MEDGENOME

Vol 23 | October 2022

GeKNOWme

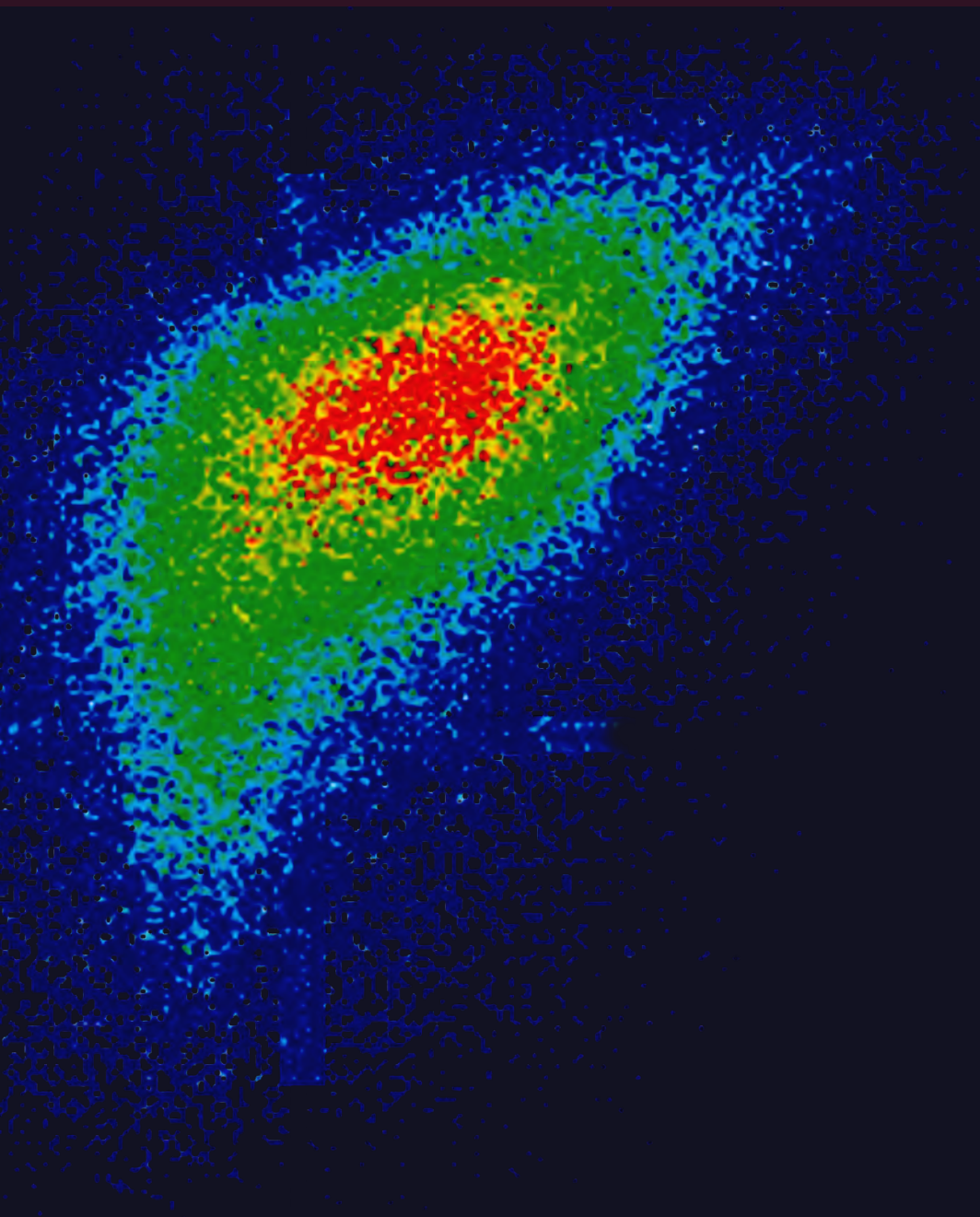
Internal Quarterly Newsletter

Cover Story

Leukemia Beyond Morphology
Flowcytometry in hematological malignancies

Scientific Article

Nature vs Nurture
An Epigenetic view



WORDS FROM THE **FRONTLINE**

Sakthivel Murugan, PhD
VP, Lab Operations

Dear MedGenome Team !!!

I am immensely pleased to share my thoughts with you all through this newsletter. It has been a long journey for me in this company and I am happy and privileged to be a part of the team that has built the largest Genomics company in South Asia, something I didn't even dream of when I joined this company in 2013. A journey in which we introduced several breakthrough genomic tests to the Indian market, brought genetic testing to affordable prices, set the benchmark for quality in India for genetic testing, and took it to the areas in India where it was hitherto unknown. It has been a journey where I learnt a lot, taught a lot, and grew as a person.

Even before we joined SciGenom (where MedGenome was incubated), Ram had sold the first MiSeq in India to Scigenom and I was the first to install the system in India. Within months, we ended up joining the company. Our responsibility was to establish the NGS facility there and grow it. What started off with a single Miseq, grew into a facility with HiSeq 2500's, MiSeqs, followed by HiSeq4000s, HiSeqXs, NextSeqs and then Novaseq. It is not as simple as it sounds here.

We were first a fee for a service company, but soon the management realized that the growth lied in Genomics and we slowly, but steadily, entered genetic diagnosis. We started off with Whole exome sequencing and did the gene filtering and interpretation on excel sheets. We invested in software support to develop in-house LIMS and interpretation software, the VARMINER.

From the beginning, we always aimed to give quality results and quality defines our company in the market. Keeping quality as our utmost priority, we decided to go for CAP accreditation instead of NABL. CAP has proficiency testing samples which helped us place ourselves among world's several top-quality labs. Even if it came with a cost to us, it gave us the confidence that we were giving the right results. We were able to validate several new tests and released it to the market. Some of the tests that we introduced to the Indian market are:

- Clinical exome
- NIPT by NGS
- High resolution HLA by NGS
- Comprehensive tumor panels, both solid tumors and liquid tumors
- Liquid biopsy

Even while releasing several new tests, the below differentiators made us stand apart from the competition.

- Thorough validation of tests – helps ensure quality
- In-house developed tests – which aims to reduce cost and increase efficiency with better control on outcomes. We are the only company who upgrade the panels on regular intervals
- In-house developed bioinformatic pipelines – innovative, time saving and faster data outputs
- Quality lab personnel and training – more than 90% of our lab, GA and Bioinformatics personnel are trained by our seasoned and professional leadership team
- Fine scientific and technical support
- Strong support system – Logistics, infrastructure, software, IT, etc.
- Finally, our inspirational and committed Management team who have confidently invested on the infra and instruments.

Now, we are the largest Genomics company in India. But, competition is catching up. Competitors have understood the market value of genomics and have started investing in a big way by identifying gaps and targeting potential customers and thus actively that penetrating the market. The only way we can keep up with the growing competition is, by ensuring that we do not lose on the quality of our services. When I say quality, it is not only the results or reports that we give but it encompasses end-to-end services, starting from collection of samples, the proficiency with which it is collected, communication skills of the phlebotomists and the approach towards the patients, sales coordination, logistics time and quality, experience with our customer support, quality of the tests performed, reporting, TAT adherence, and last but not the least, customer engagement.

Every aspect mentioned above are critical. We should never take any aspect for granted, and rather focus on improving these to provide a better customer experience.

It is not desirable to see anyone lagging or taking their responsibility lightly. Remember, we are in a crucial diagnostics field and every report we give affects a patient's treatment or management. Even a negative report means a lot to the patient. What we do, touches a patient's life and if we have this in our mind, I am sure we will focus on delivering a high-quality work.

Finally, please don't look at MedGenome as a place for work only but look at it as a place to learn and evolve. There is no lab in India where so much of genomics is happening, with many high end and latest technologies at one place and wide range of disease portfolio handled.

MedGenome, as a company gives its staff the opportunity to learn things not only related to their work, but also across departments. We always encourage our staff to grow in science and you will not find a better place to explore and learn.

Hence, let us all work hard to grow as an individual while helping the company to grow as well.

Contents

Most Talked About

The News

THE TIMES OF INDIA

Care before carrying: The significant role of Preimplantation Genetic Testing during IVF

August 10, 2022, 5:48 PM IST / Dr Rashmi Yogish and Dr Priya Kadam in Voices, Lifestyle, TOI

Dr Rashmi Yogish and Dr Priya Kadam

Dr Rashmi Yogish, Khushi Fertility Clinic and IVF centre; Dr Priya Kadam, MedGenome Labs

India welcomed its first In Vitro Fertilization (IVF) child Kanupriya Agarwal in the year 1978. Since then, IVF treatment has given hope to millions of childless Indian couples. It is a treatment that aids in the conception of a child and a method to treat infertility or genetic abnormalities. Even though IVF is the most effective method of assisted reproductive technology, the chances of having children are still dependent on many factors. A single IVF cycle lasts about two to three weeks and involves several steps. In addition to that, the treatment requires multiple cycles, and is both time-consuming and expensive.

Even though IVF is a very effective procedure, there is a chance that it will fail due to chromosomal defects in the embryos, such as missing, extra or irregular portion of chromosomal DNA. According to various studies, IVF tests have a success rate of 20-35 percent per cycle. At the same time, with each IVF subsequent cycle, the chances of conceiving decrease. Genetic tests can assist you in having a best chance of success.

