MEDGENOME

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Internal Quarterly Newsletter

WOMEN'S DAY SPECIAL

Featured article

Breast Cancer

Be Informed - Knowledge is Power!

SCIENTIFIC ARTICLE

An Overview on
PHARMACOGENOMICS

WORDS FROM THE **FRONTLINE**

Ravi Gupta, *PhD*
Chief Scientist

My Journey with MedGenome and Science

My journey with science started in 2004. I joined a PhD program at IIT Roorkee in the Electronics & Computer Science Department after my master's professor - Mrinal Das convinced me that PhD is the way to explore the world of science. I did my Postdoc at the Wistar Institute, Philadelphia under Supervision of Ramana Davuluri, who was the developer of the FirstEF program (that predicts promoters from DNA sequence features) when he worked with Michael Zang at Cold Spring Harbor. When I joined as a postdoc, I was still a programmer with minimal biology knowledge. My NGS training and understanding of biology happened during my postdoc tenure (2008 - 2011) with full support from colleagues and collaborators.

In 2011, I made up my mind to return to India. I first met Sam in New York at Intercontinental hotel in the month of March. We discussed the opportunities in SciGenom and also about the data of an Indian genome sequenced by SciGenom. In December, I landed in Trivandrum with my wife to participate in the first SGRF meeting (NGBT) and workshop and in January 2012, I joined SciGenom. After working here for a decade, this decision turned out to be a goldmine of learning and achievements.

While working on the Indian genome project, the idea of VariMAT (Variant and Mutation Annotation Toolkit) was born. There were no good comprehensive variant annotation pipelines so we decided to build an in-house generic framework that would annotate variants not in the human genome but also for other genomes, for e.g., Rice, Mouse. We published our first paper on the South Asian genome in BMC Genomics journal in 2012. We also started our human diagnostics work after Ram joined SciGenom. MedGenome was incubated under SciGenom.

In 2015, I moved to Bangalore to head the MedGenome bioinformatics department. My focus changed completely to human genomics and its application in diagnostics and disease. I again started building a team and analysis ecosystem for human genomics. The idea of QC-STATS, TracPro, NextGEM (now as nextflow-MANGO), VarMiner, MedVarDb (now SAS-ATLAS) and CRDb were born and executed. MedVarDb in the coming years will become one of the key assets for the company driving diagnostics and pharma research. We organized our bioinformatics group internally into two buckets: operation and R&D. Vivek took over the charge of clinical operations whereas I started focusing on the R&D front. After a year in 2016 we also expanded in the research services business as the third wing of bioinformatics. The focus of the R&D group was to enhance the diagnostics pipeline feature, population genomics, OncoPept and support internal research and publications. One of the first things that we did in MedGenome was the design of a custom clinical exome that was more focused towards known disease genes.

One of the first R&D diagnostics projects that we did was on liquid biopsy. We came with a unique bioinformatics approach to analyze high depth liquid biopsy samples and performed a large validation which was published in 2017. This study not only helped us in developing a new test but also gave insights into gaps that exist in current gold standard tests. In 2016, we also started our operations in the USA, and worked closely with Amit Choudhary to build the OncoPept platform and solutions like

OncoPeptVAC and OncoPeptTUME. Many interesting projects with US clients especially in the Pharma space were done and we also published papers on in-silico tumor microenvironment assessment and cancer vaccines.

After looking into the challenges that the genome analysts were facing to prioritize variants for the clinical report generation, in 2018 we decided to build a solution that would predict the variant pathogenicity. We named the project VaRTK (Variant Ranking Toolkit) rhyming with GATK. By now we had aggregated enough clinical samples in our MedVarDb and CRDb databases that would help us in building the model. We were confident that the knowledge put by the genome analysts in the clinical report will be very useful for training and building a computational model. After deeper understanding of various available options we successfully built a machine learning model based on Random Forest that would rank the 90% of pathogenic variants in top 10 just like how the Google search works. We received excellent support from VarMiner and the genome analyst team for its integration in the interpretation process.

Parallelly, we also started our infectious disease program. The task given to us was to develop a targeted approach to sequence the tuberculosis genome technique. Tuberculosis is the biggest killer and more than 1 billion people have died over the past 2000 years and still kills 1.5 million people worldwide every year. Apart from detecting tuberculosis, identification of drug resistance mutations are very crucial to decide the drug regimen for management of patient disease. We designed the probes and data was generated by Lakshmi Soundararajan and team. The real challenge in the analysis came due to the similarity of tuberculosis genomes with other bacteria, hence our sputum samples contained other bacteria as well. We came up with an idea of a composite genome and added a few additional steps that would get rid of the non-tuberculosis genome from Sputum data. We had excellent collaboration with John Hopkins and Hinduja hospital from Mumbai for this project. Our work was published in the tuberculosis journal in 2019.

We contributed to the Genome Asia phase1 study which was later on published in Nature in 2019 and was a big milestone for many of us. While working on this we built an ancestry and imputation workflow which is now used for the Direct-to-Consumer (DTC) service. We also built a unique program (SVR-Admix) that could predict the ancestry of individuals from clinical or whole exome that was integrated into production for QC purposes. In 2019, we started working on CAD polygenic risk score (PRS) project taking help from Sekar Kathiresan from the Broad institute and a pioneer in this area. This was a new area, and we weren't sure whether this would work on the Indian population. Also, we were skeptical about the whole idea of PRS wondering how 6 million markers can be aggregated to generate a single score. I was thinking more from a computational background and related this to a typical overfitting problem in the machine learning area. Sanghamitra and her team did an excellent job in coordinating the data generation. In 2020, we published an article describing our CAD PRS work in the Indian population. We now provide this as a test under the Kardiogen label.

After spending a decade at MedGenome and SciGenom, I can proudly say that we have built a world class bioinformatics ecosystem for analysis of human genomics data and especially for clinical diagnostics application. The most satisfactory part of this achievement is that the complete ecosystem has been built indigenously with paramount quality and strong scientific foundation.

All this was possible because of hard work and dedication of the team and full support from operation, software & IT and most importantly the management. One important lesson that I learned is that don't wait for things to happen but rather make things happen.

> “ Don't crib for resources but rather make best use of the available resources. ”

We have grown from a startup with a small lab space in Cochin to the leading diagnostics service provider based on NGS technology. Our sequencing throughput has grown from a single MiSeq machine to the largest sequencing lab in South Asia. The bioinformatics team has grown from a 4 to a strong 50+ member team. MedGenome success and journey is an achievement not only in my professional life but a great personal milestone. MedGenome has provided a great platform to me and many young minds to experiment their ideas.

I tell everyone in the team that they are lucky as they cannot find a better place to learn genomics and bioinformatics in India. Learning and improving from failures and mistakes has been the motto of my life.

The coming years are very crucial to scale and diversify our business. The bioinformatics department is the fulcrum to achieve our scientific and business goals. The team is gearing up for complete automation of the clinical pipeline so that results are just a click away. The informatics team is heavily focusing on improving our variant interpretation capabilities by integrating new features which will scale up our diagnostics business. Cancer diagnostics is receiving our special focus to bring new diagnostics markers in solid tumor testing and improvise our cfDNA offering. We are developing the SAS-ATLAS platform to perform genotype-phenotype analysis of the patient data. We are also gearing up to enter personal genomics with strong science and tested products.

I have just one mantra to achieve our goals.
Just do it and don't worry about failures.

