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Internal Quarterly Newsletter



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Management speaks















Rohit Gupta
Chief Information Officer

Dear Colleagues,

Greetings and wishing you all a very Happy New Year 2018!

First let me take this opportunity to congratulate everyone on our last year's performance. We are now a CAP accredited lab in Bangalore with many tests under one roof. Several new diagnostic tests such as liquid biopsy, carrier screening were launched with end-to-end in-house developed methods. On the research and services side of the business, lab capabilities and capacity has been increased in both India and the US lab, disease-focused research programs have been accelerated with revamping of the Scientific Affairs Committee (SAC), new genomic tools specially in the area of cancer immunotherapy and clinical knowledgebases in Diabetes and Ophthalmology have been created, publications and patents have been filed.

With all this hard work and past achievements, I believe MedGenome is now at a tipping point and therefore 2018 will prove to be a very important year. We are committed to use genomics at a deeper level for both clinical diagnostics and research which is clearly reflected by investments in setting up disease - focused research centers across the country in collaborations with the leading institutions. While diagnostics business will continue to grow in India and few other countries with increase in awareness and adoption, the time is ripe for us to leverage all the past work and use rich clinical and genomics data collected from collaborating institutions to enable drug discovery and grow up the value chain. The advantages of using the data from Indian population to research complex diseases, find novel biomarkers, validate known drug targets, conduct drug repurposing studies, and provide support in running clinical trials, appears to be a good proposition for the company.

We are also strategically very suitably placed to make significant headway into developing Artificial Intelligence and Machine Learning techniques in-house for analyzing multi-modal clinical and genomics data. These advances can play a crucial role in solving bigger and more complex problems like prediction of complex diseases and associated complications at an early stage, role of genetics in response to drugs and predicting adverse events, identifying the disease sub-types, segmentation of patients based on their genetic profile for risks and clinical trials, etc. Our understanding in these areas will also help us to reach the consumer market directly which is one of the important segments that company would like to develop going forward.

Finally, we should realize that success comes with even bigger responsibility. Therefore, while celebrating our past achievements is gratifying and fulfilling, we need to be more focused now and strive for quality to make MedGenome a globally known company solving complex problems that improve peoples lives worldwide. Clearly, people are the pillars of any organization and with the kind of enthusiasm, skills and dedication we have as a team, I have no doubt that this will happen rather soon. Most importantly, let us have fun doing it!

Best wishes, Rohit

Highlights



Most talked about

MedGenome in news

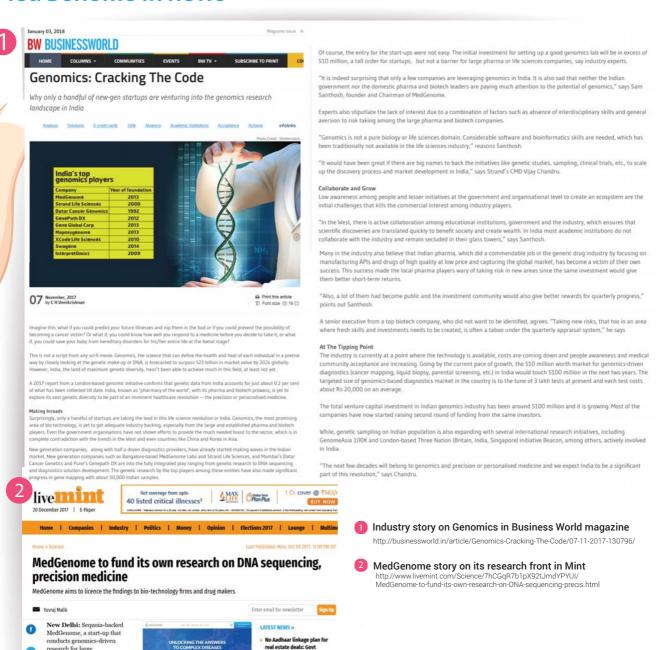
research for large pharmaceutical companies, is planning to fund its own research in the area of DNA sequencing and precision medicine, with an aim to licence the findings to bio-technology firms and drug makers, a top

executive said

Francisco - and Bengaluru-based MedGenome Labs Pvt. Ltd has a network of Next Generation Sequencing (NGS) laboratories in India, Singapore and the US. In August, it raised \$30 million from Sequoia and Brussels-based Sofina

"Currently, a lot of it (research) is done on project basis, but we are also creating our own IP (intellectual property), so that in two-three years' tic an license some of the knowledge," said Sam Samhosh, founder and chairman, MedGenome. Its research is in four main areas: cancer immunotherapy, inherited diseases, diabetes and ophthalmology.