Genetic tests examine your DNA, the chemical database that

THE TIMES OF INDIA

Keychain-sized ECG devices to under-mattress health trackers

ARTICLES

Dozee's sensor under the mattress

BW Healthcare WORLD.com

Potential, Promise & Pitfalls Of Genomic Medicine

Follow

It will evolve in the next 6 to7 years as the pharma companies will come up with more cost-effective treatments. In the years ahead genomics will transform the treatments of more common diseases like heart diseases and hypertension

12 September, 2022 by Md. Zakariya Khan

HEALTHCARERADIUS ≡ Menu

Home > Projects > MedGenome Labs offers clonoSEQ Assay to assess MRD in patients

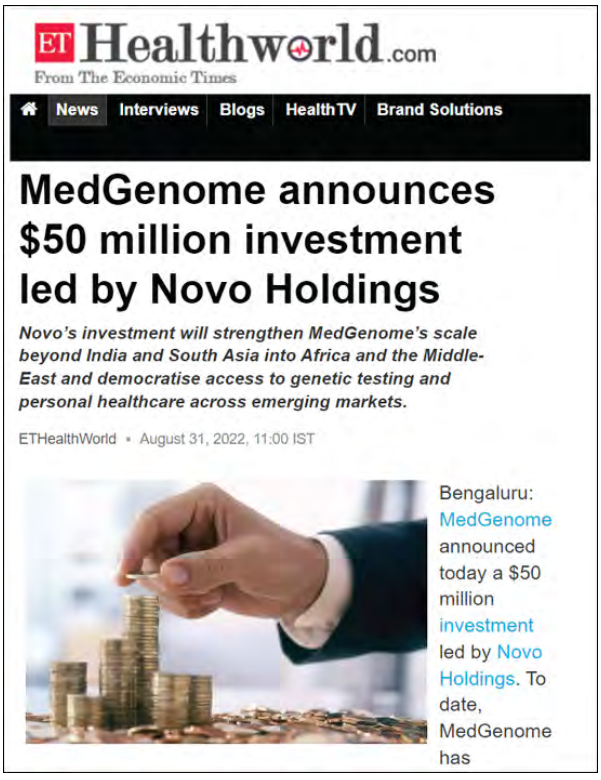
PROJECTS

MedGenome Labs offers clonoSEQ Assay to assess MRD in patients

clonoSEQ is the 1st U. S. Food and Drug Administration (FDA) cleared MRD test for Multiple Myeloma, Chronic Lymphoblastic Leukaemia (CLL), and B-Acute Lymphoblastic Leukaemia (B-ALL).

by **Staff Writer** | July 18, 2022

SHARE



ET Healthworld.com
From The Economic Times

News Interviews Blogs HealthTV Brand Solutions

MedGenome announces $50 million investment led by Novo Holdings

Novo's investment will strengthen MedGenome's scale beyond India and South Asia into Africa and the Middle-East and democratise access to genetic testing and personal healthcare across emerging markets.

ETHealthWorld • August 31, 2022, 11:00 IST

Bengaluru: MedGenome announced today a $50 million investment led by Novo Holdings. To date, MedGenome has

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

ANNOUNCEMENT!!

Novo Holdings Invests $50 Million In MedGenome For Expansion Into New Markets

Novo's investment will strengthen MedGenome's scale beyond India and South Asia into Africa and the Middle East and democratize access to genetic testing and personal healthcare across emerging markets.

> The success that the MedGenome team has achieved over the last decade is extraordinary," said Amit Kakar at Novo Holdings. "MedGenome's mission to transform the future of personalized healthcare, one that is affordable, inclusive, and equitable is a perfect fit with Novo's investment strategy and broader portfolio."

> "The MedGenome team has built a model of accessibility across South Asia that delivers cutting-edge diagnostic tests, at the same global standard of quality as other market leaders, and at a fraction of the cost," said **Mahesh Pratapneni, Group CEO of MedGenome**.

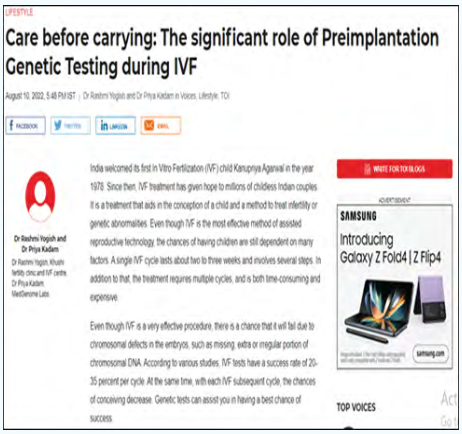
> "We're thrilled to have the support of the leader in international life sciences investing behind us as we expand into new global markets and scale access to affordable and life-changing testing. MedGenome is leading the cultural shift of healthcare, taking it from one of generalization to a model that prioritizes precision medicine," said **Dr. Felix Olale, Chairman of MedGenome's Board of Directors**, and Global Co-Lead for Healthcare Investments at LeapFrog Investments.

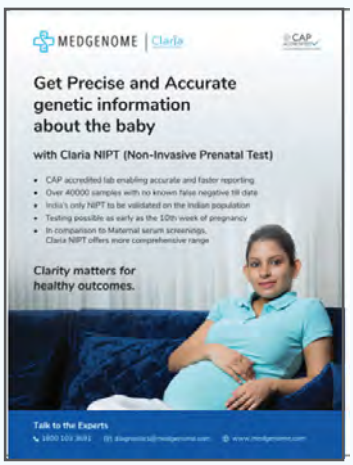
MedGenome Connect

Claria
Reproductive Genetics

The last quarter was very campaign focused as we engaged our key doctors across the country, both centrally through corporate driven campaigns as well as local level initiatives. One such successful corporate campaign was for the IVF Day (25th July) where we engaged KOLs across the four zones of the country. Our campaign was highly appreciated as it was focused on increasing awareness on IVF & the role of genetic testing in IVF.

Our article on 'Care before carrying: The significant role of Preimplantation Genetic Testing during IVF' by Dr. Rashmi Yogish & Dr. Priya Kadam was covered in TOI & Firstpost to create awareness on role of PGT during IVF. We also featured advertisement in Association of Obstetricians & Gynecologists of Delhi and Journal of Fetal Medicine to highlight Claria offerings & Rhesus D Genotyping and Claria NIPT respectively.



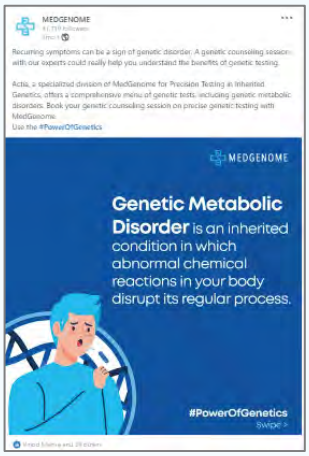


We have also initiated an email campaign to announce our newly launched test in Claria - Rhesus D Track.

ACTIA
Inherited Genetics

Through the quarter we executed four dimensional activities across the product segment – Brand awareness, Sales Support, Clinician Engagement and patient education using both online and offline channels. We also engaged the with leading hospitals/institutions for continued medical education where our expert scientific team provided necessary information about genetic testing in each therapy area.

We also launched a new test in this quarter “ExomeMAX”. This test provides over 99% coverage of exons, India's first from MedGenome,



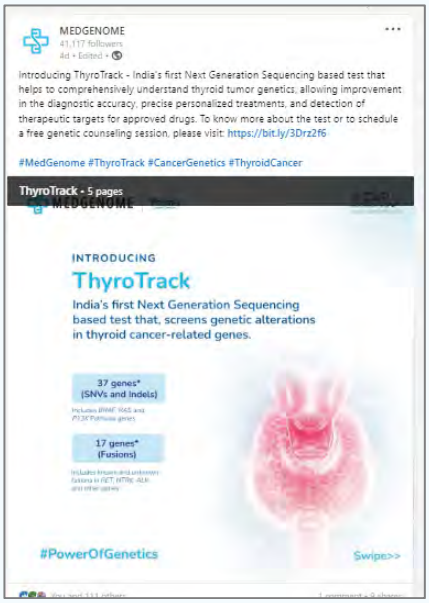
Prima
Cancer Genetics

This quarter we focused on engaging with clinicians across the country and make them aware about benefits of genetic testing to patients. We also used digital along with offline activities as a key medium to engage these stakeholders and help them know more about cancer genetics. We also did a lot of other relevant activities such as taking video of clinician talking about early detection and treatment of lung cancer on World Lung Cancer Day. Our engagement with leading hospitals/institutions continued this quarter as well where our expert scientific team provided necessary information about cancer genetics.

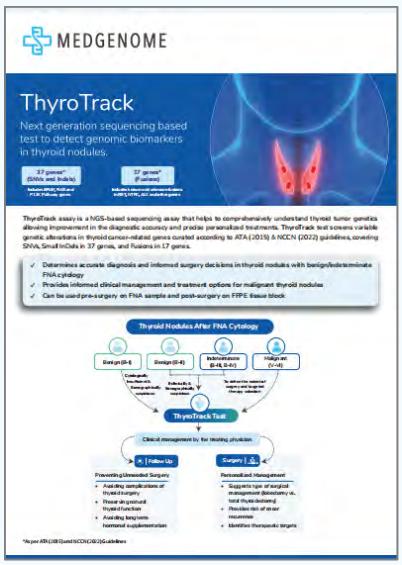
We also launched a new test in this quarter "ThyroTrack". India's first Next generation sequencing based test to detect genomic biomarkers in thyroid nodules. We also launched many new brochures such as TumorTrack Advance, Histopathology amongst other brochures.

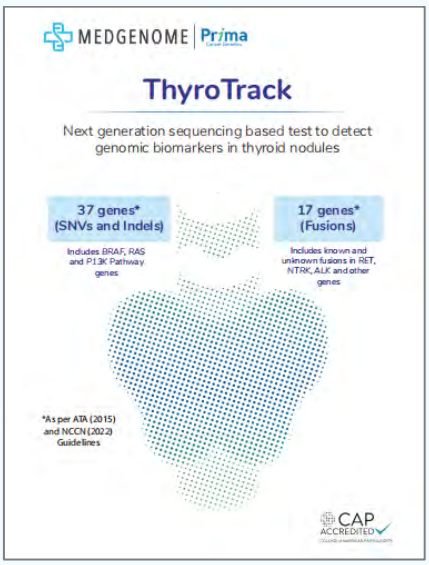
World Lung Cancer Day KOL engaement

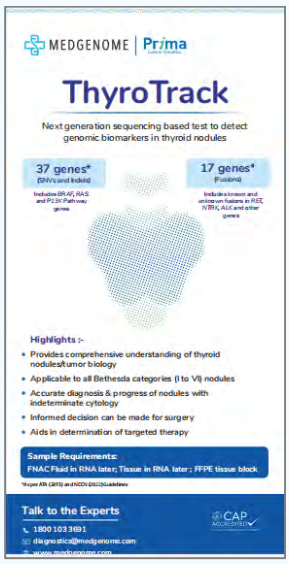
Test Awareness, CME and Conditional Awareness Posts on Social Media



Launch of New Test







micra
Infectious Disease Genetics

The last quarter was very encouraging and has been a very active for Micra with a focus to engage more clinicians with CME, conference participation, Field work and test specific mailers and sales master training on Micra for sales support.

The team is also working on a comprehensive Micra catalogue which contains in depth information about all the tests along new tests launched in Micra.

SALES MASTERS PROGRAM

Training is very vital because it represents a good opportunity for sales team to grow their knowledge base and improve their skills to become more effective in the work

Last Quarter Our Marketing Team successfully Conducted Eight sales Master Training session on important topics based on tests and sales skills development.