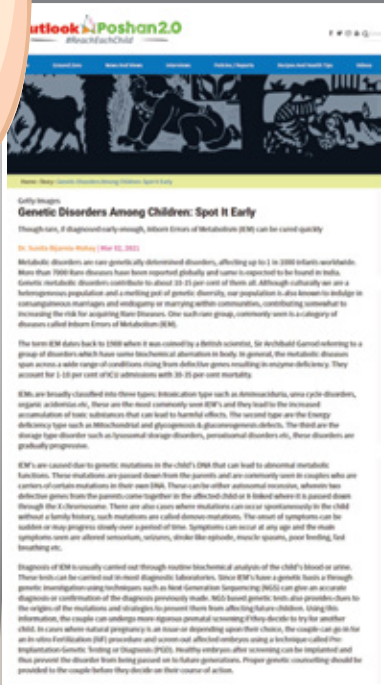
Contents

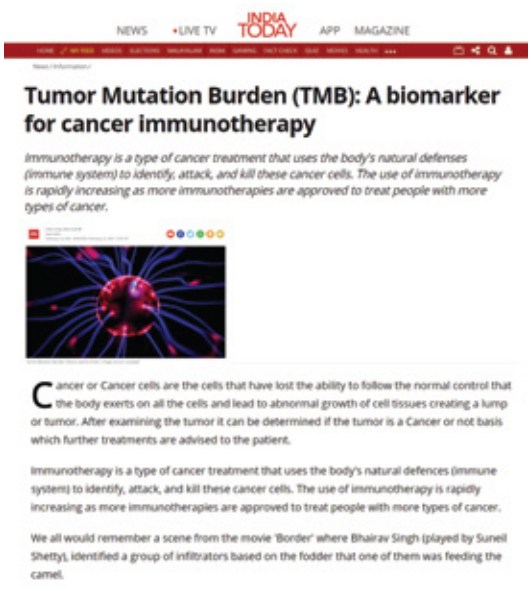
Most Talked About

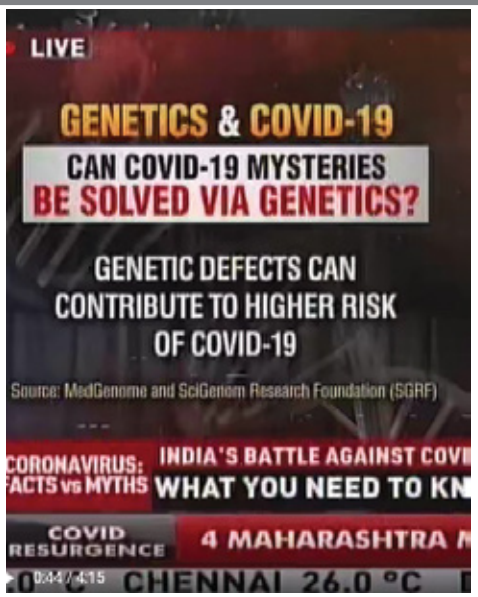
The News

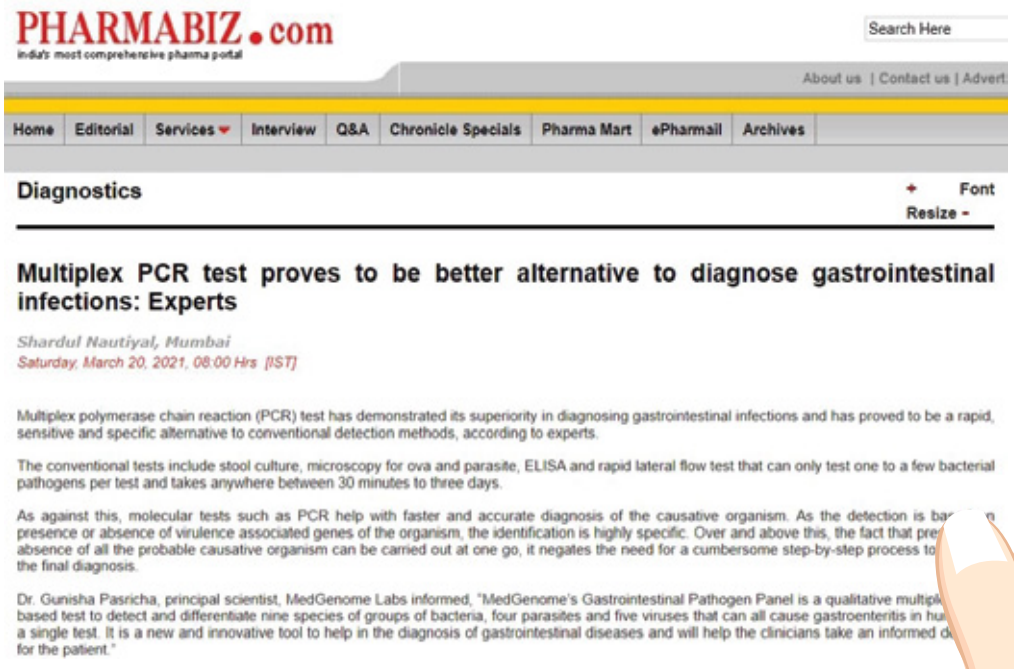
MEDGENOME NEWS | January to March 2021 | MEDGENOME NEWS

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









For press articles, please click

https://diagnostics.medgenome.com/press/

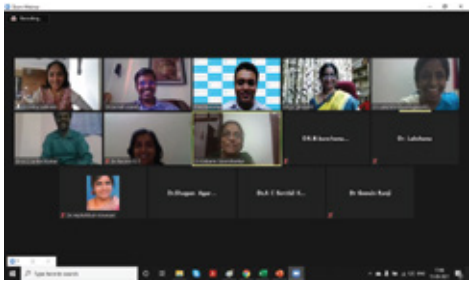
MedGenome Connect

Claria and Actia events summary since the lock down:

It has been a year since the world started going into lockdowns and work from home. Although physical events and interactions have been non-existent it has not stopped our digital engagements from carrying on full steam. In the past year we have conducted 21 webinars with 6038 doctors registering and 3650 doctors attending these webinars. 16 KOLs have been engaged through these activities with our database of doctors increasing by 2700 for Claria and 925 for Actia. More webinars with KOLs are planned should increase our visibility among doctors.

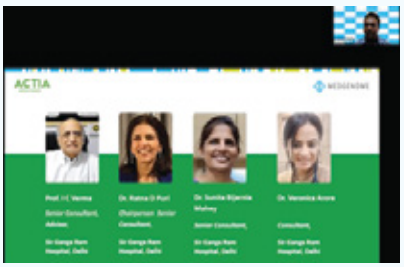
Claria
Reproductive Genetics

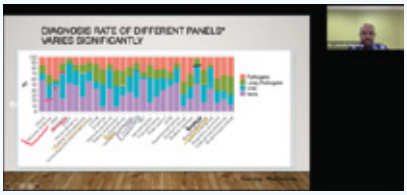
The last quarter was a very busy one for Claria with multiple events. Claria continued its focus on digital events with a series of Webinars and online symposiums with organisations such as Federation of Obstetrics and Gynaecological Society of India (FOGSI), Madras Medical Mission, Institute of Reproductive Medicine (MMM, IRM). With FOSGI, we did a series of 3 webinars on the reproductive genetics chaired by Dr Mandakini Pradhan of SGPGI, Lucknow and who also heads the Genetics and Fetal Medicine Committee. This series was very well received by doctors with a total registration of 1250 doctors and an attendance of close to 700 doctors. February was a quiet month but in March we were back with more webinars in partnership with Association of Obstetrics and Gynaecological Society of Delhi (AOGD) and MMM IRM with whom we did a 2day symposium. We also started doing some live CME's first of which was held at CloudNine Mumbai. In addition to this, our Recurrent Pregnancy Loss article by Dr Priya Kadam was published online by India Today.



ACTIA
Inherited Genetics

The focus for Actia too was on online events. We had webinars with leading doctors Dr Lokesh Lingappa on Neurogenetics and Dr Rajiv Sinha on Nephrogenetics on the occasion of World Kidney Day. The last Sunday of February is Rare Disease day and on this occasion, we organised a panel discussion called "Care for Rare" with leading doctors including Prof I C Verma, Dr Ratna Puri and Dr Sunita Bijarnia Mahey. In addition to these formats, we explored a new format of Podcasts with leading publications in the country, the first of which was on our CAD PRS test with Dr Rajeev Gupta and the second with Dr Vivek Jain, Neurologist from Jaipur talking about our Infantile spasm study. Both podcasts were with Aaj Tak radio in Hindi. The third one was with Deccan Herald with Dr Sunita Bijarnia Mahey who spoke about Rare Diseases. In addition to these, we go a lot of press coverage for our Epilepsy study publication and for Rare Disease day articles.

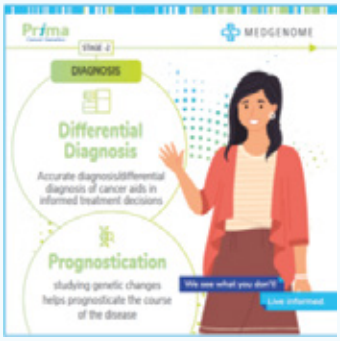


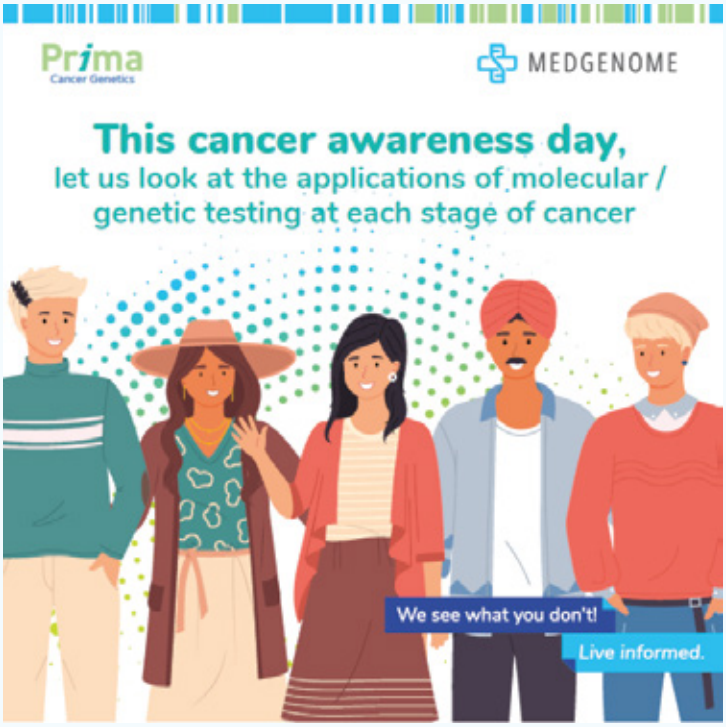


MedGenome Connect

Prima Cancer Genetics

We continued to focus on digital platforms and leveraged it for various digital campaigns. February 4th being the world cancer awareness day, we launched a campaign showcasing the applications of genetic / molecular testing at different stages of cancer.





mocra Infectious Disease Genetics

As a part of our efforts in spreading awareness about Syndrome Evaluation System (SES), we conducted 2 webinars in February. The first webinar was on 22nd Feb (World Encephalitis Day), where Dr Ravikumar was the speaker. The second webinar was on 28th Feb on molecular testing in Eye Infections, where the speakers were Dr Ravikumar and Dr Abhishek Kothari. Both the webinars were well-received by the audiences.

What's new

Publications

1. ***Clinical and whole genome characterization of SARS-CoV-2 in India, published in Plos One***

   To read, click-
   https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0246173

2. ***Recent Evolutionary History of Tigers Highlights Contrasting Roles of Genetic Drift and Selection, published in Molecular Biology and Evolution***

   To read, click-
   https://academic.oup.com/mbe/advance-article/doi/10.1093/molbev/msab032/6133235

New Test launch

3. ***Gastrointestinal Pathogen Panel***

From our US Office

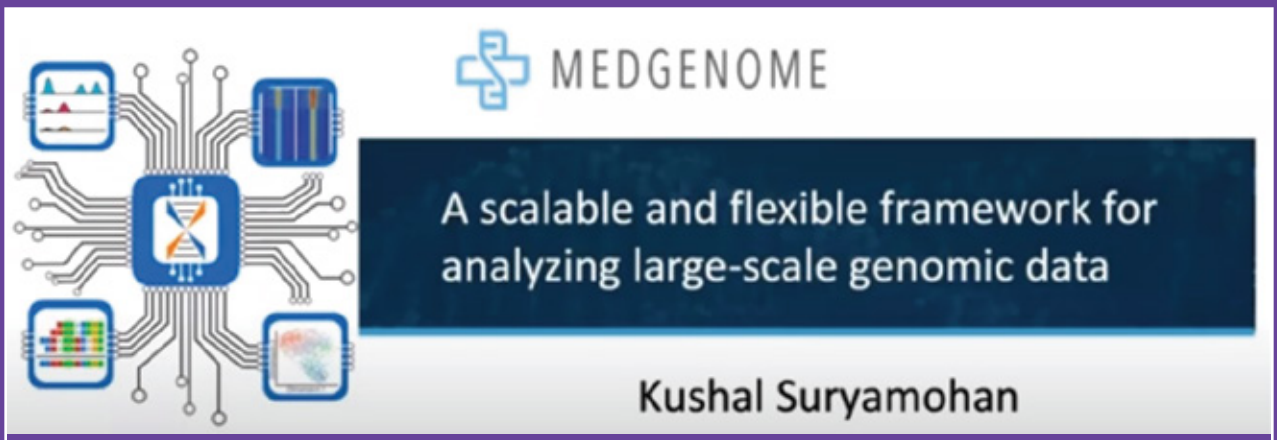
This quarter we made efforts towards growing our strength by adding new assays and streamlining processes in the Lab as well as aiming at charting new territories in the US.