About 70% of the company's revenue is earned from project-based research mainly for US-based pharmaceutical clients, while the rest is from consumer diagnostic tests in Asia. Its labs combine state-of-the-art testing equipments and powerful computers to perform DNA sequencing that is used for a wide



4



Tracing their fear









Telangana Today

Virinchi Hospitals, MedGeome tie up

Y V PHANI RAJ

Hyderabad Abased Virinchi Hospitals, a subsidiary of IT company Virinchi has entered into a strategic collaboration with MedGenome, a genomice-based diagnostics and research company for molecular diagnostics. The construction of the control of th

ertiary healthcare provider. Dr Chirantan Bose, V-P.



inchi nospitals.

MedGenome is helping in reduce the costs of previously expensive genetic tests, and empowering clinicians with actionable insights to provide better outcomes for their patients."

He told Telanguna Today, "Virinchi wants to use mo-

MedGenome receives accreditation from College of American Pathologists

The CAP laboratory accreditation programme i globally recognised and is the only one of its kind that utilises teams of practicing laboratory professionals as

BENGALURU,13 DECEMBER

MedGenome, a major play-er in genetic diagnostics, announced today that its next generation sequencing technology based clinical laboratory in the IT capital, has been awarded accredi-tation from the College of American Pathologists . The CAP laboratory accreditation programme is globally recognized and is the only one of its kind that uti-lizesteams of practicing lab-oratory professionals as inspectors.

oratory professionals as inspectors.

It is designed to go well beyond regulatory compliance.

A company release here said that during the accreditation process, inspectors do a detailed check of the laboratory's records and quality control procedures besides assessing the laboratory's staff competency, qualifications,

This accreditation is This accreditation is awarded to facilities meeting the highest standard of excellance in clinical laboratory practices. With this accreditation, MedGenome's India laboratory joins the ranks of the most elite laboratories in themost elitelaboratories in theworld. Dr Ramprasad, coo, Med Genome, said that hav-ing launched India's first validated liquid biopsy and thecarrier screening tests, "we are trying to find answers to some of the most complex dis-

Story on genetic testing in Bangalore Mirror

http://bangaloremirror.indiatimes.com/opinion/sunday-read/tracing-their-fear/articleshow/61799652.cms

MedGenome collboration with Virinchi Hospital in Telangana Today https://telanganatoday.com/hyderabad-based-virinchi-hospitals-ties-up-with-medgenome

MedGenome CAP accreditation news in Statesman https://diagnostics.medgenome.com/pdf/2017/13thStatesman2017.pdf

MedGenome connect

ACTIA



Rasopathy (Kochi)

In this quarter i.e. between Oct-Dec 2017 we participated in 4 conferences, 5 CMEs & relationship meetings in 8 cities. These events covered various aspects of Neuro and Nephrogenetics to promote our services among Key Opinion Leaders (KOLs) and clinicians.

The aim was to reach out to more than 850 clinicians with a special focus on Renal and Neurological Disorders with genetic origins and the utility of genomics in helping their patients with these disorders. Dr. Sheetal Sharda and Dr. Gaurav Verma were the speakers for these CMEs. One of the major events wherein we participated was ISPNCON, the annual event of Pediatric Nephrologists of India from 14th to 15th October. Nearly 300 doctors attended this annual event 2017.

This quarter also saw our foray into other important specialties like Ophthalmology and Cardiology by

participating in RTM at Kolkata and RASopathy conference at Kochi. The next 2 months are promising as we have plans to connect with leading clinicians thus providing us enhanced visibility, with some of the important events of geneticists and Pediatrics, Neurology and Nephrology lined up during this period.

PRIMA

In the last quarter we participated in two key events:

• 2nd Indian Cancer Congress 2017, 8th to 12th Nov, held at Bangalore

At the Indian Cancer Congress we had a stall where we could showcase our expertise and interact with customers. We had 2 sessions on Molecular oncology by Dr. Ramprasad and Dr. Chirantan Bose. About 250 plus doctors visited our stall during the event.