1) Directory of Services (DOS)
Month- June
Trainer - Dr. Priyadarshini Pande
Participants-58
Quiz- not conducted

2) Chromosomal Microarrays
Month- July
Trainer - Senthilkumar Thasarathan
Participants-92
Quiz- not conducted

3) Genetics in Ophthalmology
Month- July
Trainer : Dr. Priyadarshini Pande
Participants-90
Quiz responses-88

4) Maternal Markers
Month- August
Trainer - Dr. Sudhesna Mohapatra
Participants-81
Quiz responses-58

5) Thyroid Prognostication panel
Month- August
Trainer - Dr. Suruchi Aggarwal
Participants-57
Quiz responses-24

6) Micra Basics and Overview
Month- August
Trainer - Dr. Gunisha Pasricha
Participants-57
Quiz responses-22

7) Effective Call Process: Part-1
Month- September
Trainer - Dr. Priyadarshini Pande
Participants- 92
Quiz responses-19

8) Effective Call Process: Part-2
Month- September
Trainer - Dr. Priyadarshini Pande
Participants-65
Quiz responses-09

9) TPMT and NUDT Genotyping
Month-September
Trainer - Dr. Suruchi Aggarwal
Participants- 55
Quiz- not conducted

10) Rhesus D genotyping
Month- September
Trainer - Dr. Shweta Mahalingam
Participants- 83
Quiz responses-15

What's new

Research Publications

1. ***Molecular epidemiology of SARS-CoV-2 in healthcare workers and identification of viral genomic correlates of transmissibility and vaccine break through infection: A retrospective observational study from a cancer hospital in eastern India***

   Journal : Indian Journal of Medical Microbiology

   Click here for more

Tests launched

1. Thyrocare
2. Non-invasive Fetal RhD Screening
3. EXOME MAX

CAP accredition

From Our US Office

We recently launched “TruSight Pan Cancer Targeted Panels – TSO500&TST170”. It offers a wide variety of benefits in analyzing multiple tumor variant types in 523 genes in a single assay. The assay is highly effective in identifying all types of relevant DNA and RNA variants in different types of solid tumors including lung, melanoma, ovarian, breast, gastric, bladder, sarcoma etc. It also helps in providing an indepth view into cancer genetics, effective in assessing fusions, splice variants, insertions/deletions and single-nucleotide variants (SNVs), and amplifications.

To know more visit our webpage:

https://research.medgenome.com/ngs-services/trusight-oncology-500/

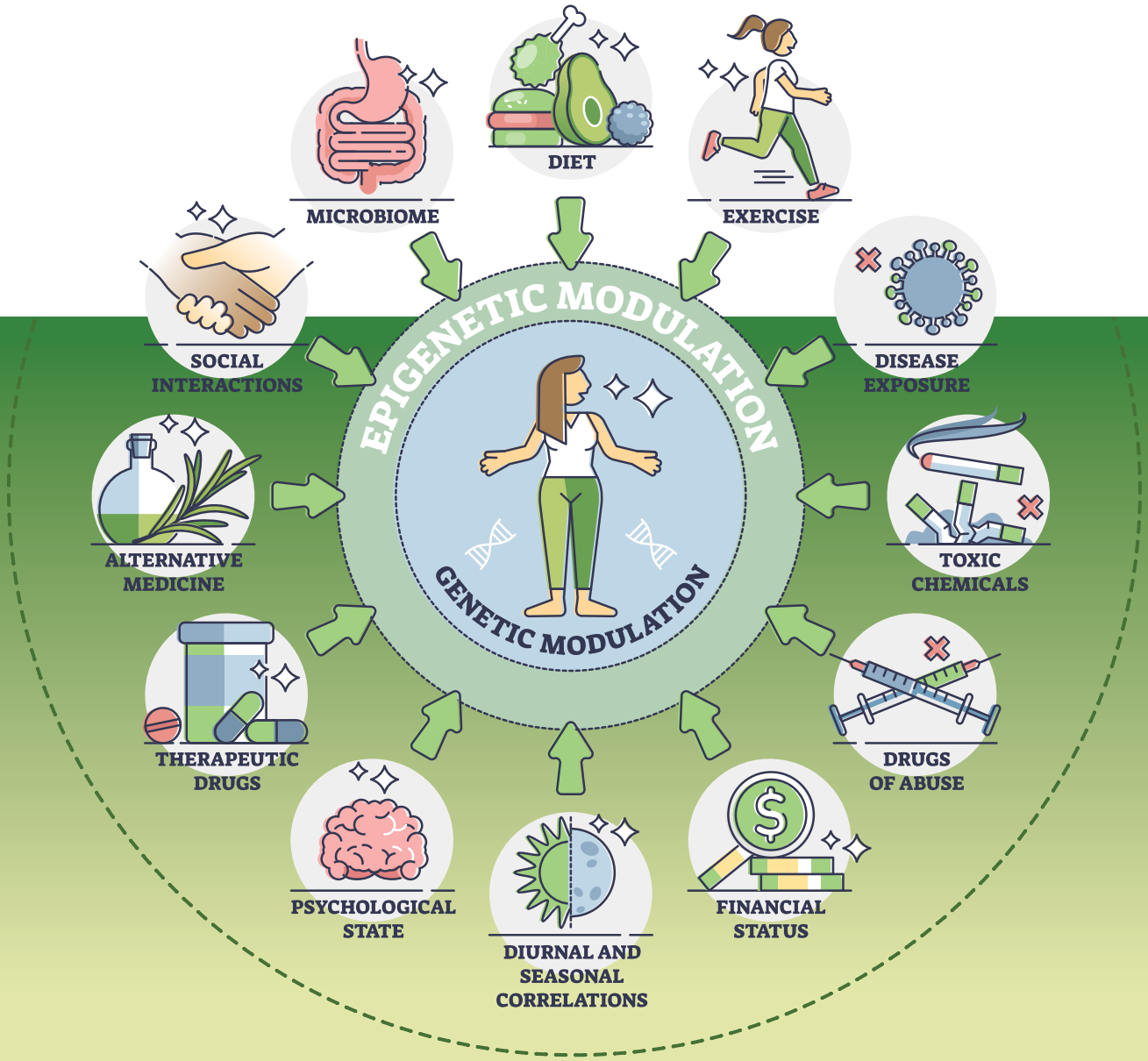
We have recently published new articles on
https://research.medgenome.com/blog/

1. How MedGenome’s unique next-generation sequencing solutions are helping precision therapies / personalized medicine
2. MedGenome’s advanced bioinformatics workflows for the analysis of Multi-modal Single-cell Data

We encourage you to share your viewpoints and articles of interest at **mgus-blog@medgenome.com**

Nature vs Nurture

An Epigenetic view



Anup Chugani, PhD
Senior Scientist

Nature has presented each and every one of us with a specific set of genes - one copy from the mother and the other copy from the father. If we argue then that all the traits which we have inherited are fixed and cannot be changed, you might be partly right. And partly wrong. This debate has been waging since more than a century now where some proponents advocate that the traits are hardwired and cannot be changed until there is a spontaneous modification in the genes and some argue that the changes are acquired by an organism through the interactions with the environment. The latter is due to a phenomenon called Epigenetics which was hypothesised half a century ago, however, it was not until recent times that we have some understanding on the working of this malleable modification.

Extensive work has been done to understand how nature and nurture work together in twin studies (Farga et al., 2005, Wong et al., 2005, Poulsen et al., 2007). Monozygotic twins are genetically identical yet, they are often discordant for some phenotypes. To understand this discordance, one of the studies tested the level of methylation (a form of epigenetic modification; explained in later sections) between the 3-year-old twins and 5-year-old twins (Figure 1 and 2). It was found that the twins are epigenetically similar when they are younger however, as they age, they diverge with respect to the epigenetic modifications. The divergence was prominent if the twins had difference lifestyles and have spent less time together. This could be explained due to external (lifestyle, peer influence, smoking, physical activity etc.) or internal (accumulation of defects while transmitting the epigenetic signatures during successive cell divisions) factors. This process of aging related accumulation of differences is termed as "epigenetic drift".

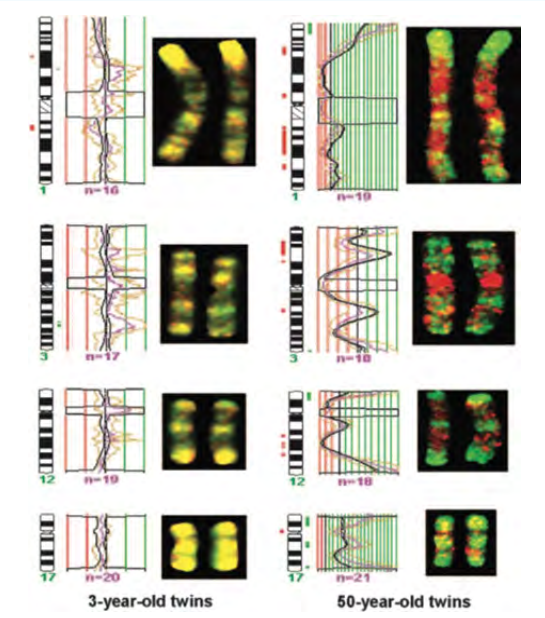


Figure 1: Relative methylation differences between each of twins at 2 different ages. Green and red indicate methylation changes and yellow represents no change. (Fraga et al., 2005)

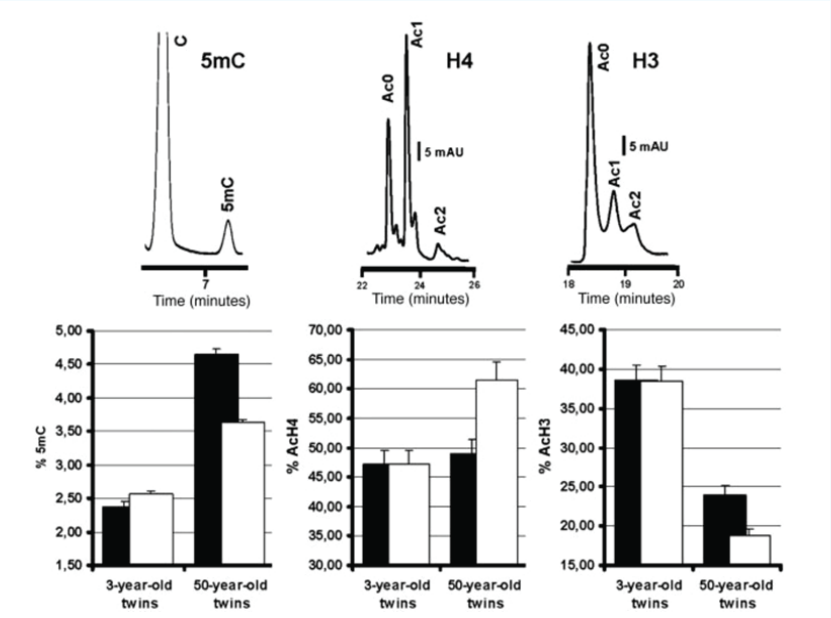


Figure 2: Global methylation and acetylation changes between each of the twins at 2 different ages. The difference is pronounced for aged twins (Farga et al., 2005)