We are happy to share that we are adding many more technical key resources inside every department thus enhancing our capability and widening our service scope.

We also recently conducted a webinar on our Bioinformatics capabilities titled “A scalable and flexible framework for analysing large-scale genomic data”.

Further details are available on our Blog:

https://research.medgenome.com/scalable-flexible-framework-analyzing-large-scale-genomic-data/



And, we have recently added a few 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/

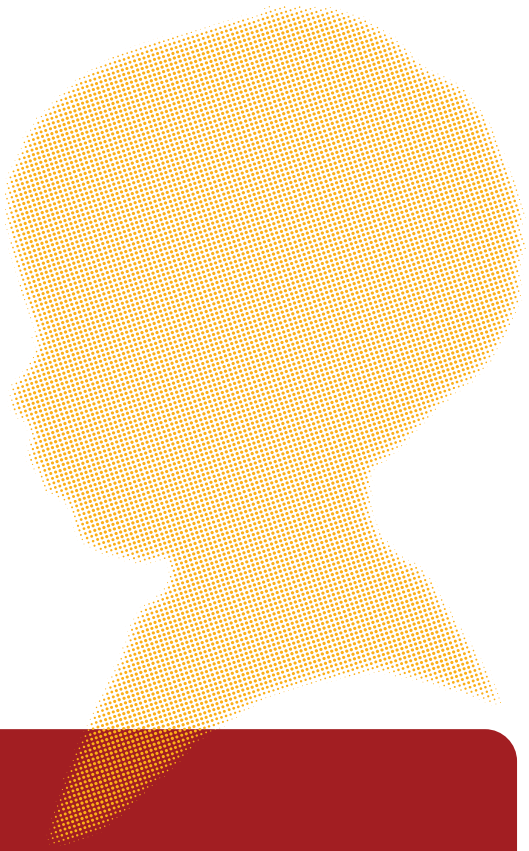
Do not miss out on the recent article on Single Cell Omics: Merging Single-Cell Sequencing Technologies to Uncover Complexity of Cell Diversity

URL:

https://research.medgenome.com/merging-single-cell-sequencing-technologies-uncover-complexity-cell-diversity/

Making a difference

Genetic testing at Baseline and post-induction chemotherapy *helps in informed treatment decision for a* **leukemia patient**



Master Arjun (name changed), a 5-year-old boy presented with fever, fatigue, chest discomfort, weight loss & loss of appetite had consulted Dr Mahadev Swamy, a leading Hemato-Oncologist based at Goa, for further clinical examination as referred by a General Physician from a community hospital. Basic workup on blood sample revealed suspected acute leukemia, which was confirmed on Bone marrow examination. The diagnosis was further refined, by flow-cytometry findings which revealed T-cell acute lymphoblastic leukaemia (T-ALL).

Case Discussion

T-cell acute lymphoblastic leukaemia (T-ALL) is a type of acute leukaemia that is aggressive and progresses quickly. It affects the lymphoid-cell-producing stem cells, in particular a type of white blood cell called T lymphocytes as opposed to B-cell acute lymphoblastic leukaemia (B-ALL) which commonly affects B lymphocytes.

Post clinical examination, his bone marrow sample was sent for genetic testing to MedGenome Labs Ltd, Bangalore to assess the gene mutations. The results showed the presence of mutation on the *NOTCH1* gene. Based on the report, Arjun was started on BFM-2009 chemotherapy which is a standard protocol.

Post induction chemotherapy, minimal residual disease (MRD) analysis was done both by flowcytometry and next generation sequencing (NGS, for *NOTCH1*), to assess the efficacy of the treatment. Minimal residual disease (MRD) is a concept used to assess the residual number of cancer cells in the body after cancer treatment. In case of childhood T-cell acute lymphoblastic leukemia (T-ALL), risk stratification of an individual is mainly based on minimal residual disease (MRD) quantification. Oncogenic mutation profiles can improve the discrimination of MRD-defined risk categories.

During the second phase of testing (follow-up), the *NOTCH1* gene mutation was not detected on NGS. No other clinically relevant mutations were detected in Arjun's sample. In view of Flow cytometry-MRD showing complete remission along with absence of baseline mutation, Arjun was continued on the same chemotherapy regimen and there was no need of intensification to high risk chemotherapy.

NGS based comprehensive molecular profiling at baseline and subsequent follow-up with the spectrum of mutations would help to assess the risk for relapse. Mutation profile of an individual is an independent predictor of response to chemotherapy. The NGS technology has a very high sensitivity to detect samples with mutation loads as low as even 1%. When combined with MRD analysis, it identifies a significant subgroup of patients with a low risk of relapse.

Summary

- Base line genetic testing helped in detection of clinically relevant variants in *NOTCH1* gene. Based on this result, the patient was started with low risk chemotherapy.
- Post induction chemotherapy, mutation in *NOTCH1* gene was not detected, which nullified the need for therapy intensification.

An Overview on PHARMACOGENOMICS

By: Christina Devanboo
Genome Analyst

Pharmacogenomics is the study of how an individual's genetic makeup affects his/her response to drugs. Pharmacogenetics (PGt) is another term more often interchangeably used with pharmacogenomics (PGx). Although both the terms relate to drug response based on genetic makeup there is a diversity of opinion regarding their definitions and benefits. In 2002, The European Agency for Evaluation of Medicinal Products (EMEA) defined "pharmacogenetics" as "the study of inter-individual variations in DNA sequence related to drug response mainly single-gene mutations" (Figure 1) and "pharmacogenomics" as "the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at the cellular, tissue, individual or population level". Pharmacogenomics gained recognition in the late 1950s. Key events that created interest in pharmacogenetics were the discoveries of the genetic lack of butyryl-cholinesterase ('pseudocholinesterase') in patients who had died following a succinylcholine injection in 1956[23] and the genetic deficiency of N-acetyltransferase, the enzyme which destroyed the then-revolutionary anti-tuberculosis drug isoniazid in 1957[24]. The term "pharmacogenetics" was coined in 1959 by Friedrich Vogel. The advent of pharmacogenomics, however, truly began through the late 20th and early 21st century due to the ready availability of new genotyping and sequencing technologies, that have helped in identifying many genetic variations that may lead to inter-individual variability in drug response. The completion of the Human Genome Project[1], the HapMap Project[2], and the 1000 genome[3] project have significantly contributed to the rapid expansion of this field.

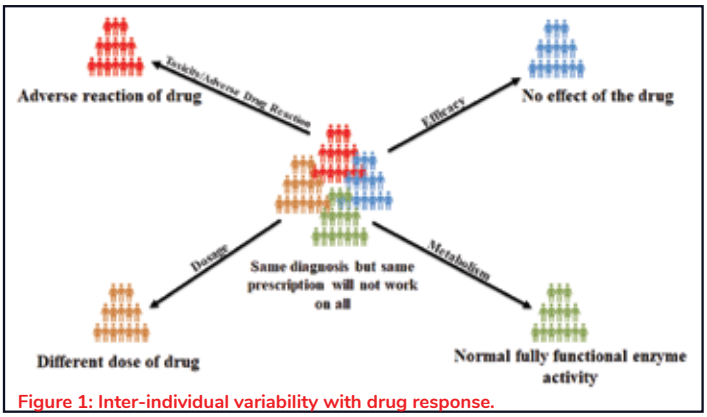


Figure 1: Inter-individual variability with drug response.

Factors contributing to altered drug response

The completion of the Human Genome Project (HGP) revealed that humans have about 20,500 genes and that 99.5 percent of the genes are similar[1]. The remaining 0.5 percent are variations that are responsible for the individual's blood group, predisposition toward diseases, eye colour, etc. Single nucleotide polymorphism or SNP is the most common type of variant found in the DNA sequence. Insertions, deletions, inversions, and copy number variations (CNV) are another type of variants called structural variants. When any of these genetic variants influence the absorption, distribution, metabolism, and elimination (ADME) of drugs, they are considered as pharmacogenetic biomarkers. A response towards a drug is based on pharmacokinetics (how the body processes the drug), pharmacodynamics (how the drug impacts the body), or in some cases, a combination of the two. Depending on the genetic variations, an individual will have different drug metabolism activity, responses, and adverse drug reactions (ADRs) post-drug administration[4]. Other factors like the individual's age, diet, environment, lifestyle, and current state of health must be taken into consideration along with the PGx testing results to guide therapy choice and dosing modifications (Figure 2). To improve treatment efficacy and reduce the incidence of ADRs, important peer-reviewed PGx-based drug dosing guidelines are published by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[5,21,22], the Royal Dutch Association for the Advancement of Pharmacy—Pharmacogenetics Working Group (DPWG)[6], and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS)[7] for the prescription of actionable drugs, pharmacogenetic tests and their translation in clinical practice. The first PGx dose recommendations for antidepressant and psychiatric drugs were published in 2001, even before the first human genome was sequenced. The Pharmacogenomics Knowledge Base (PharmGKB) is another publicly available database for genetic variation and drug response[8].