 Genetics Conference at Kochi from 10th to 12th Nov 2017

In this event MedGenome showcased its capabilities in the field of genomics with active participation and collaboration with the genomics department of TMH (Tata Memorial Hospital) Mumbai. Dr. Ramprasad participated as a Panelist in one of the important sessions on genomics.

MedGenome connect

CLARIA



 $\label{lem:conference} \mbox{Dr Kamini Rao at the MedGenome stall at Life conference in Bangalore}$

October was a month of conference for Claria. We were at three conferences and presented at one of them, the Asia Pacific Institute of Embryology conference in Mysore. Our stall at the CIMAR PERICON attracted a lot of attention thanks to the quiz competition, the winner of which received an Amazon Kindle. November was relatively quiet with just one conference and two CME's where in Dr. Priya showcased our NIPT capabilities at a CME conducted for CloudNine Gurgoan. Dr. Sam Balu presented our NIPT capabilities at the 39th annual Association of Obstetricians and Gynaecologists of Delhi (AOGD) conference in New Delhi. His talk was very well received with a lot of audience interaction.

There was also a public endorsement of our service from one of the panellists at the conference. In December we did 3 conference in Delhi, Trivandrum and Bangalore and 1 CME in Kolkata.

Introducing The Claria Webinar Series

The Claria Webinar Series initiative is designed to make genomics-guided clinical treatment strategies more accessible to clinicians. Till date we have conducted three webinar's on PGS/PGD, Micro-deletion detection using NIPT and the Importance of Carrier Screening Testing in India. The recordings of these webinar are available on providers.medgenomeclaria.com/events.

Making a difference

Embryo biopsy with presence of Partial trisomy & monosomy in chromosome 16 detected by VeriSeq NGS method:

A Case Report

Introduction

A couple, 35-year-old wife with history of multiple spontaneous abortions and 39-year-old husband underwent IVF procedure. The karyotype results of the mother showed presence of balanced chromosomal translocation t(16;19) (q11.2;p13.3) whereas the father was completely normal. We received a high grade embryo biopsy (Two day 5 trophectoderm biopsies) for the above case to perform "Pre-implantation Genetic Screening/Diagnosis" (PGS/PGD) procedure in order to look for chromosomal aneuploidies in the embryo prior to implantation.

Alternatively, based on karyotype data from the father and mother we predicted the probability of possible outcomes w.r.t. t(16;19) (q11.2;p13.3) in the embryo (Figure 1).



Figure 1: Diagrams to predict the probability possible outcomes w.r.t. t(16;19) (q11.2;p13.3) in the embryo

Making a difference

Scenario I and IV — Cannot differentiate between the normal and balanced translocation by VeriSeq PGS as both will appear normal (limitation of the technology used)

Scenario II and III – Can be detected by Veriseq PGS, Scenario 2 is a case of partial trisomy 16 (gain> 40 mb for chr16:). And scenario III is a case of monosomy 16 (loss> 40mb for chr16) {Size of Gain & loss confirmed by Ensemble Genome browser}

Based on the above findings, the following observations were made:

- ✓ 25% chances for the presence of cases with balanced translocation
- √ 25% chances for normal cases
- ✓ 50% chances for presence of unbalanced translocation

We performed PGS screening by Next Generation Sequencing method using Veriseq library preparation method. The DNA obtained from trophectoderm cells was subjected to whole genome amplification procedure (SurePlex method) which ultimately was used as a starting material for NGS library preparation. Data was generated using Nextera based library preparation method on the MiSeq sequencer for screening of all 23 pairs of chromosomes for aneuploidies.

The highlights of this method are: it uses an engineered transposome to simultaneously fragment and tagment DNA which is obtained from single or few cells after whole genome amplification. The technology assists in selection of euploid embryos for implantation.

The PGS data generated for this case showed the Gain in Chromosome 13 (Mosaic) and partial trisomy in chromosome 16 whereas another embryo from the same couple showed the presence of monosomy in chromosome 16 in embryo DNA i.e. A case of unbalanced translocation (Figure 2A & 2B). Consequently, both the embryos were reported as "Not recommended for implantation".