Another important regulator of epigenetic mechanisms is found to be early nutrition (during development). One experiment shown by Waterlane et al., 2003 (and also Cropley et al., 2006) on Agouti mice evidences this. Agouti gene makes the mouse yellow, obese and susceptible to diseases like cancer and diabetes. And this gene and trait is passed down from generation to generation through DNA. So, the off-springs from agouti mother will be yellow, fat and susceptible to diseases. Here's the catch, agouti gene can be turned off if the epigenetic marks (specifically methylation) are accumulated around it. It turns out if the pregnant agouti mother is fed with a diet supplemented with methyl donors like folic acid, Vit B12, Choline and Betaine, it can alter the phenotype of the offspring via increased CpG methylation of the agouti locus. So the pups are born thin, brown and healthy. This has implications beyond the mouse world, because studies in humans have shown that women who don't eat well during their pregnancy, who eat bad foods, will go on to have children who are more susceptible to developing obesity and cardiovascular disease. Likewise, if women smoke during their pregnancy, their children will grow up to have a greater chance of developing asthma (Rogers, 2019).

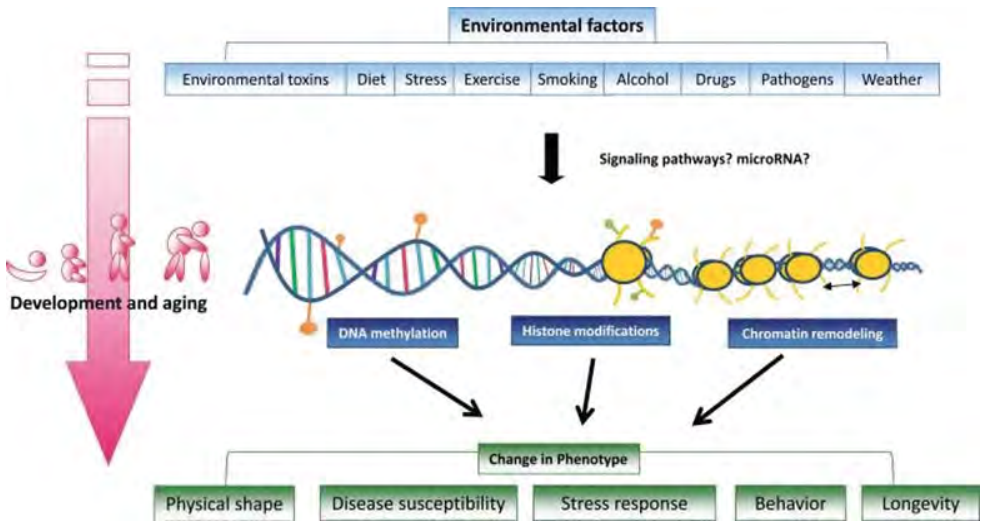


Figure 3: Epigenetic changes are the link between environmental signals and the phenotype (Tammen et al., 2013)

The effect of epigenetics is not limited to the lifestyle of women. Men are equally susceptible to environmental exposures which may influence the development and health of their offsprings. Seminal work published by Pembrey et al., 2005, showed that the young boys (in England and Sweden) who were smoking by the age of 11 (pre-puberty) went on the have sons and grandsons who had significantly shorter lifespan. Although, there are mounting evidences of transgenerational inheritance of epigenetic marks in other animals, this is the first study which pointed out with evidence (Figure 4). More studies conducted recently reported on similar lines (Svanes et al., 2021, Lite et al., 2020, Golding et al., 2021).

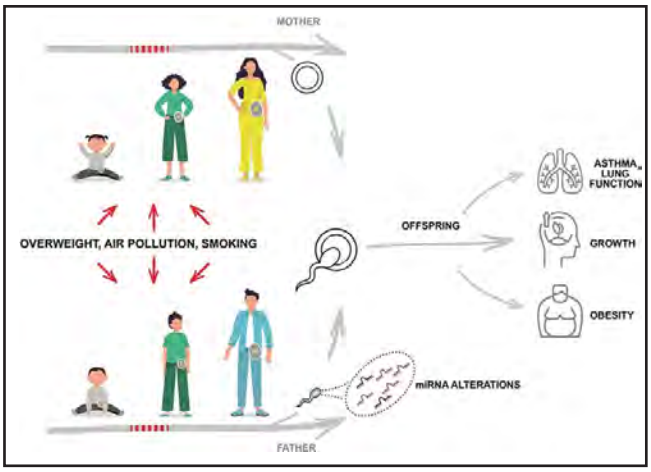


Figure 4: Exposure to the pollution and lifestyle influences the germ cells. The germ cells transmit these changes to future generations. (Svanes et al., 2021)

Epigenetic changes don't just show its effects during the development stages, they can also affect after birth. For example, rats contain a gene called the glucocorticoid receptor which is expressed in certain regions of rat's brain. It helps the rat cope with stressful situations. The more receptor rat has in its brain, the better it will handle stress. This study by Weaver et al., 2004 showed that the interactions between a rat mother and her pups during the first week of their life can have a long term impact on how much glucocorticoid receptor those pups will grow up to have in their brains, thereby, how well they will handle stress. When the rat pups are born, the glucocorticoid receptors are surrounded by silencing epigenetic marks (methylation) which renders the gene inactive. When rat mother licks and grooms her pups during the first week of their birth, those epigenetic marks are removed from the gene allowing the glucocorticoid receptor gene to turn back on and stay that way through out their lives. This will allow the pups to deal with stress. Conversely, if the rat mother ignores her pups, the glucocorticoid receptor gene will remain silenced in those pups' brains throughout their lives eventually leading the rats to grow up to be anxious in stressful situations. These findings suggest that the epigenetic state of the gene can be established through behavioural programming in a potentially reversible manner. Similar study was done in humans by the same group where they reported something similar (McGowan et al., 2020).

Epigenetic marks have critical roles in maintaining cellular homeostasis. Usually, the genome (especially the CpG islands) in normal cells are unmethylated. This corresponds to the genes being actively transcribed in the presence of necessary transcriptional activators. In cancer cells, hypermethylation of CpG islands is noticed which will lead to the silencing of tumour suppressor genes, in turn leading to the tumorigenic process (Figure 6) (Feinberg et al., 1983, Esterller et al., 2007 and Allis et al., 2016). To reverse the methylation marks in cancer cells, chemical inhibitors have been applied which would reactivate the aberrantly silenced tumour suppressor genes. In 2006, US Food and Drug Administration (FDA)-approved epigenetic drugs (decitabine and vorinostat) for the treatment of human cancers.

What is Epigenetics?

The term Epigenetics was first coined by Conrad Hal Waddington (Waddington CH, 1942) from a greek word "epigenesis" to describe how the cells differentiated and how the phenotypes could be linked to genotypes. But, the contemporary definition emerged only a few decades later as follows - "a hereditable change in gene expression that occurred without a change in the DNA sequence". Early work by Muller (Position effect variegation) and McClintock (transposable elements) laid the foundation of this non-mendelian inheritance. Also, the work by Lyon 1961 and Surani 1984 on X-chromosome inactivation and imprinting respectively led to the concept that same genetic material can be maintained in different states. Picture this for a moment - although virtually all the cells in a given organism have exact same copy of the genome, yet there are different type of cells - liver cells, neurons, immune cells, muscles cells, which are not similar functionally. They differ because some of the genes on each of the cells are turned on (activated) and some turned off (inactivated/silenced). In association with transcriptomics (the study of transcriptome - the complete set of RNA transcripts produced by cell or tissue), epigenomics has experienced quite a bit of hype in the past few decades. These 2 branches serve as missing pieces in the pursuit of understanding complex genetic interactions and disorders.

Types of Epigenetic modifications

There are two major type of epigenetic modifications existing in nature.

DNA Methylation

Histone/chromatin modifications.

Methylation

DNA methylation is a major epigenetic mark influencing gene activation. It is a direct chemical modification of DNA bases (largely Cytosine). It was discovered in mammals as early as DNA itself (Hotchkiss et al., 1948). The biological role of methylation, especially 5-methylcytosine in gene regulation was proposed by Holliday and Pugh in 1975. DNA methylation is essential for regulating tissue-specific gene expression, genomic imprinting, X chromosome inactivation and silencing of retroviral elements. And methylation in different genomic regions may exert different influences on gene regulation. It is also found that most of the methylation signatures are found within intergenic regions. This region harbours transposable and retroviral elements. One of the main role of methylation in intergenic regions is to repress potentially harmful genetic elements which have been accumulated evolutionarily.

Methylation is carried out by a specific class of enzymes called as DNA methyltransferases. Dnmt1 functions during replication to copy the methylation pattern from the parent DNA strand onto the daughter strand (Figure 5). On the other hand, Dnmt3a and Dnmt3b are *de novo* methyltransferases which can establish new methylation patterns to unmodified DNA (Moore et al., 2013). Apart from the methylation enzymes, there are 2 different classes of enzymes which are responsible for maintaining homeostasis - demethylases and readers (Moore et al., 2013). The readers are closely associated with methylation enzymes (viz., Dnmt1, Dnmt3a and Dnmt3b) which targets hemi-methylated DNA in order to maintain DNA methylation. On the other hand, demethylation occurs either actively or passively. Active demethylation occurs in the presence of enzymes whereas passive demethylation occurs during cell replication. In either cases, the end product is unmethylated Cytosine.