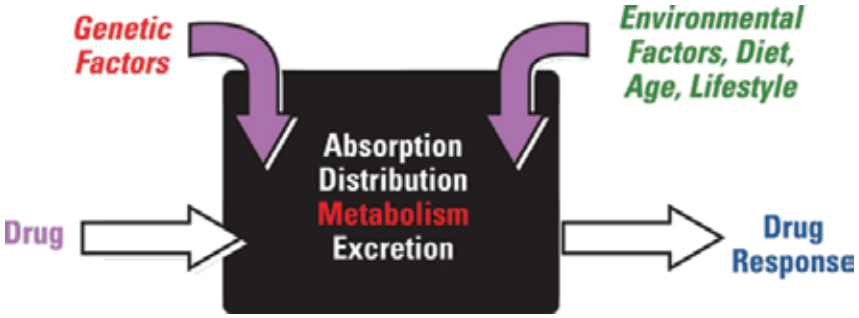


Figure 2: Factors responsible for variations in drug response. Picture courtesy: https://www.mlo-online.com/continuing-education/article/13009247/the-role-of-pharmacogenomics-in-precision-medicine

Methods for variant analysis

In the last 20 years, there has not only been progress in the development of PGx guidelines, but also advancement in the rise of new significant technologies for assessing genetic variants. "A good genotyping test must identify all or most of the variants that have a significant impact on the expression or function of drug-metabolizing enzymes, transporter proteins, and/or drug receptors[10]." Real-time polymerase chain reaction (RT-PCR), restriction length fragment polymorphism (RFLP) analysis, microarray, Sanger sequencing, and Next Generation Sequencing (NGS) are some of the clinically accepted genotyping options. During the development of the first PGx guidelines, only Sanger sequencing and SNV (single nucleotide variant) arrays were available. Although SNV panel testing remains the most used technology in clinical practice, this panel cannot detect all-important genetic variations such as rare and structural variants[9]. In recent years, NGS has been gaining more attention because it is highly cost-effective, enables testing of many individuals simultaneously, and yields an abundance of genetic information concerning an individual's ADME-toxicity gene variants. Each of these methods has specific advantages and limitations. It is imperative to have a better understanding of the strengths and weakness during the analysis of complex genes, such as CYP2D6, because this pharmacogene is highly polymorphic and is paired with most

of the drugs for which pharmacogenomic guidelines recommend changes to medical management based on the variants identified in this gene[11]. Therefore, "the selection of appropriate technology will be based on factors such as prior knowledge of the mutation/polymorphism, sensitivity/specificity, sample requirements, and cost."Newer technologies that do not require PCR will help to minimize the turnaround time and labour for genetic tests. Ultimately, the success and clinical application of pharmacogenomics depends on having simplistic, sensitive, rapid, and accurate techniques[12].

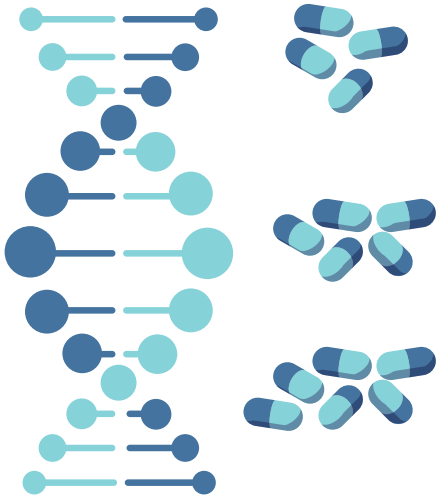
Benefits of pharmacogenomics

The general approach in most clinical practices is "one drug fits all" irrespective of the genetically based differences in drug response among individuals. India, home to one-sixth of the global population and one among the leading global pharmaceutical markets has faced challenges in the form of ADRs during drug development due to the extensively diversified genetic constitution and ancestry components[4]. To overcome this challenge, India is rapidly building therapeutic, diagnostic, and infrastructure capabilities, and also various companies supporting the same have been established[14]. The ApnaGenome drug response genetic test offered by MedGenome Labs Ltd. is primarily based on the data curated from the genomic analysis of the Indian population. This test utilizes NGS technology to assess an individual's response to approximately 60 drugs covering 18 genes and more than 600 variants across a range of diseases such as Cardiovascular disease, Infectious disease, Oncology, etc. This test result helps in tailoring drug regimens based on CPIC guidelines[13]. The potential benefits that can be offered by pharmacogenomics over the next several years are[15]:

Doctors will be able to prescribe the best available drug based on a patient's genetic profile. For example: During a doctor's visit, the oncologist had decided to use mercaptopurine to treat a child with leukemia based on his experience with prior patients. However, the child begins to experience unexpected bone marrow toxicity, immunosuppression, and life-threatening infections. On doing PGx testing, an SNP was identified which altered the child's metabolism of the drug, causing the drug to linger in the body at dangerous levels. Based on the test results, an alternative drug was prescribed to treat the child.

The drug dosages will be based on a person's genetics and how well their body processes and metabolizes the drug instead of prescribing the drug based on their age and weight. For instance, two patients with similar clinical presentations and weight were given the same dose of the anti-platelet drug clopidogrel. One was adequately protected against cardiovascular events while the other experiences a myocardial infarction due to inadequate therapeutic protection. On testing, it was identified that the patient with inadequate therapeutic protection likely had a polymorphism of CYP2C19 causing a decreased activity of drug metabolism.

Potential therapies can be discovered more easily using genome targets. The cost and risk of clinical trials will be reduced by targeting only those individuals capable of responding to a drug.



An individual can make adequate lifestyle and environmental changes based on his/her genetic profile to avoid or decrease the severity of the disease. Prior knowledge will allow careful monitoring of treatments to maximize their therapy.

Vaccines will be inexpensive, stable, easy to store, and capable of being engineered to carry several strains of a pathogen at once.

Promote a net decrease in the cost of health care due to a decrease in the number of ADRs, failed drug trials, time taken to get a drug approved, the length of time patients are on medication, the number of medications patients must take for effective therapy, and an increase in the range of possible drug targets[16].

Barriers to pharmacogenomics

Though the integration of pharmacogenetic testing into clinical practice has evolved, there have been many challenges in implementing it in a clinical setup. A few of the most notable challenges include:

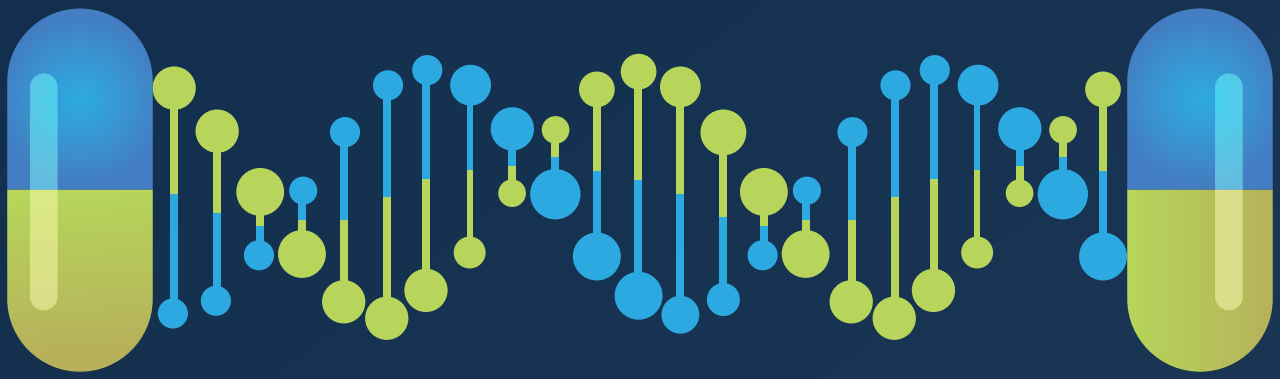
1. Firstly, clinicians need to have a clear understanding of the use of genetic testing available to make appropriate therapeutic decisions. Even though CPIC guidelines help to alleviate the problem by explaining the test options and how to use pharmacogenetic information in case a gene variant is confirmed, the list of drugs addressed currently is limited[17].

2. A lack of confidence regarding the validity of a pharmacogenetic test among clinicians, causes hesitation to proceed with ordering one. However, clinicians must be further educated regarding the validity of the tests[17].

3. Another challenge is the lack of understanding of applying pharmacogenetic test results to patient care. As mentioned above, the CPIC guidelines is one of the best resources to assist with this challenge. Also, the information available on the FDA website offers valuable assistance[18].

4. The most prevalent challenge in implementing pharmacogenetics in healthcare is the cost of genetic testing. The approval and reimbursement for genetic testing by healthcare companies do not facilitate easy access since only a few tests are covered by insurance. Therefore, new policies are necessary to expand the use of genetic testing in healthcare settings[19].

5. And lastly finding alternative treatments for patients when medications are not effective for a specific disease or condition is another limitation for implementing pharmacogenetics[20].



Conclusion

Pharmacogenomics and precision medicine are the future of healthcare. Many surveys have reported that high percentages of healthcare professionals believe in the concept of pharmacogenomics and find it relevant in clinical practice. But more time should be dedicated to training the clinicians to feel more comfortable interpreting the results. Resources such as PharmGKB, practice guidelines, pharmacists, and genetic counselors are available to support clinicians to implement this testing in their practice. As research continues, the evidence of gene-drug associations will increase and the implementation barriers faced today will be resolved. In the very near future, it will not be unusual for patients to have their PGx information available for improved treatment success and decreased societal costs.

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Featured Article

BE INFORMED
Knowledge is Power!

By: **Madhavilatha**

Genetic Counsellor, Level II

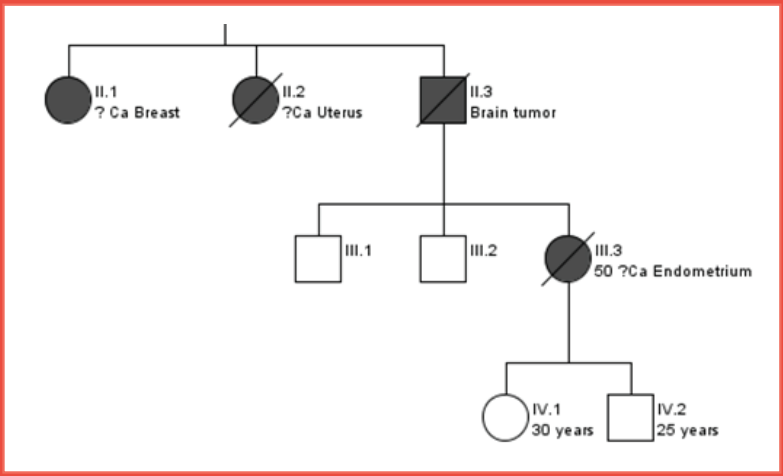
41-year-old Asma is a healthy individual, but with a strong family history of cancer. One of her sisters, her mother and her maternal aunt succumbed to cervical cancer, another sister succumbed to breast cancer, and father succumbed to an unknown cancer. She approached the MedGenome GC team for counselling and wanted to know her risk, and if 'anything' can be done! After pre-test counselling by our genetic counsellor Ms. Prachi, she decided to go ahead with genetic testing. On evaluation, she was found to have termination variations in both BRCA1 and ATM genes. Post-test counselling was done, and risk assessment was provided. Screening and management options were discussed, and she was asked to consult with her referring clinician for more details. Genetic testing gave her a clarity regarding her risk and She is now ready to face her risk.