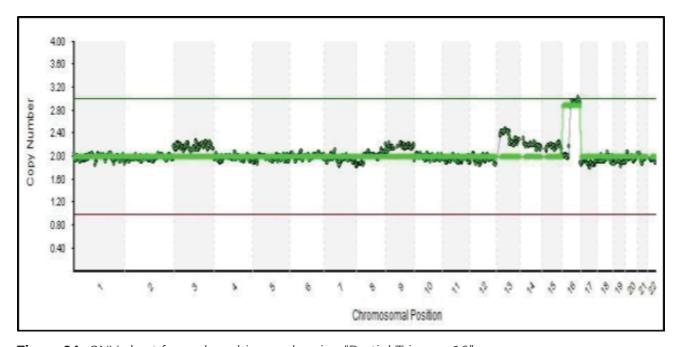


Figure 2A: CNV chart for embryo biopsy showing "Partial Trisomy 16"

Making a difference

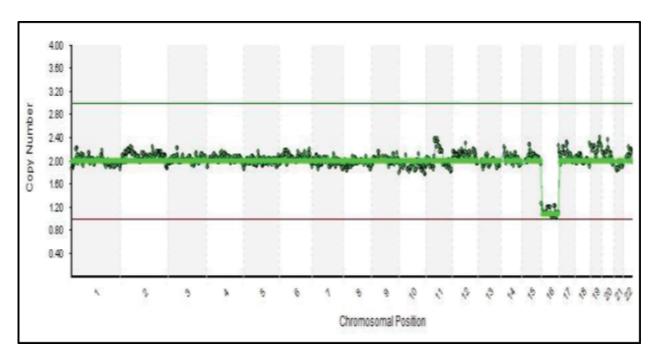


Figure 2B: CNV chart for embryo biopsy showing "Monosomy 16"

In conclusion Pre-implantation genetic screening using NGS can be used to detect chromosomal abnormalities in the embryo. In the present case, implantation of genetically abnormal embryo could have led to either selective pregnancy termination or birth of an abnormal child. Therefore, Pre-implantation genetic screening procedure is very much helpful for the clinicians, in better decision making which is also a preventive measure for physical as well as emotional trauma for the patient.

From our US office



Congress
2017
4-8 December
Abu Dhabi

www.idf.org/congress #IDF2017

diabetes



This quarter we attended few key conferences which provided us an opportunity to showcase our lead products OncoPept and Diabetome.

At the recently held International Diabetes Federation event in Abu Dhabi - our product Diabetome was presented to an elite group of scientists and academicians. Diabetome is a novel clinical knowledge base/analytic platform designed based on 320,000 individuals with diabetes. It provides data and tools to promote continued understanding of diabetes, its risk factors and complications for research, development and clinical diagnosis.

The event included more than 200 speakers, both world-renowned and newcomers, 230 national diabetes associations from 170 countries and high level participation from the Health Authority Abu Dhabi (HAAD) and other health organisations.

We also took part in the Neoantigen Summit 2017, where our tumor microenvironment analysis and neo-epitope prioritization solutions were presented to the scientific community. This event is considered to be the premier platform to benchmark against the industry and network with the crème de la crème of neoantigen therapy developers.

We also presented OncoPept at other conferences namely: Society for Immunotherapy of Cancer (SITC), Impact Immunotherapy Progress & Clinical Trials and World Vaccine Congress.

At ASHG, we had an opportunity to present a poster on Diabetome that involved a case study depicting how Diabetome can be applied in disease management and treatment strategies.

The sales team in US had a team meeting in MedGenome Foster City office and discussed our offerings with our scientists in-depth.

This involved a deliberation on critical customer feedbacks that would allow MedGenome to scale up our offerings in the US market.

On October 30, 2017 - our chairman Sam Santhosh addressed the Staff at Foster city – delving deep in defining the vision and mission of MedGenome Inc. He also took part in a Radio Interview organised by Wharton Business Radio – where he provided insights into the future of MedGenome and elaborated on how MedGenome is playing a major role in tapping the genetic diversity of India which has a huge bearing on Global Genetic Research programmes/studies. The below link provides the recording of the interview

https://soundcloud.com/user-414944777/sam-santhosh

As we enter the New Year, we have an opportunity to position ourselves as a global player in biomarker discovery services and solutions across various disease areas including Oncology and Diabetes.

We wish you a happy new year and a great year ahead. Thank you for all your support and at the turn of the New Year we hope to bring some more exciting news.

