definition of life, consciousness and intelligence will be critical for the next level of legal frameworks in our society. As we all know, society cannot progress without adequate laws, so framing these with a fundamental understanding of science will determine the future of our civilization.



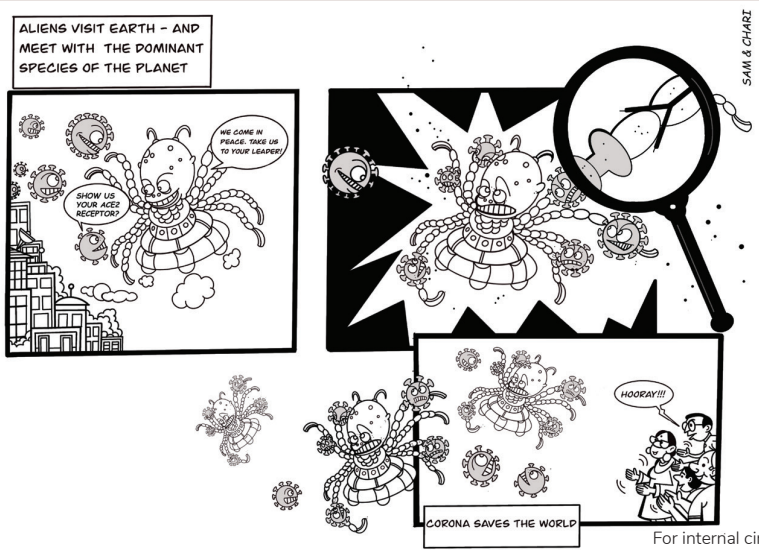
The Future of AI

Now to get back to Tegmark's book that I started this article with – let's look at his major concern that AI might take over our world. It is difficult to deny that AI has started to make a big impact in our day to day lives, whether we are doing a search through Google, booking a flight ticket or trying out Siri on the iPhone. What used to be very difficult tasks for AI, like face recognition or speech processing, have become very routine now. The immediate promise of AI saving countless lives through self-driving cars (which will reduce accidents), robotic surgeries, diagnostics and medical treatment by automated systems and many such innovations are also clear. But none of them really threatens our 'human intelligence' as they are all very narrow systems which cannot do anything more than what they are programmed to do. On the other hand, Tegmark explains the tremendous progress made by programs like Alpha Zero (and now MuZero) which can learn by itself in a dramatically short time. For example, the Alpha Zero program can learn games like Chess or Go by playing with itself (starting with the basic rules and goals of the game) and beat the best human players within 24 hours of first learning the game! This is so different from the earlier approaches where the AI systems were 'taught' by experts to play the game and it had still taken years to develop the computer which would finally beat the World Chess champion Kasparov a few years back.

But the biggest question is when will AI develop to become AGI, or artificial general intelligence, if at all it is possible? Experts like Ray Kurzweil or Max Tegmark have no doubts that it will happen, and their guess is that it should be possible within decades. Most of the second half of Tegmark's book in fact talks about how to control this and have the necessary rules and structures to handle AI development, like how we managed bio-warfare and nuclear weapons. And Tegmark's bigger worry is that if AGI is reached, it will automatically lead to 'Super Intelligence' since AGI enabled robots will be able to improve and reprogram themselves to an astronomically higher level of intelligence that we cannot even imagine. And how will these super intelligent beings consider us humans? Will we go extinct or become slaves?

Unfortunately, we have no benchmark to measure intelligent civilizations. On earth, we seem to have been the first intelligent species in its 4.5 billion year history to become self-aware and reach this level of progress. And we have yet to detect any life in the small area of the cosmos that we have been able to explore so far. We know there are billions of stars in our galaxy itself, and there are billions of galaxies in the universe, and so chances are pretty high that there should be life somewhere else as well. But did life in those places become intelligent enough to make their presence felt in the universe? Or did they remain at Life 1.0 or Life 2.0 level as it remained on the earth for a couple of billion years?

The dinosaurs ruled the earth for a couple of hundred million years but stagnated, while it took Homo Sapiens only two hundred thousand years to get out of the forests to travel in space! But how long will we or any such technologically advanced civilization survive? I will explore this more in a later issue of the newsletter, and for the time being let me leave you with this cartoon...



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