Kartika a 38-year-old mother of two children, who was recently diagnosed with Stage III breast cancer came to us asking about genetic testing. She was worried, and wanted to do genetic testing to take a decision regarding mastectomy and oophorectomy. Genetic counselling and genetic testing helped her make an informed decision, and later on understand her risk. No pathogenic, likely pathogenic or VUS were identified in Karthika.

30-year-old Brinda and her 25-year-old brother are asymptomatic, and approached the MedGenome GC team to understand their risk for cancer. They had a family history of cancer with mother succumbed to Ca endometrium, maternal grandfather to brain tumor, and maternal grandaunts to Ca ovary and breast. Both of them had inherited a pathogenic variant in BRCA1.

Everyday the GC team at MedGenome counsels at least one family with breast cancer or with a family history of breast cancer. So, this woman's day we pledge to inform and be informed about breast cancer.

Female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated **2.3 million new cases, representing 11.7% of all cancer cases**. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths.



Cancer Statistics

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world. In men, lung cancer is the most frequently occurring cancer and the leading cause of cancer death, followed by prostate and colorectal cancer for incidence and liver and colorectal cancer for mortality. In women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer for incidence, and vice versa for mortality.

What is Breast Cancer?

Cancer happens when cells grow and divide in an uncontrolled way, creating a mass of tissue called a tumor. Cancers are named after the part of the body from which they originate. Breast cancer originates in the breast tissue. Sometimes these cells may also travel to other places in the body, and when that happens, the cancer is called metastatic.

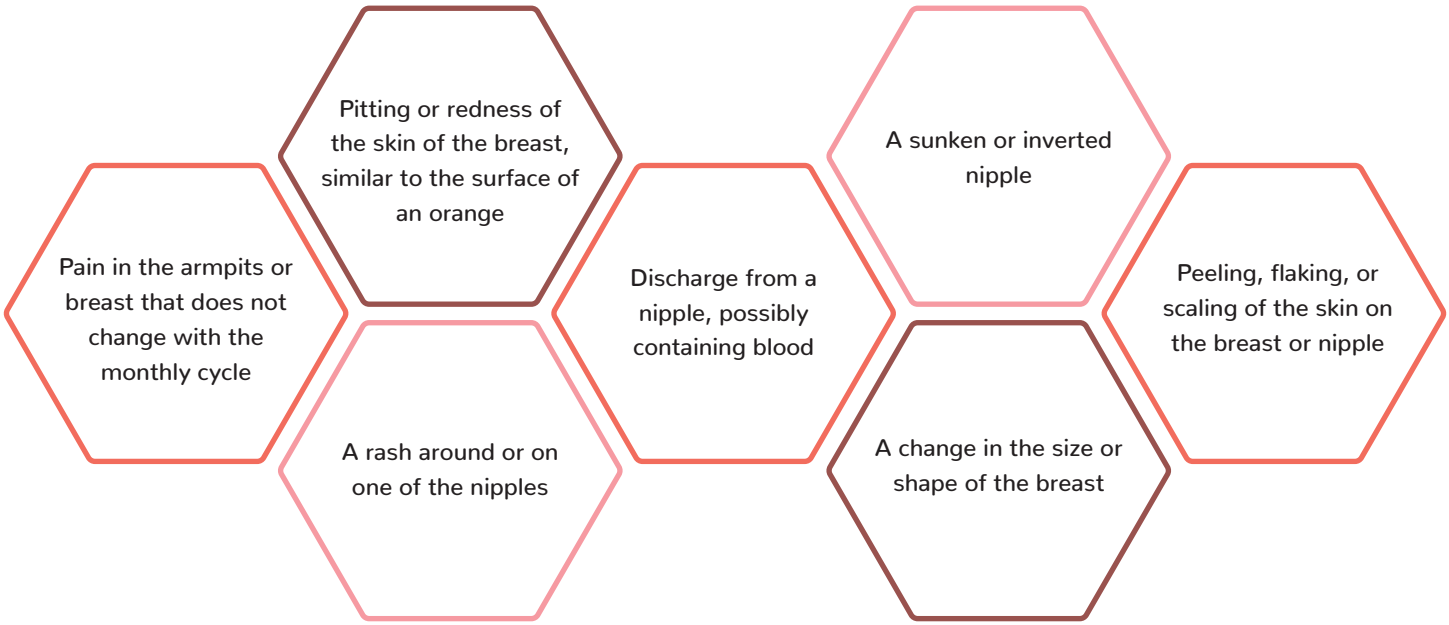
Who can get it?

Men can get breast cancer too, but they account for less than 1% of all breast cancer cases. In women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death accounting for 1 in 4 cancer cases and for 1 in 6 cancer deaths.

What are the symptoms?

The first symptoms of breast cancer usually appear as an area of thickened tissue in the breast or a lump in the breast or an armpit.

Other symptoms include:



These changes may be found when performing monthly breast self-exams. Breast self-examination should be performed at the same time each month, three to five days the after menstrual period ends. If menstruation has stopped, the examination should be done on the same day of each month.

Most breast lumps are not cancerous. However, a woman should visit a doctor for an examination if she notices a lump in the breast.

What are the *risk factors?*

A woman's age, genetic factors, family history, personal health history, and diet all contribute to breast cancer risk. Like many conditions, risk factors for breast cancer fall into the categories of things we can control and things that we cannot control.

Controllable risk factors are alcohol consumption, physical activity, weight and diet, reproductive history, breast implants and using hormone-based prescriptions.

Non-controllable risk factors for breast cancer include being a woman, breast density, getting older, reproductive factors, exposure to radiation, having a family history of breast cancer, having a genetic mutation associated with breast cancer or having a personal history of breast cancer.

Types of Breast Cancer

Ductal carcinoma begins in the milk duct and is the most common type, and Lobular carcinoma that starts in the lobules. And these can be either *in situ* cancers that haven't spread past the duct or lobule where they started, or invasive cancers that have spread or invaded the surrounding breast tissue.

Diagnosis of Breast cancer

Along with breast examination, imaging tests like Digital mammography, Scintimammography, ultrasonography, magnetic resonance imaging, and positron emission tomography. A biopsy is done to test for tumour factors and its grade.

Breast Cancer Treatment

Local treatment for breast cancer includes breast-conserving surgery, mastectomy and radiation; systemic treatment includes chemotherapy and hormone therapy.

Hereditary cancer and Role of genetic counselling in breast cancer care

About 5% to 10% of breast cancers are hereditary. Hereditary cancer means cancer runs in the family, and could be caused by a change in certain genes that were inherited from either parent. In certain cases, the change might also be *de novo* in the patient.

Individuals who have been diagnosed with breast cancer are often referred to see a genetic counsellor, especially in cases where there is a family history of cancer or if the cancer has a young age of onset.

Most inherited cases of breast cancer are associated with mutations in two genes, BRCA1 and BRCA2. The average woman has about 12% risk of developing breast cancer in her lifetime. Women who have a BRCA1 mutation or BRCA2 mutation (or both) can have up to a 72% risk of being diagnosed with breast cancer during their lifetimes. Inherited mutations in other genes are also associated with breast cancer, but most of them don't.

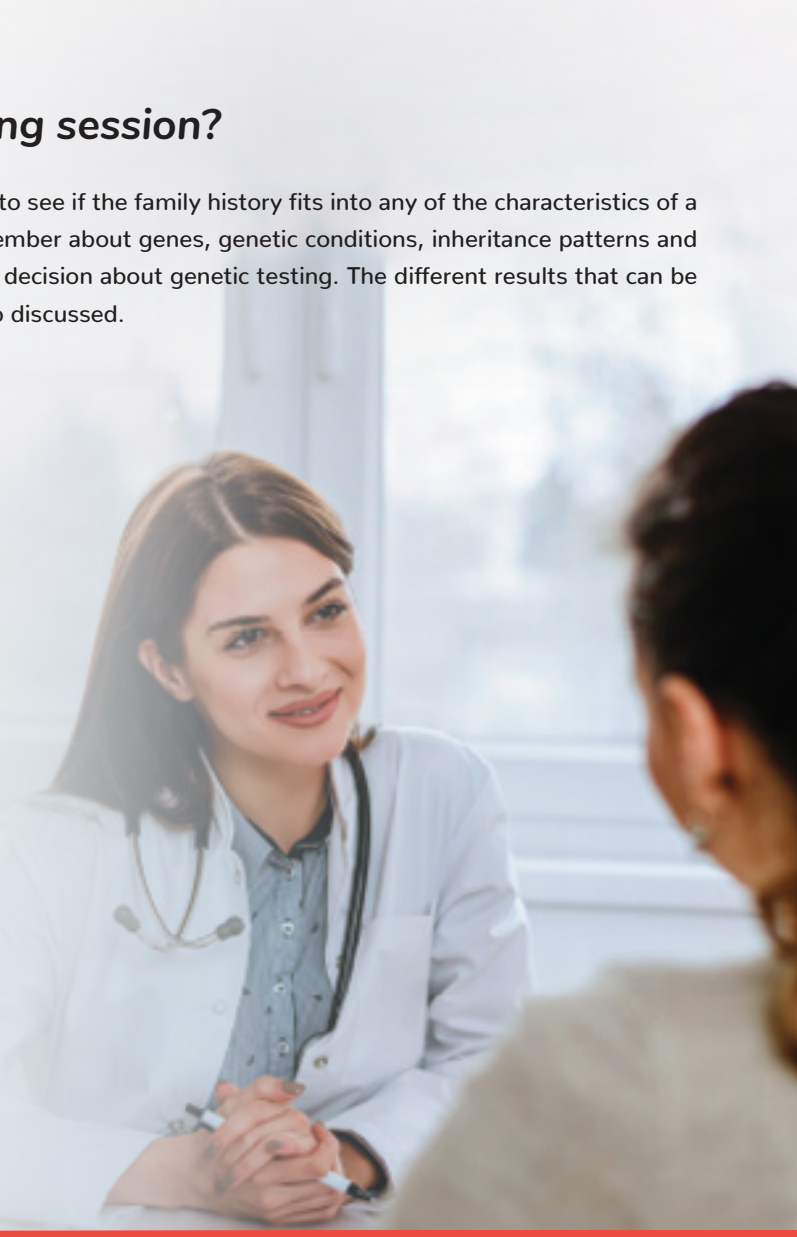
What happens in a genetic counselling session?