Sneak peek into the world of science

Cancer Vaccine: Promises, Challenges and MedGenome Solution

by Ravi Gupta, PhD, Associate Director - Bioinformatics



Introduction

High-throughput sequencing of cancer patients has enabled rapid identification of somatic coding mutations that could generate neoantigens^{1,2}. The tumor neoantigens are ideal targets for immunotherapy because they are expressed only by the tumor cells³. Several studies have suggested that neoantigens are important targets for effective antitumor immune response and their use for developing personalized vaccines⁴⁻⁶. Many studies have been published that showed that higher mutation burden is linked to stronger T-cell responses and better survival of the patients^{7,8}. Associations have been reported in endometrial cancers, melanoma, non-small cell lung cancer (NSCLC) and colorectal cancer ⁹⁻¹².

The neoantigens-specific T cell population have also been found to be expanded in effective antitumor immunity 9,10 . Both animal and human studies the tumor cell presenting immunogenic peptides can be selectively targeted by T cells which leads to complete or partial regression of tumor $^{13-15}$.

Challenges in developing cancer vaccine

The vaccine has to be designed such that the patient's immune cell (T cells) selectively hunts and kills only those specific tumor cells that present the targeted neoantigens. Finding a solution to train patient's immune systems to specifically target and kill cancer cells has proven to be a difficult task. The first success of molecular identification of neoantigen was reported by *Plaen et al.* in 1998¹⁶.

Identification of right immunogenic neoantigens is one of the central problems in the successful development of cancer vaccine. A patient's tumor contains candidate neoantigens ranging from few hundred to several thousand. The real challenge is in selecting the candidate that would be best for stimulating the patient's T cells. Computational algorithms have been developed but these programs suffer from lack of sensitivity and specificity because they rely heavily on features associated with antigen presentation alone, without considering features required for T cell receptor (TCR) binding. A recent paper describes a novel approach of quantifying neoantigen fitness in tumors to predict immunogenic peptides, in which both HLA presentation and TCR recognition are used as fitness components¹⁷. The neoantigen fitness model predicts immunogenic epitopes without examining structural features in a peptide that enables interaction with TCR. The model was used to predict long-term survivors of pancreatic cancer in a recent study¹⁸.

MedGenome solution

MedGenome computational group has developed a highly accurate new method (IPepPredicT) to select immunogenic peptide¹⁹. IPepPredicT applies ensemble voting-based machine learning approach to identify immunogenic peptides from patient's somatic mutations.

Our method is the first in-silico model that combines physicochemical properties of amino acids favorable for TCR binding with features relevant for antigen presentation and processing. IPepPredicT is trained on MHC Class I HLA-A*02:01 9mer peptides present in IEDB data. Our analysis revealed enrichment of helix/turn features at TCR contact residues along with hydrophobicity features enriched at the HLA-binding anchor residues. Our analysis also provides a feature spatial enrichment map that provides a guideline for selecting immunogenic peptides. While developing the method we also analyzed MHC-peptide-TCR complex crystal structures. Our analysis revealed that many of the features selected by our prediction algorithm are in agreement with finding from crystal structure analysis. Performance evaluation on unseen peptides provided sensitivity and specificity of 90.23% and 99.14% respectively.

Promising results from recent clinical trials

Recently, two clinical trials reported have shown encouraging results. The first study was conducted at Boston's Dana-Farber Cancer Institute on six melanoma patients⁴. The cancer vaccine targeted 20 neoantigens. Of the six patients given cancer vaccine, four of them are disease free for 25 months. For the remaining two patients, the disease reoccurred and was treated with anti-PD-1 therapy. The neoantigen specific T cells was found to be expanded that lead to complete tumor regression. The second clinical trial was conducted on 13 melanoma patients by Biopharmaceutical New Technologies (BioNTech) in Germany⁵. The cancer vaccine in this trial targeted 10 neoantigens for each patient. Eight patients were disease free for 12 – 23 months. These studies clearly indicate that the personalized vaccine has the ability to make cancer patient disease free.

By accurately predicting neoantigens, we believe IPepPredicT could help in effective personalized cancer vaccines.