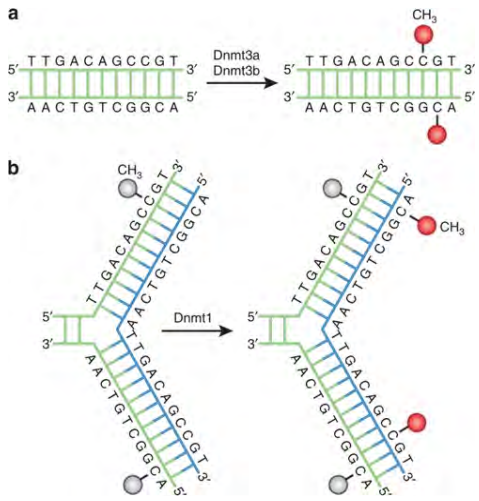


Figure 5: DNA Methylation by DNA methyltransferases catalysing the transfer of methyl group from S- adenyl methionine (SAM) to Cytosine. Dnmt1 is maintains methylation patterns during replication. Dnmt3/3a are de novo methyl transferases. (Moore et al., 2013)

Methylation detection methods

Methylation signatures can be detected using several direct and indirect techniques. While the methods range from qPCR to HPLC to Mass spectrometry, for the purpose of this write-up, only sequencing and Array based methods have been described. One important advancement which is common pre-processing step for both the methods is the treatment with sodium bisulfite which reproducibly changes unmethylated cytosines to uracil but leaves methylated cytosines unchanged.

A. Array based

Microarray has been a reliable and efficient technology for multiple genomic applications. It is basically a glass slide with locus specific marked etched on the surface. There are not many vendors who design methylation arrays. One popular vendor is Illumina with their EPIC Methylation array chip. The chip covers around 850,000 loci which range from CpG islands, shores, enhancers, TF binding sites and promoter regions. Using data from control samples, we can analyse the differentially methylated regions across the sites. Compared to NGS based approach, it is less analysis intensive.

B. Sequencing based

In whole genome bisulfite sequencing (WGBS) approach, as the name suggests, the entire bisulfite treated DNA is sequenced on Illumina platform. Unlike the array approach, data generated is not limited to particular regions of the genome. Due to the scale of the data collected, data analysis is resource intensive.

Another approach using NGS is targeted methylation sequencing. Here, instead of sequencing the entire genome, some of the methylation hotspots are captured using probe based or amplification approaches. This generates a fraction of the data generated in WGBS and the analysis not that resource intensive.

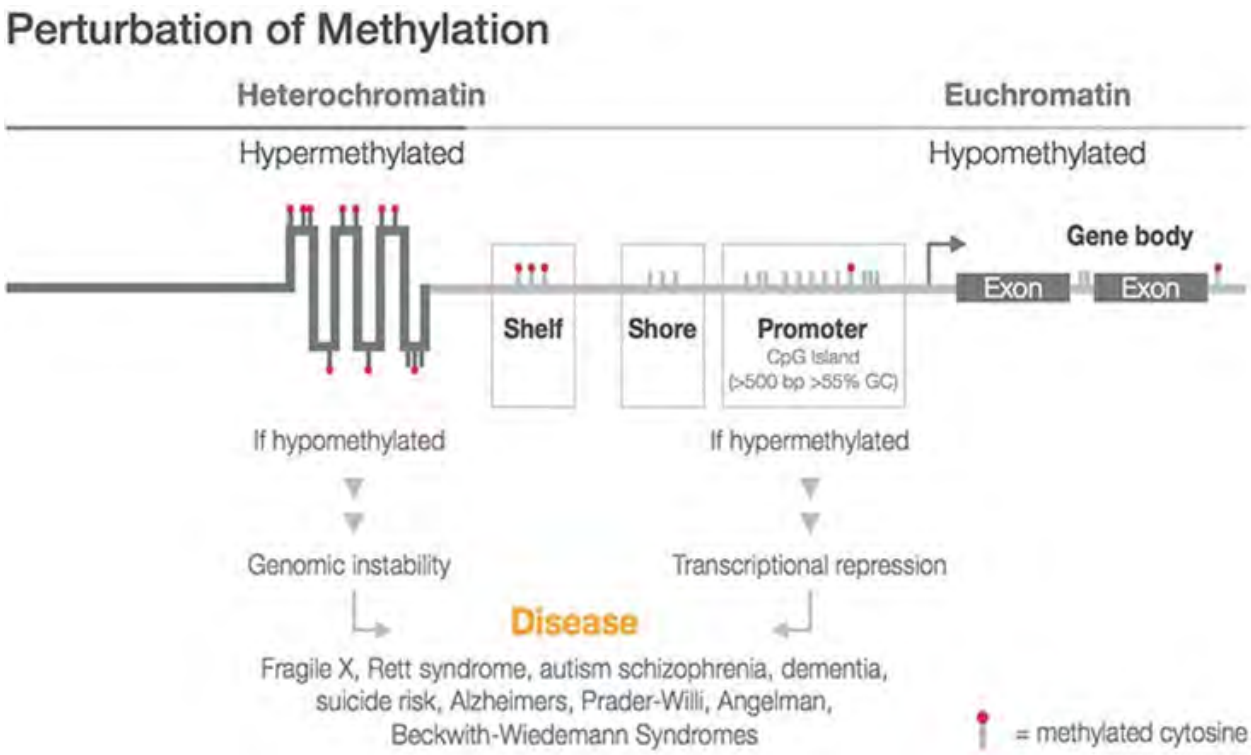


Figure 6: Perturbation of methylation (Illumina) Link to the site: https://sapac.illumina.com/techniques/sequencing/ methylation-sequencing.html

Histone modifications

Histones are the proteins which act like spools which can wrap DNA around it so that ~6 feet of DNA (diploid) can be packed inside the cell nucleus. Approximately, 150bp of DNA is wrapped around a histone octamer consisting of 2 copies each of the histone H2A, H2B, H3, H4 (Figure 7) to form a nucleosome. There are about 30 million of these nucleosomes in a given human cell. This tight packaging creates a new problem of accessibility of DNA to the DNA binding proteins like the transcription factors. Fortunately, thanks to epigenetic marks, histones can either positively or negatively regulate the gene functions. These epigenetic marks are mainly found on specific amino acid residues on the histone proteins. Now, unlike DNA epigenetic modifications which is mostly 5-methylcyotsine (discussed in the previous section), histones are prone to a variety of modifications including acetylation, methylation and phosphorylation on different amino acid residues (Figure 8). Most of the modifications reside on the amino acids found in N-terminal tails where they are presumably more accessible to the "reader" proteins since they are extruded from the domain.

Specifically, acetylation and methylation on certain lysine residues are important for epigenetic gene regulation. For example, acetylation of histone H3 is correlated with transcriptional activation at transcription start sites and/or enhancers. In contrast, methylation on H3 can either activate or repress transcription. For example, methylation of H3K4 is associated with transcription activation where as methylation of H3K9 represses transcription.

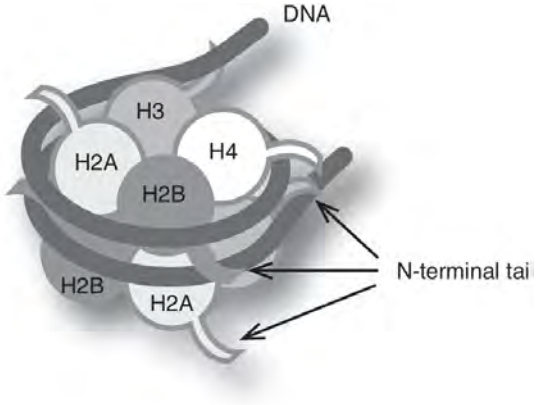


Figure 7: Schematic of nucleosome structure (Kimura, 2013)

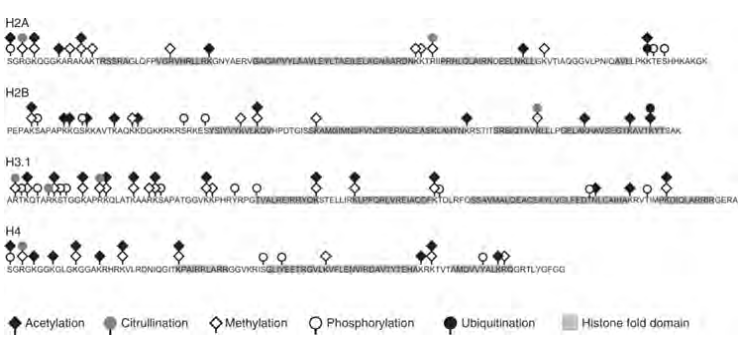


Figure 8: Modifications of core histones (Kimura, 2013)

Histone modification detection methods

Histone modifications can be detected using a variety of techniques including mass spectrometry and genomics approaches such as ChIP-chip and ChIP-seq. The genomics approaches combine chromatin immunoprecipitation (ChIP) of specific, modified histones and their associated DNA with microarray (chip) or NGS (seq) of the DNA molecules to identify regions of the genome associated with these modifications (Figure 9).

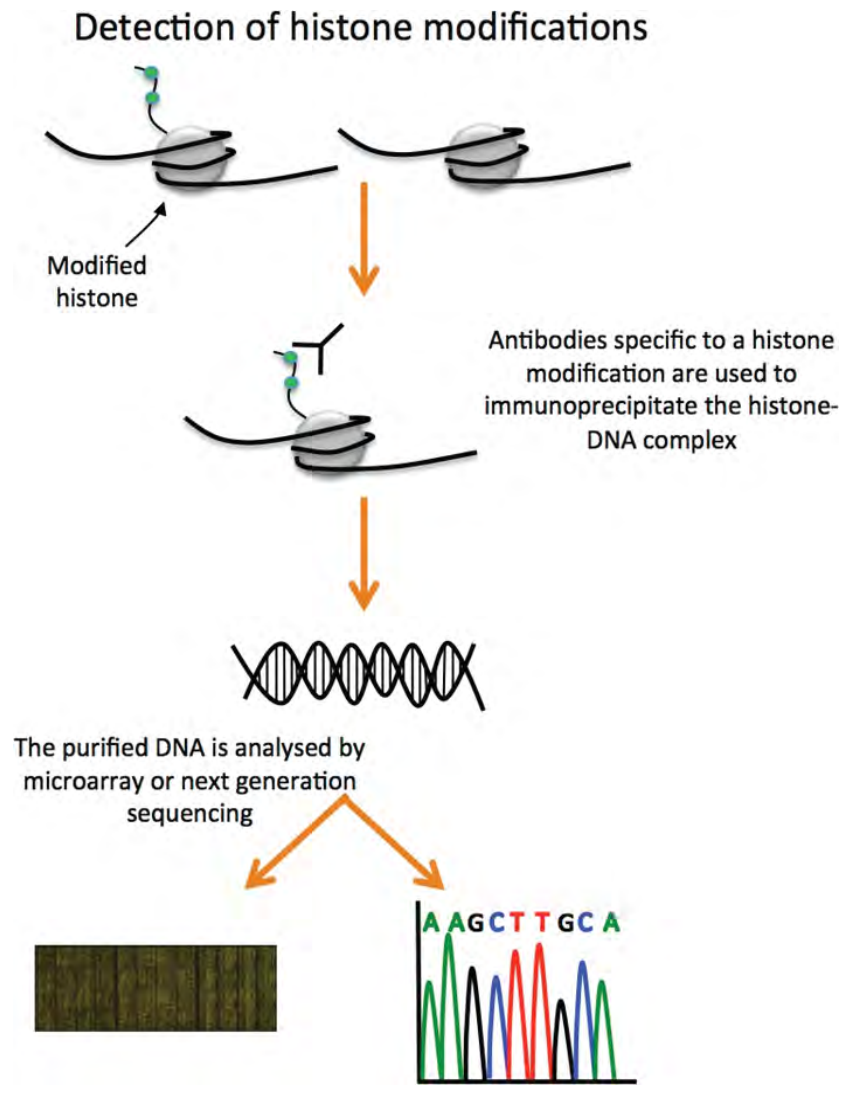


Figure 9: ChIP - Chromatin Immuno Precipitation method to identify the DNA binding to certain histones (www.ebi.ac.uk)