The first thing a counsellor does is to review the patient's history to see if the family history fits into any of the characteristics of a hereditary cancer syndrome. If yes, information patient/family member about genes, genetic conditions, inheritance patterns and the testing options available so as to help them take an informed decision about genetic testing. The different results that can be expected, and how they will impact them and their family are also discussed.

If there is a family history of breast cancer, it's important to start with an affected family member first if possible. This is because the counsellor can determine if the cancer is associated with one of the genes, and use this information to determine if there is a need for earlier screenings and preventive management. Unaffected individuals in the family can be tested first, but a negative (or sometimes even a VUS) result will not tell for certain if there is a mutation in the family that wasn't inherited.

The counsellor also always makes it a point to explain that testing positive for a gene mutation does not automatically mean cancer will develop in the future, and testing negative doesn't mean that the individual will be cancer free in the future. Many women live their whole lives with disease causing variations and never develop cancer.

Women or family members who are interested in testing should instead talk to their doctor and a certified genetic counsellor.



Tips to help prevent breast cancer:

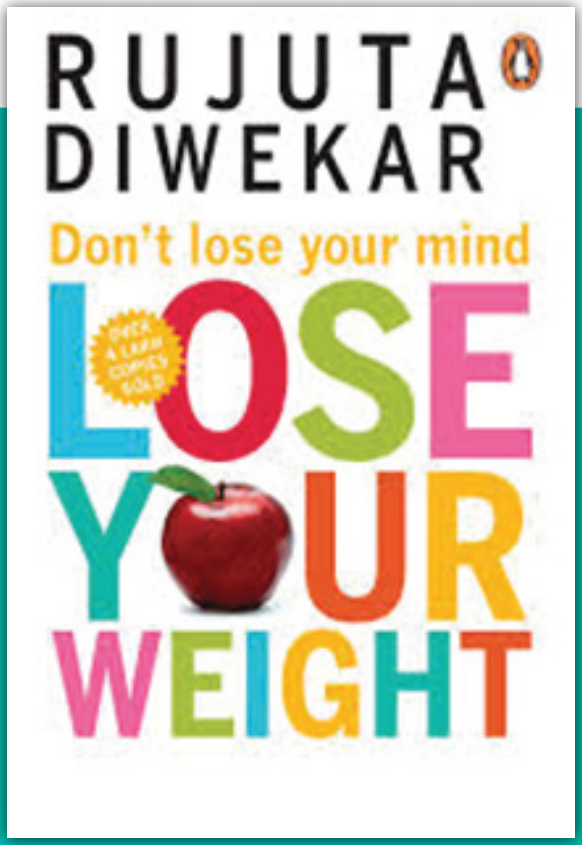
- Know your body
- Know the risk factors
- Know what changes to watch out for
- Know your medical and family history
- Know that it's ok to ask questions
- Do some research
- Seek a second opinion
- Control your weight and stay active
- Breastfeed
- Limit hormone therapy after menopause
- Get screened
- Limit or skip alcohol

If you're at high risk

- Genetic testing to look for a change in your genes that raises your risk
- More frequent doctor visits and screening tests
- Talk to your clinician about risk reducing surgery

From our Colleagues

Book Review



Book

Don’t lose your mind Lose your weight!

Book review by

Vinay CG,

Associate Director, Content and Communications

When it hits you dead simple! that is when you have that aha moment! - Your neurons get excited and fire rapidly. Most of the times we ignore the wisdom that comes with common sense and ancient traditional knowledge. In a the world filled with more information, it is common to lose our sense sometimes and do many things which do not have scientific foundations.

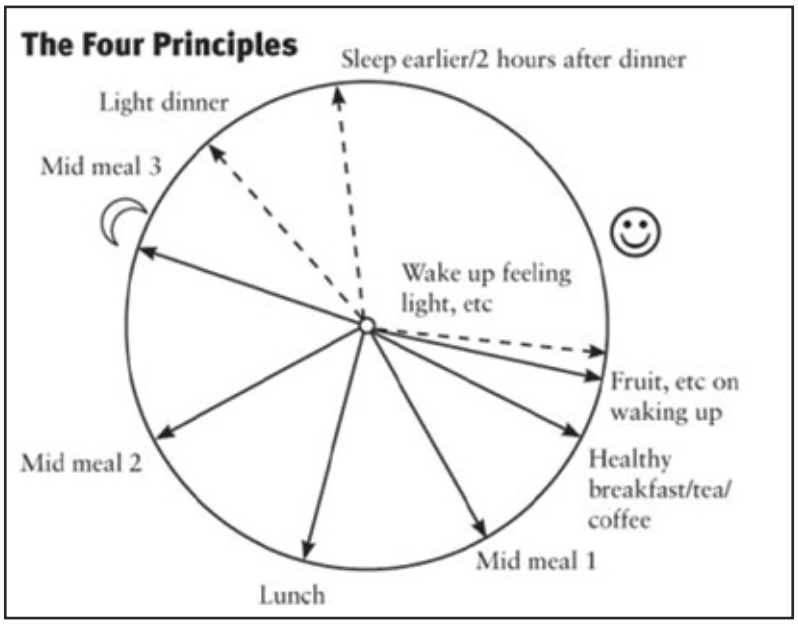
There is this social media always demanding your attention and the market solely designed to empty your pocket by making you buy from slim teas, fat burning coffees to meal replacements. I found Rujuta Diwekar’s book “Do not lose your mind lose your weight!” down to earth and very impressive in the way she has combined the modern science of food with common sense eating patterns.

A few one liners that I always liked from this book is as below:

1	Do not Diet. Eat Right!
2	Think Nutrition not calories! How many of us use apps to track calories ☺
3	Do not make angels and demons out of different foods.

4	Never wake up to tea or coffee but do eat some fruit first thing in the morning – it upstarts your metabolism
5	You can digest the most amount of food between 7 am and 10 am (So do not skip your breakfast)
6	Eat every 2 hours, does not mean you indulge in it ☺
7	Eat more when you are more active and less when you are less active - Eating more food when you are more active will make your body an efficient calorie burner
8	Finish your last meal at least 2 hours prior to sleeping
9	Eat Local and seasonal food items
10	Listen to your Grandma and not to your dietitian! Quoting the author, "Our grandmothers have always done what the current USDA guidelines are asking health professionals to do"!

A self-explanatory chart (extracted from the book) below elaborates everything:



Apart from the above principles, she goes in depth into explaining the most common factors such as food biochemistry and the way one should plan their food with some easy-to-follow examples for different age groups, profession, and regional food habits.

Few interesting pointers:

Eating after every 2 hours will lead to:

1. Conducive environment in the body to burn fat and fewer calories converted to fat - because the brain gets a regular flow of sugar.

CARBOHYDRATES

2. High glycemic index foods (fast carbs) get converted to fat quickly and low glycemic index foods (slow carbs) have a much better chance of getting utilised for energy instead of getting stored as fat.
3. Where the glycemic index is very high, reduce the load.

PROTEINS

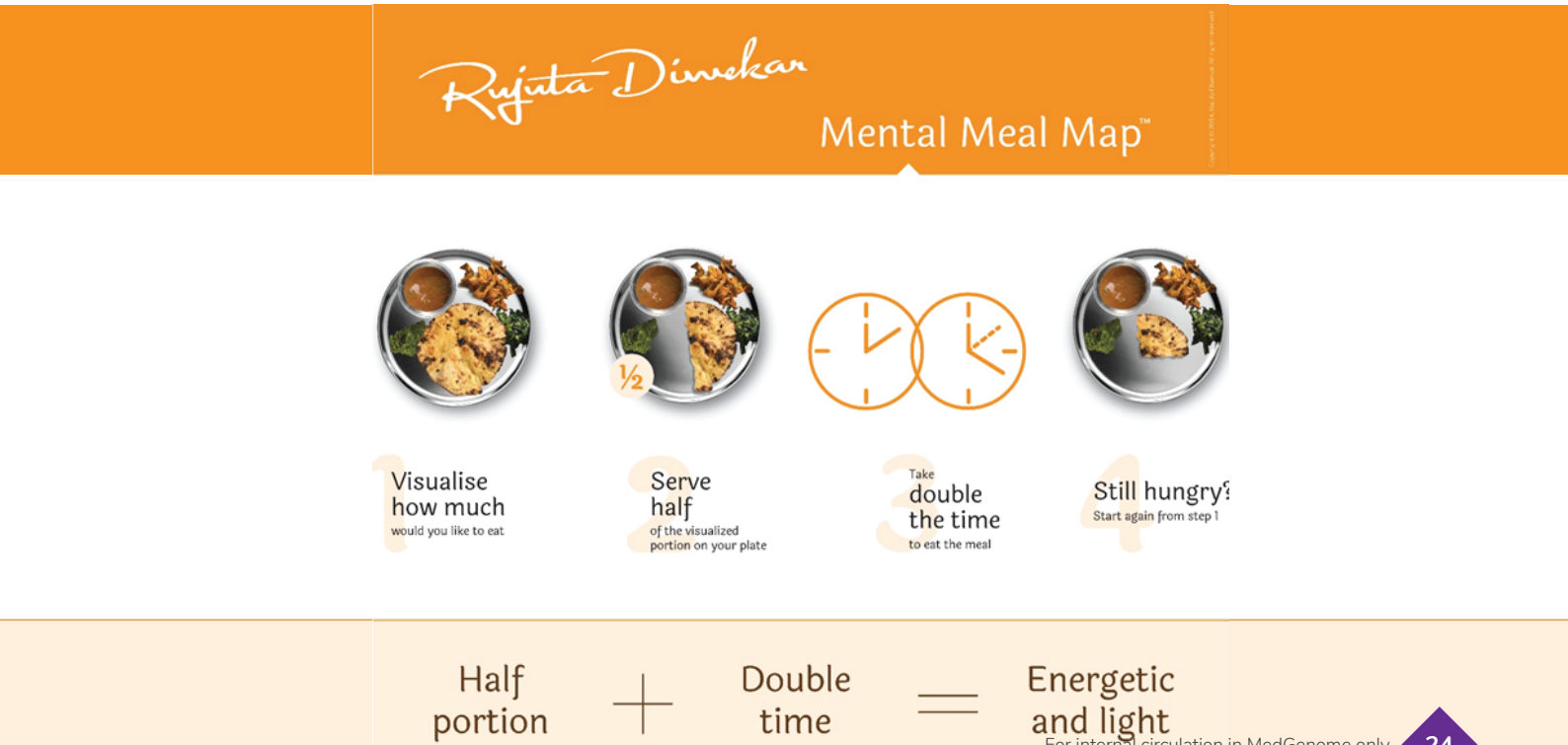
4. Loss of muscle tissue or its breakdown is associated with ageing and the one thing that will turn exercise into an anti-ageing activity is protein. Proteins help in catalysing metabolic and biochemical reactions through enzymes.
5. When too much of protein is consumed at one time, it does not get stacked away for future use, instead it is converted to fat by a process called deamination.