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Sneak peek into the world of science

Product of conception testing - Implications and Methods

by Sakthivel Murugan SM, PhD, Associate Director - Diagnostics



Introduction

Recurrent Pregnancy Loss (RPL) is defined as two or more consecutive spontaneous abortions. RPL affects about 1 percent of the child-bearing population and it is estimated that 15–20% of clinically recognized pregnancies end in miscarriage. Although a few cases of RPL are sporadic, most have a genetic basis. The proposed causes of RPL are parental chromosomal abnormalities, uterine anatomic anomalies, endometrial infections, endocrine etiologies (leuteal phase defect, thyroid dysfunction, uncontrolled diabetes mellitus), antiphospholipid syndrome, inherited thrombophilias, alloimmune causes and environmental factors as mentioned in the table 1. Among the various proposed etiologies, genetic factors appear to be highly associated with reproductive loss.

The single most common cause of early (first-trimester) pregnancy loss is the presence of a major fetal chromosomal abnormality, which is responsible for 50 to 80 percent of losses in the first trimester, depending on maternal age and gestational age at the time of the loss. Cytogenetically abnormal embryos are usually aneuploid because of sporadic events, such as meiotic nondisjunction, or polyploid from fertilization abnormalities. Incidence of numerical and structural chromosome abnormalities in spontaneous abortuses is reported to be almost half (47.9%), 9.8 percent, polyploid (mostly triploid) 8.6 percent 45, X, and 26.8 percent trisomic for one or another chromosome. Fetal chromosomal abnormalities account for approximately 8–10% of intrauterine fetal deaths occurring after 20 weeks of gestation and/or stillbirths occurring in the second or third trimester. The etiologic analysis of pregnancy loss can provide important information for medical management, reproductive counseling, and supportive patient care.

Table 1: Etiologies of pregnancy loss

Anatomic Causes Genetic Causes Immunologic Causes Infectious Causes **Endocrine Factors** o Aneuploidy o Alloimmune causes o Autoimmune causes o Smoking o Diabetes mellitus o Somatic o Uterine mullerian o Alloimmune causes o Excessive alcohol o Antithyroid o Sex chromosome anomaly consumption Listeria monocytogenes, antibodies o Mendelian disorders o Uterine septum Toxoplasma gondii, o Caffeine o Luteal phase o Multifactorial disorders (the anomaly most rubella, herpes simplex deficiency o Parental chromosomal commonly associated virus (HSV), measles. abnormalities with pregnancy loss) cytomegalovirus (translocations) o Hemiuterus and coxsackieviruses o Chromosomal inversions. (unicornuate uterus) o Bicornuate uterus o Diethylstilbestrollinked condition o Acquired defects (eg. Asherman syndrome) o Incompetent cervix o Leiomyomas o Uterine polyps

Genetic Testing Methods

Several methods have been used for POC testing. Conventional karyotyping is the gold standard in genetic testing and effectiveness of new methods was proven in comparison with GTG karyotyping results. Conventional G-banding karyotyping enables direct visualisation and assessment of the number and structure of all chromosomes under a light microscope during metaphase. After embryonic or fetal demise, culture failure is common and the results may be unavailable in up to 10–40% of samples. Moreover, conventional karyotyping is time consuming and expensive as it requires a highly qualified staff. The resolution is usually 5–10 Mb but when structural aberration occurs in atypical bands or the quality of digestion or dyeing during chromosome preparation is insufficient, segmental changes exceeding 10 Mb may be missed.

Other methods include whole genome approaches like Comparative Genomic Hybridization (CGH), Array-CGH, Chromosomal microarray (CMA), BAC (Bacterial artificial chromosome) on Beads (BoBs) and NGS and Targeted approaches like Fluorescence in-situ hybridization (FISH), Quantitative Fluorescence- PCR (QF-PCR), Multiplex Ligation-dependent Probe Amplification (MLPA) etc. A comparison of the advantages and limitations of the methods used in miscarried tissue analysis is presented in Table 2.

Selection of Miscarriage Tissue for Genetic Testing

The most reliable material for genetic analysis is the fetus (embryo), but its separation from the remaining miscarried tissue may be difficult or even impossible, especially in early pregnancy. Moreover, the fetus is often spontaneously evacuated from the uterus, its tissue is lost and an alternative material has to be collected.