Conclusions

While geneticist will tell you that some of the traits are due to bad genes which are inherited from the parents, epigeneticist will tell you that it is due to the environment where the kids were raised which makes a difference. In essence, it is a mix of both. It is the interplay of both nature and nurture that guides the development of an organism. Although what we inherit is unchangeable, a part of it is actually shaped by our experience. We have come a long way in understanding the epigenome however, there is still much to be understood about this complicated modification which will allow us to design diagnostic solutions and treatment options for some complex diseases like cancers and immune disorders.

Leukemia Beyond Morphology:

Flowcytometry in hematological malignancies

Dr. Shruthi PS (MBBS, MD)
Senior Hematopathologist

Introduction

An appropriate categorization is the key for success of therapy in cases of acute leukaemia. This first came to light in 1948 when the report on the treatment of acute leukaemia with aminopterin was published.

The first impedance-based flow cytometry device, which made use of the coulter-principle , was disclosed in U.S. 1953. In addition to this, Mack Fulwyler was the inventor of the forerunner to present-day flow cytometers - particularly the cell sorter. The first fluorescence-based flow cytometry device (ICP 11) was developed in 1968 by Wolfgang Göhde from the University of Münster and first commercialized in 1968/69 by German developer and manufacturer Partec through Phywe AG in Göttingen.

The original name of the fluorescence-based flow cytometry technology was called "pulse cytophotometry" based on the patent application on fluorescence-based flow cytometry.

Traditionally, morphology and cyto-chemistry have been used to identify broad categories of acute leukaemia such as acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML) with a useful degree of homogeneity for diagnostic and therapeutic purposes. The initial observation of the heterogeneity of acute leukaemia has been found to be far more extensive and therapeutically meaningful as a result of their further characterization, using latest state-of-the-art technologies including flow cytometry. Thus, the diagnostic work-up of a case of acute leukaemia must incorporate the detailed phenotypical as well as the genotypical characteristics of the leukemic cells. This information on phenotypical details not only helps in prognosis but also bears certain therapeutic implications. The present “state-of-the- art” flow cytometers are capable of analysing up to thirteen parameters.

The current article shows the application of FCM as a subsequent adjunct to morphology and cytochemistry in the diagnosis and classification of acute leukaemia and residual disease.

What is Flowcytometry?

Flow cytometry is a technology that provides rapid multi-parametric analysis of single cells in solution. It is used to detect and measure physical and chemical characteristics of a population of cells or particles. Flow cytometers utilize lasers as light sources to produce both scattered and fluorescent light signals that are read by detectors such as photodiodes or photomultiplier tubes. Cell populations can be analysed and/or purified based on their fluorescent or light scattering characteristics.

Flow cytometry is a technique used to analyse cells for a variety of purposes, including cell counting, phenotyping, cell cycle assessment, and viability.

How does a Flow cytometer work?

The Sheath fluid focuses the cell suspension, causing cells to pass through a laser beam one cell at a time. Forward and side scattered light is subsequently detected, as well as fluorescence emitted from stained cells.

Light scattered from the cells or particles is detected as they go through the laser beam. A detector in front of the light beam measures forward scatter (FS) and several detectors to the side measure side scatter (SS). The Fluorescence detectors measure the fluorescence emitted from positively stained cells or particles.

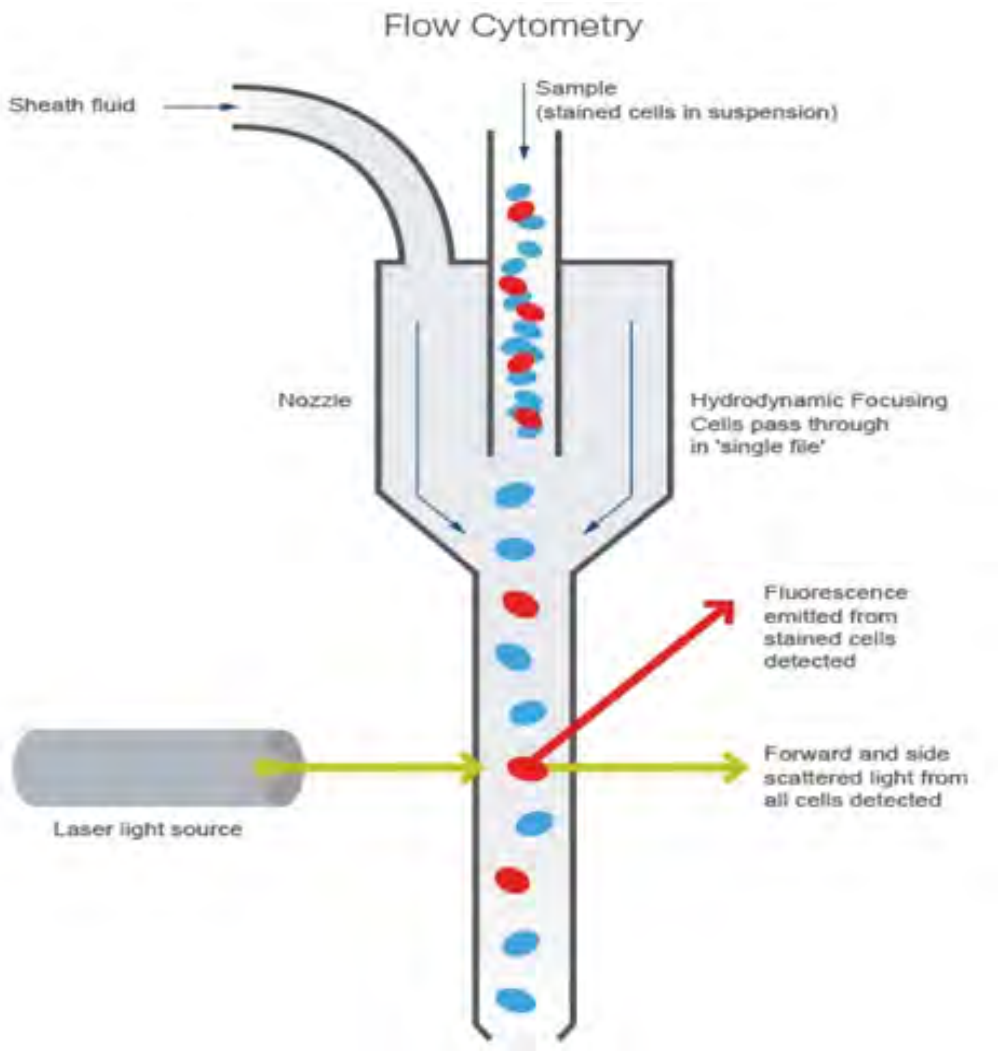
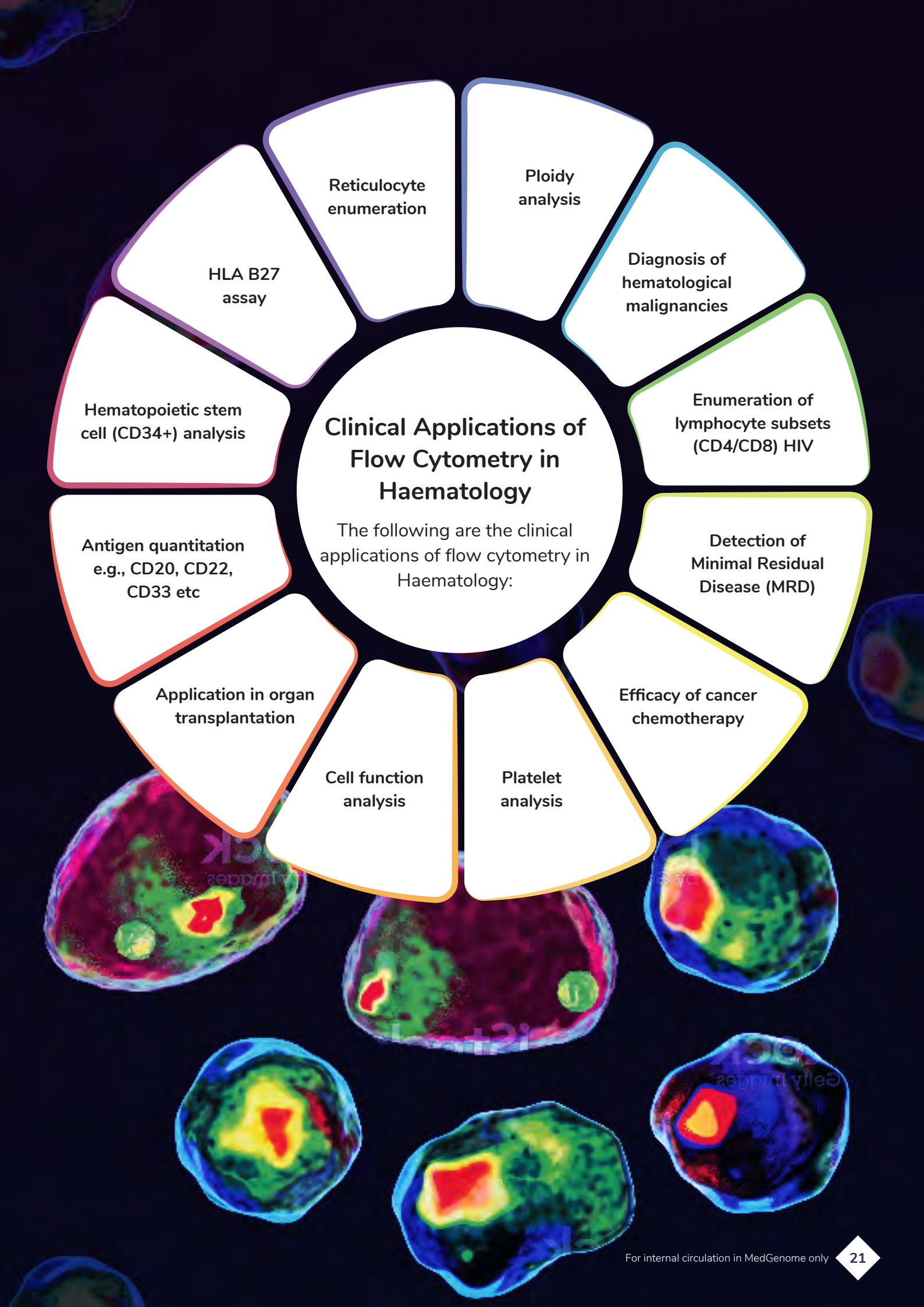