FATS

6. Fats transports vitamin A, E, K, D, which are also known as fat soluble vitamins.
7. Fats protect vital organs like heart, kidney, liver, lungs, etc.
9. Fats stimulate flow of bile and emptying of gall bladder.
10. Makes up much of the brain (more than 60% of the brain is composed of fat), and helps it function smoothly – (so include Ghee in your diet – the only saturated fat good for your health – but consume in moderation).

With a witty and colloquial language, she blends biochemistry with Sāmbhar and a pickle with science. Did you know what is the best probiotic available? You guessed it right, it is the age-old pickle☺. It keeps your gut healthy. It is impossible to cover all such interesting and fun-filled facts in a book review. One must read it to know better. Blended with the wisdom of food, Rujuta's "Do not lose your mind lose your weight!" is just as refreshing as a fresh cup of coffee – but remember don't wake up to it first thing in the morning.

Finally, a tip to always bear in mind:



From our Colleagues

Art meets Science

Art has a double face, of expression and illusion, just like science has a double face: the reality of error and the phantom of truth. — René Daumal

By: Aman Saxena
Assistant General Manager, IT

By: Vishnu Nair
Research Associate

From our Colleagues

Our employee's little Picasso :)

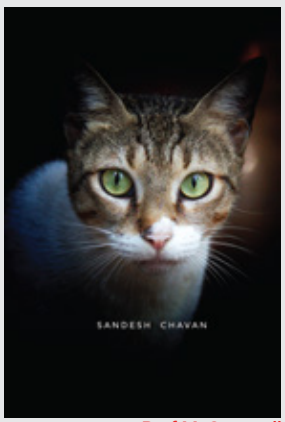
By: Abeer Saxena (12 years)
DNA of Aman Saxena

By: Ayush Chavan (4 years)
DNA of Sandesh Chavan

From our Colleagues

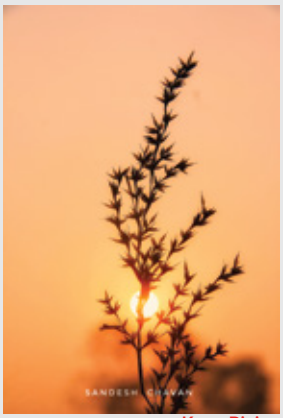
Street Vendors

Say Cheese

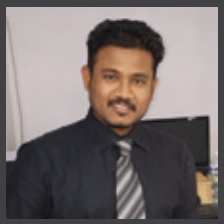


Prof McGonagall

Royal



Keep Rising



By: Sandesh Chavan,

Manager - Admin and Operations

Poetry

Ma (Mother)

Wo ma hai, sab kuch janti hai

Tujhe khud se jyada pehechanati hai
Lakh koshish kar tu chupane ki
Tere har sukh dukh ko janti hai
Wo waqt nahi, jazbaat badal deti hai
hamare liye jine ka andaz badal deti hai

Khud jaagkar tujhe sulaati hai
Khud ro kar tujhe hasaati hai
Tanha rehti hai khud magar
Tera saath hamesha nibhati hain

Bachpan ki shararato ko, masumiyat samaj deti hai
hamaari berukhiyon ko, apni parvarish samaj leti hai
tujhe na ho fursat ek pal bhi uske liye
uska har ek pal, har ek lamha, tere naam karti hai

Wo ma hai, sab kuch janti hai.

By: Nikhil Sharma,
Software Engineer

Employee Connect

WELCOME

Our New-Joiners


A K Bojamma


Abhijeet Shahi


Abhradeep Majumdar


Ajith T O


Akheel Anees


Aman Mishra


Anusha N J


Arun


Aswathi M P


B Prasanth


Bandi Nikhil Kumar


Basavaraj


Bhagyashree Chauhan


Debadrita Mukherjee


Divyya R


Gatika Agrawal


J Lochana


Kavinkumar N K

Employee Connect


Laxmi Aditya Bajaj


Mahendra Kalane


Anusha Hegde


Milner Kumar M


Muniyappan M


Pratishtha Sawhney


Neha Ghorpade


P Madhusudana Patra


Pavithra N


Prajnya Madur


Prasad Ramchandra


Sagar Upadhyay


Rajan Singh


Ram Murthy A


Soundaryalahari


Rugved Rane


Sabba Farhin


Sneha Khairnar


Saldanha Pradeep


Sangeethraj V


Saylee Janardan


Sharanya J


Smitha C


Vijayalakshmi R

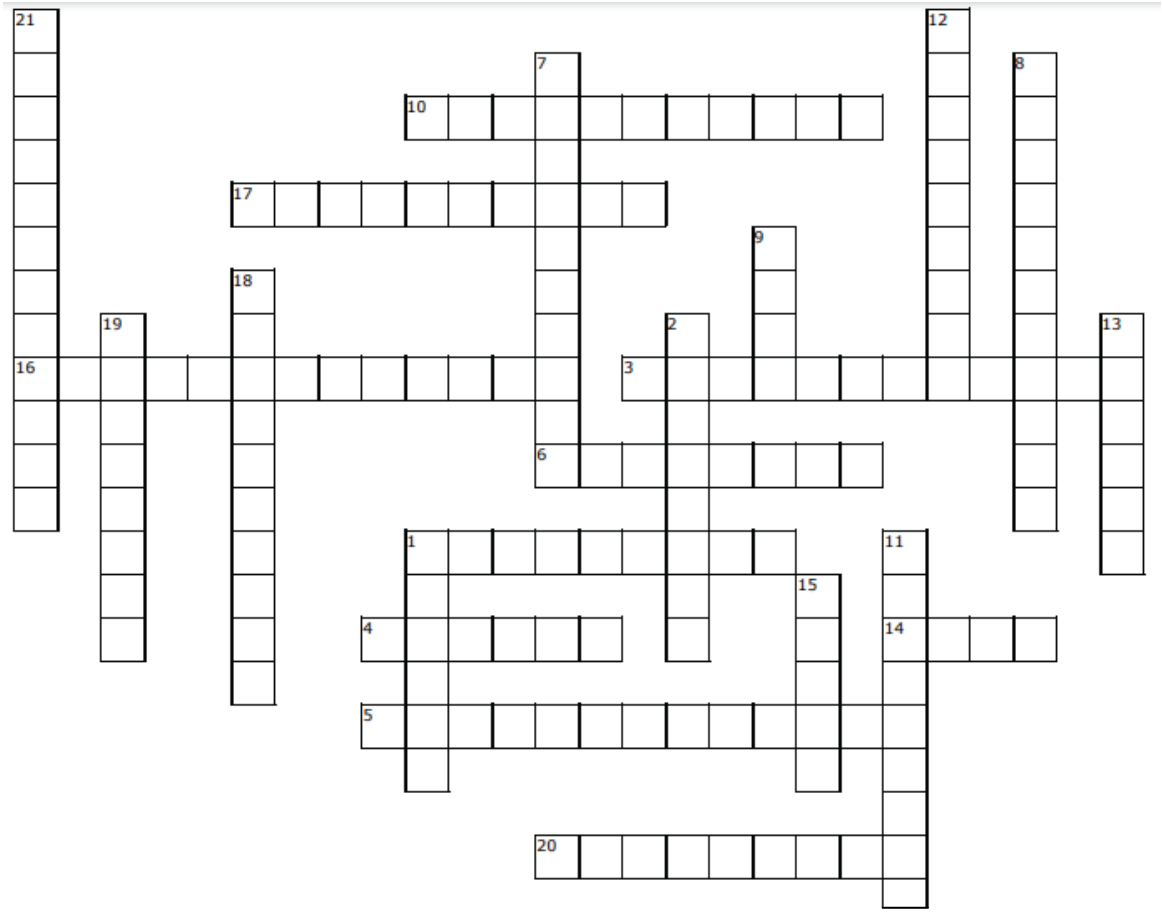

Sourabrata Mukherjee


Supreeth H R


V Saranya Rangan


Vanishree

Employee Connect



Across

1. phyical characteristics
3. the process of changing a gene that causes a genetic disorder
4. The different forms of a gene
5. union male and female reproductive cells
6. any chromosome that is not a sex chromosome
10. The principle of _____ assortment states that genes for different traits can segregate independently during the formation of gametes. (independent)
14. which parent determines the sex of the offspring (male)
16. discovered genetics (gregor mendel)
17. Organisms that have 2 identical alleles for a particular trait
20. traits controlled by 2 or more genes

Down

1. plant male reproductive cells (pollen)
2. genetic makeup (genotype)
7. Lacking in the ability to clot blood (hemophilia)
8. both alleles contribute to the phenotype (spotty or checkered phenotype)(codominance)
9. segment of DNA. Carries genetic information that codes for a trait (gene)
11. The principle of _____states that some alleles are dominant while others are recessive. (dominance)
12. gene that produces its characteristic phenotype only when its allele is identical (recessive)
13. offspring of crosses with different parents (hybrid)
15. characteristic (trait)
18. compact packages of DNA. Inside nucleus.
19. the scientific study of heredity
21. Organisms that have 2 different alleles for a particular trait

Previous Winner

Sadik Sayyad

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

Photo Feature

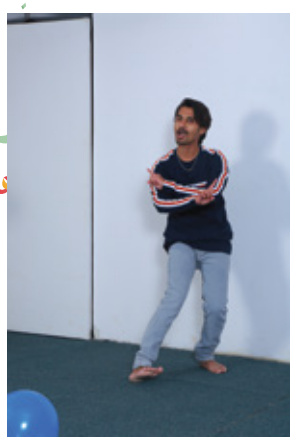
Felicitation program

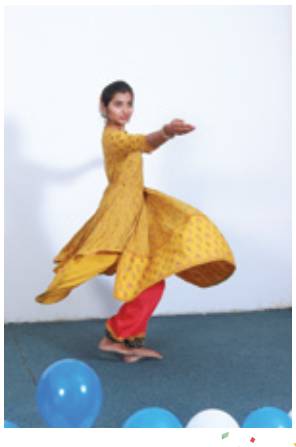
MG's first Felicitation program was organised to acknowledge the efforts of every single team member especially, those who have made expemplory contributions.