Although chorionic villi may be easily separated from the remaining tissue, in the clinical setting, improper preparation of the sample severely affects the reliability of molecular testing in over 40% of first trimester miscarriages. To prevent maternal cell contamination (MCC), miscarried tissue should be cleaned in saline solution directly after evacuation from the uterus, and white tissue (villi) should be separated from the remaining maternal decidua and blood clots and placed in sterile saline solution. Chemical contamination (such as contact with formaldehyde) should be avoided to prevent DNA degradation.

The sample should be collected either in RPMI culture media, saline or PBS with antibiotics in a sterile container. Store the sample at 2-8 degree until transport. Transport the sample with cool packs.

Table 2: Comparison of methods used in POC testing

| Karyotyping | FISH | QF-PCR | MLPA | BAC on Beads (BoBs) | СМА |
|---|---|---|---|--|---|
| Screens all 46 Chromosomes | Quick screen for 13, 18, 21, X & Y chromosome | Quick screen for 13, 18, 21, X & Y chromosome | Screens all 46 Chromosomes | Screens all 46 Chromosomes | Screens all 46 Chromosomes |
| Can detect balanced translocations | Can detect balanced translocations | Cannot detect balanced translocations | Cannot detect balanced translocations | Can detect unbalanced translocations | Cannot detect balanced translocations |
| Cannot Detect Micro deletions / duplications | Can detect deletion & duplications only in targeted probe regions | Cannot Detect Micro deletions / duplications | Cannot detect telomeric deletion / duplications | Cannot detect Microdeletions/ duplications | Can detect Micro deletions / duplications |
| Very Low Resolution | Intermediate Resolution | Intermediate Resolution | n Intermediate Resolution | Moderate Resolution | High Resolution: 1 MB for losses, 2 MB for gains, and 5 MB for LOH/AOH (Loss/Absence of Heterozygosity) |
| Higher failure rate due to dependence on cell culture | No Cell Culture Required | No Cell Culture Required | No Cell Culture Required | No Cell Culture Required | No Cell Culture Required |
| Suitable for mosaicism | Suitable for mosaicism | Not Suitable for mosaicism | Not Suitable for mosaicism | Suitable for low level mosaicism (>20%) | Suitable for low level mosaicism (>20%) |
| Poor Genome Coverage | Poor Genome Coverage | Poor Genome Coverage | Intermediate Genome Coverage | Moderate Genome Coverage. Array detects aneuploidies and also analyses 143 chromosomal regions of known clinical significance [5]. | High Genome coverage leading to improved identification of chromosomal changes (25 markers / 100 kb of the genome). Covers 396 clinically relevant regions in the genome, especially those which are implicated in prenatal complications |
| Cannot rule out maternal cell contamination | Can rule out maternal cell contamination | Can rule out maternal cell contamination | Can rule out maternal cell contamination | Cannot rule out maternal cell contamination | Cannot rule out maternal cell contamination |
| Low Throughput | Low Throughput | High Throughput | High Throughput | High Throughput | High Throughput |

Maternal cell contamination (MCC)

The separation of the chorion from the uterine wall through the stratum spongiosum inadvertently causes rupture of the uterine vessels and high contamination by the maternal blood cells. The reported MCC of the miscarried tissue rate ranges between 4% and 47% for different centers, probably reflecting the tissue preparation process. Chromosomal abnormalities are detected in 61% of samples where first trimester villi are separated and cleaned directly after evacuation from the uterus, compared with 36% in samples routinely prepared (i.e. separated in the laboratory).



Placental mosaicism

The chorion consists of two layers: an outer formed by the primitive ectoderm or trophoblast and an inner formed by the somatic mesoderm. The trophoblast is made of an internal layer of cubical or prismatic cells, the cytotrophoblast and an external layer of richly nucleated protoplasm devoid of cell boundaries, the syncytiotrophoblast. The chorion undergoes rapid proliferation and forms the chorionic villi. In nearly 2% of cases, two or more different cell lines are present in the placenta (confined placental mosaicism). When the uncultured villi are tested, trophoblastic DNA is predominant as a result of the richly nucleated syncytiotrophoblast, while in the culture the mesoderm grows more rapidly, leading to domination of mesodermal DNA. This phenomenon explains a possible discordant result of molecular testing of short and long-term cultured villi and the fact that in direct molecular analysis, some fetal abnormalities may remain undetected. In a study by van den Berg et al., abnormal fetal karyotype was discordant with short-term cultured villi in 0.42% of cases (false-negative results) compared with only 0.08% with long-term culture.