Figure 1- principle of flow cytometry


Clinical Applications of Flow Cytometry in Haematology
The following are the clinical applications of flow cytometry in Haematology:
Reticulocyte enumeration
Ploidy analysis
Diagnosis of hematological malignancies
Enumeration of lymphocyte subsets (CD4/CD8) HIV
Detection of Minimal Residual Disease (MRD)
Efficacy of cancer chemotherapy
Platelet analysis
Cell function analysis
Application in organ transplantation
Antigen quantitation e.g., CD20, CD22, CD33 etc
Hematopoietic stem cell (CD34+) analysis
HLA B27 assay

Case Scenarios

An 8-year-old boy presented to a paediatrician with complaints of fever, weakness, bruises, bony and joint pains. On examination he has mild pallor, tiny cervical lymph nodes. Per Abdomen: Mild splenomegaly. Other systems: NAD. The peripheral blood counts revealed pancytopenia with circulating? atypical cells/ reactive lymphocytes.

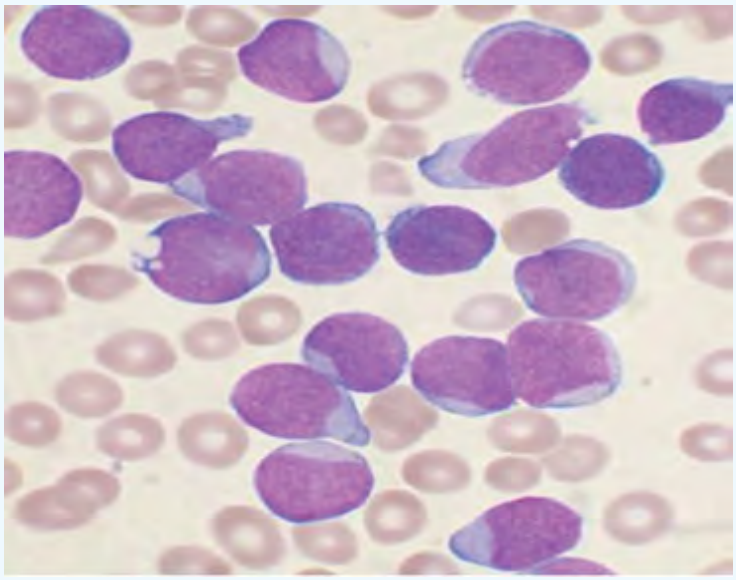


Figure 2- Smear shows lymphoblast

- Differential diagnosis of viral infection and Acute leukemia was considered.
- His bone marrow was sent for morphology and flowcytometry.
- The aspirate showed a predominance of blast cells.
- The immunophenotyping showed a dim CD45 abnormal population which expressed CD19, CD10, CD22, CD79a, CD38. These findings are consistent with the diagnosis of B-Cell Acute Lymphoblastic Leukemia.
- The below plots (fig 3) depict the expression of the abnormal population (Labelled Red).
- Patient received induction chemotherapy and a repeat bone marrow was performed on Day 31 to look for response to chemotherapy (Day 31 MRD).
- A small population constituting 0.3% (Marked Red) was identified which was positive. (fig-4)

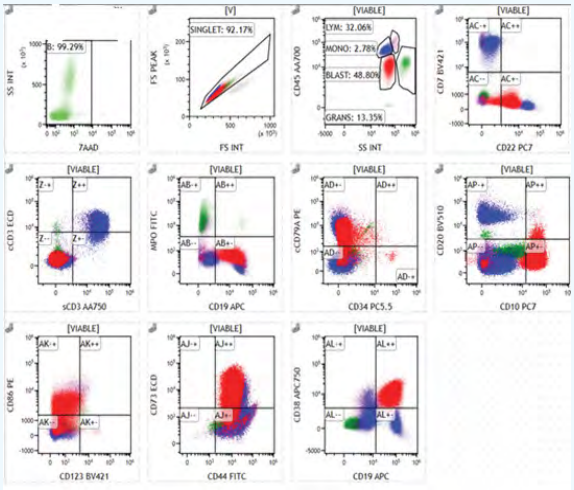


Figure 3- Immunophenotypic findings are suggestive of B cell ALL

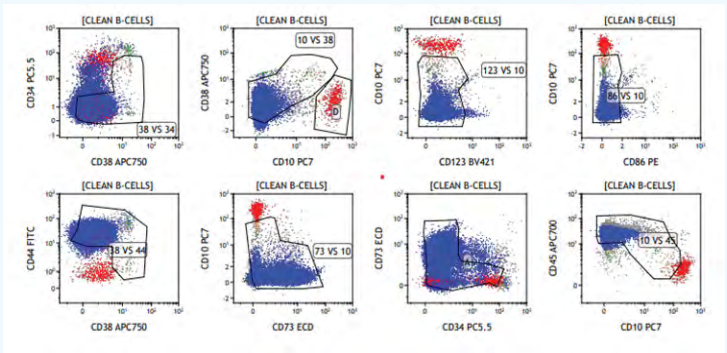


Figure 4- Post Induction MRD analysis showing positivity by using flowcytometry

Advantages

- Current flow cytometers have the capability of simultaneously measuring multiple parameters of individual cells in a cell suspension.
- Thus, many samples can be processed with a quick turnaround time.
- In addition, flow cytometry is also highly sensitive and can detect immunophenotype of cells in a specimen with thousands of cells.
- Concurrent detection of proteins associated with surface, cytosolic and nuclear compartments.
- Direct correlation of phenotype with:
  a. Intracellular protein expression
  b. Functional output, e.g., cytokine release, production of transcription factors
- Study of signalling events on a single cell basis.
- Study of the mechanism of action of pathway activation/inhibition for cells in suspension.

Disadvantages

- The process is very expensive and solicits the use of sophisticated instruments.
- Requires management by a highly trained specialist and requires on-going maintenance by service engineers.
- Complex instruments are prone to problems with the microfluidics system (blockages) and requires warm-up, laser calibration and subsequent cleaning after each use.
- Needs single cell particle.
- Tissue structure is lost.
- Little information on intra-cellular distributions

What are the limitations of flow cytometry?

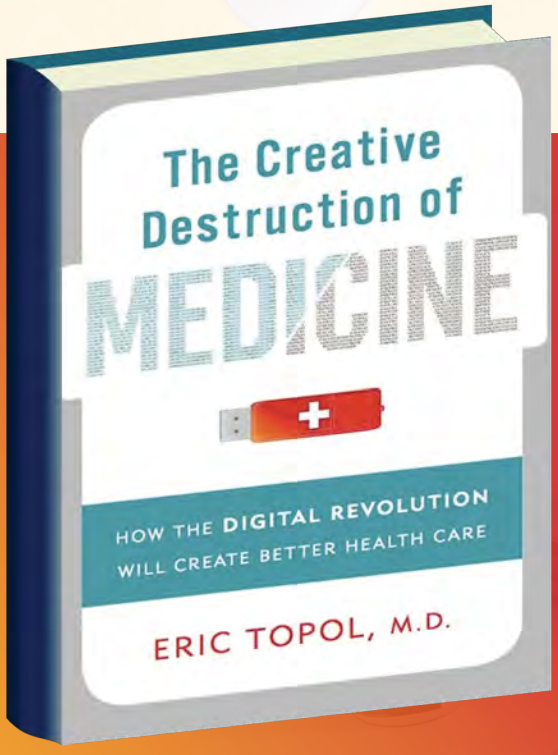
Limitations to flow cytometry include the facts that the laser can only analyze one cell at a time, cells must be in suspension to be analyzed (thereby restricting the analysis of tissue), highly trained operators are required, and cells must be viable to be analyzed.

Conclusion

Flow cytometry is a powerful tool that can be used in a significant number of cell analysis applications ranging from phenotyping to cell health/ viability and monitoring response to treatment.

The two greatest advantages of flow cytometry are its ability to measure multiple parameters (2 to 30 or more) on the same sample and its ability to collect information from millions of cells in a matter of seconds. In conclusion, it can be stated that flow cytometry plays a significant role in diagnosis and the subsequent follow up of haematological malignancies and benign disorders.

Book Review



Book

The Creative Destruction of Medicine

Book review by

Kamalika

Manager, Corporate

Secret is out! Doctors 'May Not' know the best!!

Dr. Eric Topol is a man with many hats. He is a Cardiologist, Professor of Genomics & Director (at Scripps) and most importantly, a visionary. In his book, The Creative Destruction of Medicine, Dr. Topol described how technology and digitization would transform the current (rather traditional) medical practices. Putting the digital world in two boxes- the non-medical i.e., internet, mobile, cloud computing and the medical i.e., genomics, biosensors and advanced imaging, this book encompasses the parallel journey of these two worlds, converging into '**Smart Treatment**'.

Dr. Topol has rightly pointed out that though we do not even buy a commodity without checking its reviews, when it comes to healthcare, we choose (or adjust) to stay ignorant. **Is our silence an outcome of the age-old paternalistic attitude or do doctors really know the best? Well, those who are seeking an answer, will get them in this book!**

Set in the backdrop, where there is a strong rigidity to bring any radical change in medical practices, (and reasons well explained in his second book, The Patient will see you now), the first book in the series, is an eye opener to how much we can achieve if we leverage the digital world in healthcare.