Tales from the PAST - 1

By: Sam Santhosh
Founder Chairman and Global CEO

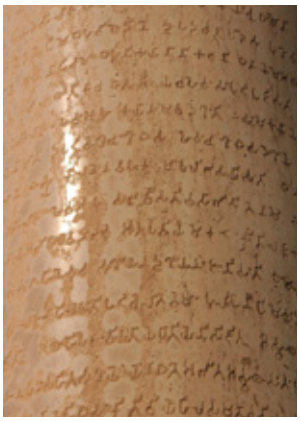
In his book '*Ocean of Churn*', Sanjeev Sanyal begins with an interesting story about the Pallava dynasty of Kanchipuram, Tamil Nadu in 731 AD. Their King Parameswara Varman II had died suddenly without an heir and the kingdom was in chaos and about to collapse. The leading scholars discussed about finding an appropriate heir (genetically correct?) for the throne and decided to reach out to a distant branch of the same family then ruling in Cambodia!! It seems that five generations back, Prince Bhima, a younger brother of the then Pallava King Simha Vishnu had gone to this distant Kingdom and married a princess there. So, a delegation from Kanchipuram reached Cambodia and requested assistance from the present king Hiranya Varman, Bhima's descendant. Luckily Hiranya Varman had four sons, and after the first three turned down the offer to come and rule in Kanchipuram, the youngest of them – a 12-year-old boy took this chance to become the Pallava King.

This boy would later come to be known as Narasimha Varman II and would rule well in Kanchipuram till 796 AD. Sanjeev Sanyal writes about his visit to the Vaikunta Perumal temple in Kanchipuram built by Narasimha Varman where this story has been described along with the history of the Pallava dynasty in bas-relief sculptures. I was intrigued enough to make a visit to the temple recently – the wall sculptures are there, but one would need some good imagination to make out the story. The temple is much smaller compared to the more famous ones that dot the landscape of Tamil Nadu. But it is quite charming with a 3 tier mandapa. (The upper two tiers are opened only on special occasions)

It seems the inscriptions there also explain the story though they are in old Tamil written in the Grantha script. I had a chat with Deva the Aiyyar (priest) who was kind enough to show me the wall panels (I had made the right phone calls as well – you know how things work in India). He had not heard of Sanjeev Sanyal but recommended that I read the book '*The Body of God*' by Dennis Hudson that covers the history of the temple in great detail. It is now on my reading list ☺. The Aiyyar also made a snide remark – 'Well, the king built the temple – he could tell any story that he wanted...' That seemed to me a pretty broad-minded view for a priest! – Well, how India has changed...

Irrespective of the veracity of this particular story, there is no doubt about the major influence of the Indian civilization in all the South East Asian countries in the first millennium AD. The flow of ideas and genes from both North and South India is well documented in Thailand, Laos, Cambodia, Indonesia and Malaysia. Sanskrit, Hinduism, Buddhism, Mathematics (including the concept of Zero), Arthasastra, Astronomy, Ayurveda, Yoga, and let us not forget Kamasutra were accepted in different degrees and forms in these places. These are all well-known and many remnants from these will strike you in the face when you travel in these countries – and whether it is temples, statues, place names and customs, it will be impossible to deny the Indian influence. Even the Chinese, who were traditionally well insulated from outside influences were mesmerized by Buddhism. This led to a number of travelers from China visiting India, the most famous among them being Hiuen Tsang (Xuan Zang) in early 7th century A.D and Fa Hien (Faxian) in the early 5th century A.D.

By the way, both of them are shown in the wall panels at the Vaikunta Perumal temple, though Deva did try to convince me that they might be strange looking rishis from exotic regions of India.



Edicts of Asoka in Brahmi script

India is uniquely blessed to be the home to two ancient languages – Sanskrit in the North and Tamil in the South. Like the lineage of our species, they would also have a common ancestral language thousands of years earlier, but we have not been able to trace those links yet. Interestingly, the concept of writing was first adopted in the North which then slowly spread to the rest of India. All the languages in India and most of the languages in all South and South East Asian countries have scripts that have evolved from the ancient script 'Brahmi'. And where did Brahmi come from? In the 3rd century B.C, India's King Asoka who for the first time had brought most of the present India (except the Southern Peninsula) and the North West regions like Pakistan and Afghanistan under one rule, desperately wanted to communicate his philosophy to all parts of his country (and also maybe leave his legacy in an appropriate way). Greek and Kharosthi scripts were in use at that time, but Asoka felt that they did not capture all the nuances of Indian pronunciation. Hence, he put a team together to create Brahmi and popularized it through his pillar and rock inscriptions across the

country, some of which though neglected, survive to this day. When Brahmi was quickly adapted by the Tamil speakers for writing Tamil, it also became the base for all future scripts of the various south Indian languages that we see today!

Well, what is the relevance of these two old stories? Firstly, it will be good to remember what a great civilization and a fountain head of knowledge that ancient India was. Secondly, how ancient India welcomed all visitors to come and learn with us and also encouraged our leaders and scholars to travel far and wide, collaborating with others across the world. Lastly, we had realized the power of language and how it can unite us and encourage communication across a diaspora of population groups. One interesting theory I have heard is that the major milestones of humanity's progress can be marked through the four language revolutions – first acquiring the ability to speak (it seems Neanderthals could not talk since they lacked the FOXP gene), then developing the ability to write, and then creating the binary language for computers that led to networking of all humans and finally getting to the 'language of life' when we deciphered life's genetic code of four letters.

Though at first glance, breaking the genetic code might look to be the most significant of these revolutions, all later progress would never have been possible for our species without first figuring out how to write and read. Speaking would have come normally as we see most animals figuring out how to communicate through sounds. And with the right genes and the vocal chords, we can thank our biology for being able to talk. But then making the big jump to actually start writing and reading was humongous and took us over fifty thousand years (or more). Starting with simple markings to count your cows and moving on to cave drawings and clay seals to celebrate memories and mark your trade products itself took thousands of years. But then as we settled down from the nomadic life to live in villages and develop agriculture about 10,000 years back, it became more important to not only communicate across larger groups but also build a civilization and culture (as Matt Ridley says in the '*Rational Optimist*', the advent of 'Chiefs, Priests and Thieves) and for which better tools were needed.

However, our brain is not at all genetically built for reading and writing. A number of features in the brain that had evolved for various other purposes had to be brought together for this capability. For example, if a group of children are brought up in isolation, they would definitely develop a rudimentary language to communicate among themselves, but there is a low chance that they will start writing! This can be seen even now in some of the isolated population groups in the Amazon forests or Andaman Islands who still have not developed a script. Hence, it was a great breakthrough when we figured out the need for a script to communicate.

The Great Stupa - Sanchi, MP

And not surprisingly, for hundreds of years this innovation was met with strong resistance. Even great thinkers like Socrates strongly resisted writing anything down. (So, when you feel antagonistic about any new technology like gene editing, you are in good company). Socrates felt that writing would corrupt the communication process and spread false notions (Trump?). Also, you should keep in mind that scripts took a long time to develop properly and there were many pitfalls during the way. In an illuminating book '*Misquoting Jesus*' Bert Eherman documents over 200,000 mistakes in the Bible that crept in during the first thousand years of its existence! I was amazed to learn that ancient Greek did not have capital letters, they did not have the 'space' between words and so whole sections of prose looked like one continuous sentence! And since neither printing nor the carbon paper had been invented yet, it was all copied again and again by hand - initially by slaves (most writing in ancient days were done by slaves) and then by priests; with the slaves being careless and making mistakes while the priests being either overly smart (hey this couldn't be right, so let me correct it in this copy) or malicious (what story can I add to control the women – so one of Jesus's most favorite disciples Magdalene becomes a prostitute) the Bible became a mess. Thus, Socrates was proven right in the short run, though in the long run writing became the fundamental technology that built the human civilization.

Now if you consider King Asoka's decision in this background (keep in mind that the Vedas were not written down yet, though they were hundreds of years old by then, mainly due to other reasons like restricting access, importance of intonation and pronunciation, and of course to ensure errors did not happen across generations) to create a new script was amazing. And he did such a good job that his script's legacy is more powerful than the messages that he tried to communicate with it. But in the subsequent millennium, as India drifted into its own 'Dark Ages' and mythology overturned history, we even forgot Asoka and it was up to the British to 'discover' him. Though then our first Prime Minister of independent India Jawaharlal Nehru ensured that Asoka's lion symbol got into our national flag, the continued lack of interest in our history and monuments has been really sad. Nehru could write '*Discovery of India*' from his prison cell (with no Libraries, Internet or Google) which is a great read even now; but how many of our current leaders can even come close to that? So, what worries me - If we don't know our past, how do we plan for the future?

Asoka Pillar - Vaishali, Bihar

I feel that we are very lucky not only to be alive at this juncture in the progress of our species but also being in a position to take advantage of the most powerful knowledge of Genetic sequencing and editing that mankind has invented. I also hope that India can play a different game than what we have played in the last thousand years. Why not take a cue from Asoka and build the tools and scripts needed to leverage the genetic code and popularize it across our part of the world? Maybe that can be the best legacy that we can leave behind.

To be continued....

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