Devil's clique- Dr. Topol's most interesting antagonist in this book, is the concept of 'one formula for all', i.e., 'one medicine fits all' and 'one test fits all'. Dr. Topol analyses the medical practitioners' selective ignorance to relate an individual's uniqueness with his health, most importantly the role of genetics in healthcare.

Rise of the smart patient

Only an empowered patient would demand the change!

Dr. Topol explained the ways to empower oneself, and the importance of being informed, right use of information and openness to explore cutting edge technologies. He cited excellent examples of 'patient activism' where patients funded a biotech company or took a job at a lab to find a cure for their disease. That is the power of knowledge. His concept of patient empowerment has been the basis of his second book The Patient will see you now.

The seeds of creative destruction and the rise of new era

Big brother

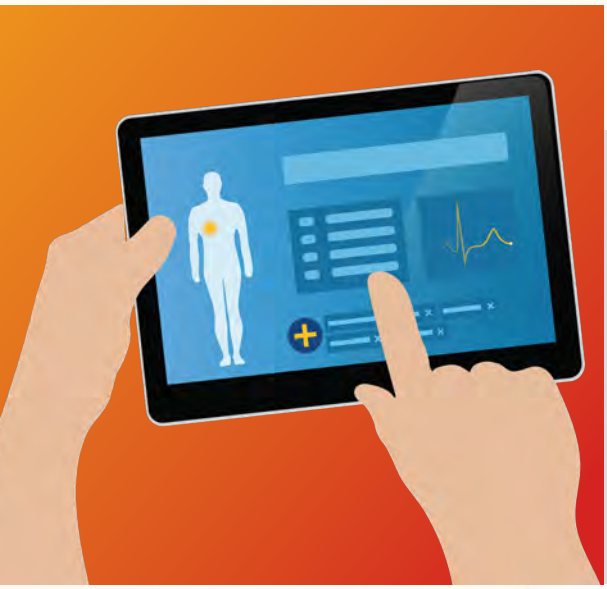
Are you really being watched?

We already know that our every action & reaction can be tracked through clicks & sensors, connected via the internet, and stored in the cloud. So, it seems logical to have a similar concept applied to track our health, such as setting up a biosensor to track and record health data which can eventually prevent a potential fatality.

Genome Squad

Genomics is the protagonist to fight the 'one formula for all'!

One of the highlights of the book is about treatment based on our genetic signatures and how the focus needs to shift on **individual-based rather than population-based healthcare.** This realisation will lead to an era of **Personalised medicine**, wherein genomics will be used to understand an individual's faulty genes, genetic predisposition to disease susceptibility, drug reactions & drug development. The key is to stratify people based on genetic factors and identify treatment that works. **Precision medicine** will be key to the future of medicine where individuals will be treated with a tailor-made solution i.e., connect mutation to drugs & treatment than administering a generalised formula.



To err or to HIIT?

An interesting feature in Dr. Topol's Wishlist!

We often hear cases of medical negligence, lack of accountability and record keeping hassles, etc. Hence, an integrated record management system in cloud to capture one's health record, lab reports, doctor feedback and reviews, diagnosis, treatment, etc. would surely make the medical industry more responsible and patient's life more manageable.

Dr. Topol has presented many innovative ideas in his book (some straight from sci fi movies 😊). However, he did not dwell much on the quality & maintenance as there will be a lot more dependency on product-based healthcare. Investment and Affordability are other key elements that needs to be well understood. Also, manipulation or misinformation due to the human-technology interaction, cannot be negated.

Nevertheless, despite a few challenges, Dr. Topol has proved that the convergence of both the boxes, would bring the ultimate destruction of old medical practices and lead to future of medicine where personalised and precision medicine, genomics & biosensors-based techniques and internet & cloud-based systems would play an active role.

Indeed, Dr Topol's projections are now becoming a reality as in the last few years, there has been a rise in precision medicine in medical practices, such as using genetics and molecular biomarkers in cancer treatment especially in breast cancer, lung carcinoma, etc. Introduction of radiogenomics which uses machine learning to analyse drug sensitivities in patients with Glioblastoma has been a great breakthrough. Also, the use of immunotherapy has been a gamechanger in cancer therapies, though other disease segments are yet to pick up. In the UK, the 100,000 Genomes Project revealed actionable findings which could be useful for potential therapy or clinical trials. And many such research are underway.

Even in the current Covid-19 scenario, there are evidence that shows how the genetic background of an individual plays an important role in drug effectiveness and disease susceptibility. As physicians and scientist all around the world are understanding the importance of personalised medicine, research is being carried out to advance in precision treatment and genetic databases are being created to understand gene variability.

Surely, this book is an incubator of futuristic approach towards 'Smart treatment' and one can say that the journey has already begun!

From our Colleagues

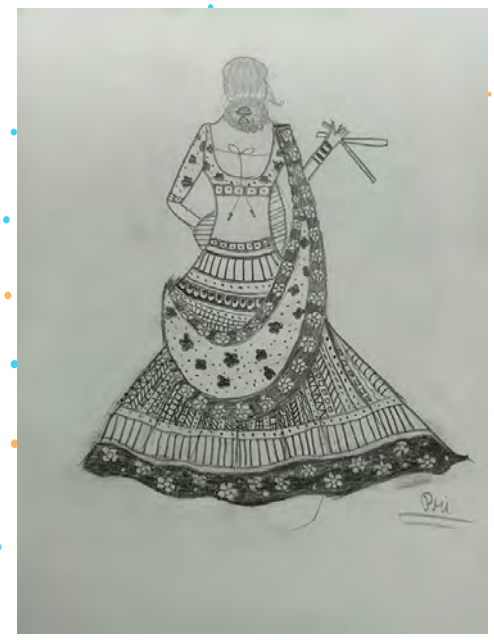
Art meets Science

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

By: Dr. Shruthi PS
Senior Hematopathologist

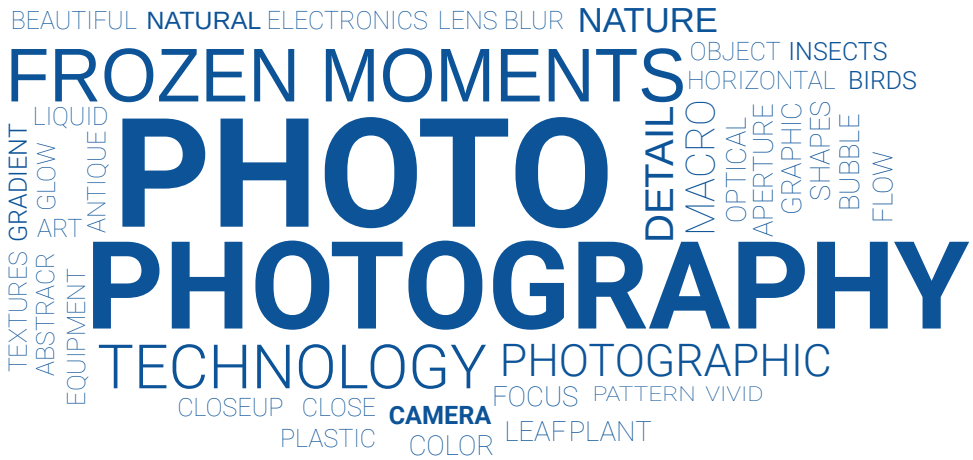
Mother Daughter duo

Our employee and her lil Picasso!



By
Prisha MS (14 Years)
DNA of Dr. Shruthi PS

From our Colleagues



By
Swarup Kumar Gotur
Sr. Graphic Designer,
Marketing Team

Employee Connect

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Akshay Sharma


Akshita Sharma


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Arijit Banga


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Chaithra


Chinmayan P Raju


Chinnappa Devaiah


Debarati Bag


Deepak T P


Deepika Rani Jena


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Diksha Mrityunjay Singh


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Dixon M D


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Manpreet Kour


Mohan Kumar V


Mohit Kumar Nishad


Narendrakumar Venkatesh


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Neeleshwar Singh


Ningthoujam Ravikanta Meitei


Niralkumar Kiranbhai Shah


Nisha Suresh Kumar


Nitin Singhal


Padmakar Madhukar Shinde


Manjusha G Y


Pradeep Kumar Verma


Pradeepa K T


Prateek Sharma


Praveen R


Preethi Sridharan


Prem Chandar


Priyadharshini G


Priyanka Sharma


R Rajkanna


Rajni Chandak


Ranjan Gupta


Ratnakar Mishra


Ravindra Reddy


Rishabh Khandelwal


Rohit Laxman Bhojane

Roshini B R

Sahib Singh

Saikat Chatterjee

Samantha S

Samit Kumar Sinha

Sandeep Kumar

Sanjana

Santhosh Sankar


Shasanka Rabindra Sahu


Shemma


Shilpa N


Shravya Gupta


Shreya Sanyal


Shreya Sharma


Shrimuki


Soumyadipta Das


Souptik Bhattacharya


Sreekar N


Sthita Prajna Kasarla


Subhalaxmi Choudhury


Subhrangsu Patranabish


Sudharshana


Suparna Maji


T Vismaya


Talari Praveen


Tamil Selvan


Tarun Prakash


Tejeswini


Tejpal Janwa


Thripureshwari Vijaykumar


Uday Sankar


Umarevathy


Vadrevu Saranya


Varun


Venkatesh


Vikas Guleria


Vipin Kumar


Vishaka


Vukku Manasvi


Yasser Neyazi


Yogesh Kumar Sharma


Yusuf Haidar Mulla

Photo Feature

Independence Day

Independence day celebration was organised in the office with tri-color themed decor, dress code and food competition. It was well received and participated by all our colleagues.

Photo Feature

Onam

Onam festival presented an ethereal ambience in the office with everyone dressed in ethnic wear, flower rangoli, decorations and delicious snacks with payasam to complete the celebrations.

Photo Feature

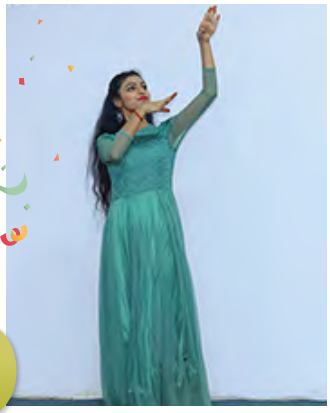
Elite Club Award Function

Elite club award witnessed MedGenome's shining stars and extraordinary contributors getting recognised and awarded for their dedication and efforts.











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