Conclusion

First trimester miscarriage is the most frequent complication of pregnancy. Chromosomal abnormalities incompatible with life are the only undisputable cause of pregnancy loss, as opposed to maternal factors (e.g. mild endocrine abnormalities), whose role remains questionable, especially in secondary sporadic cases. The detection of numerical abnormalities allows the establishment of the cause of miscarriage and influences genetic counseling, especially in recurrent cases. Moreover, genetic testing of the miscarriage enables the detection of the causes of otherwise unexplained recurrent pregnancy loss and decreases the prevalence of unexplained cases to less than 25%, which is important for psychological reasons as well as for clinical evaluation.

Conventional karyotyping is the gold standard for genetic testing. However, its clinical usefulness is limited by possible culture failure, poor metaphase chromosome quality, maternal cell overgrowth, and time and labor consumption. Array-CGH and chromosomal microarray are becoming the most efficient method of testing nowadays. They overcome the necessity of tissue culture and allow for the rapid detection of aneuploidies, unbalanced structural changes and submicroscopic abnormalities. However, the clinical significance of some of these abnormalities is unknown, while others may be benign, making the interpretation of the results challenging. Furthermore, female polyploidies, tetraploidies and balanced changes remain undetected and other methods are needed (e.g. flow cytometry for polyploidy detection).

Next generation sequencing may contribute more to the knowledge of the genetic pathogenesis of miscarriage, but it is currently only used experimentally, mainly because of its high costs. The efficacy of chromosome region specific molecular methods like MLPA, QF-PCR, FISH etc is limited and none can be used alone as a diagnostic tool. However, they are valuable screening methods, as a great majority of genetic abnormalities in miscarriage tissue are simple aneuploidies.

Genetic diagnosis should be offered in first trimester pregnancy loss, especially in recurrent cases. The material for testing should be properly prepared. Knowledge of the pathogenesis of a miscarriage, as well as advantages and limitations of diagnostic methods, is necessary for appropriate genetic counseling.

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From our Colleague

A trek into the divine serenity of Himalaya!!

by Udita Mahadevia, Scientific Communications



Trekking for me is an art of walking amidst lush greenery, rocky roads and snow-covered mountains. Trekking can be quite an exciting and thrilling experience as it inculcates a sense of adventure, value of physical exertion, sometimes to the limit of endurance, a spirit of comradeship and realization of one's responsibilities towards the cleanliness of the nature.

This is from my recent trip to a spiritual place called Sri Narayan Ashram (SNA), an ashram built by my Guru, in the Kumaon Himalaya, close to Nepal border and on the way to Kailash-Mansarovar. The ashram is located at a height of ~9,000 ft above the sea level.



This was my 8^{th} visit to the place. I still have vague memories of being carried by my father on his shoulders during my first ever-trekking trip. I used to hold his hand and walk around the mountains with baby steps. From then to now, 24 long years and I was back to the same place with my parents, but this time it was my turn to take them around the place.

We had taken up 2 treks from SNA in a span of 3 days; one was a 7 kms trek in the mountains to the nearest villages-Sirkha and Sirdang which took us about 3 hours. This was only a warm up for our actual trek scheduled the next day to the place called Narayan Peak, situated at a height of ~11,000 ft above the sea level.

The trek path all through was narrow, had slippery grass, stones and was filled with moss-coated rhododendron trees, which made it tough to walk. Walking along the mountain ridge, at the height of 11,000 ft in the Kumaon Himalaya, Uttarakhand was by far the best experience of my life. Even at that height we were still in a valley, surrounded by the sun-kissed snow covered peaks of Nanda Devi, Panchachuli, Api-Nampa, Om parvat, etc.



It took us about 5 hours to reach close to the peak, and that last slope before we could actually experience pure bliss, seemed the toughest as we were tired, exhausted and drained. After taking a halt for a while, few of us headed towards the peak. Finally, after so many years, standing on that peak, surrounded by other snow-covered mountains gave a sense of satisfaction, thrill and joy. A sense of being away from the hassles of the world, breathing the purest form of nature in absolute silence and feeling alive in the true sense.



I joined MedGenome recently and was very excited to know there are people who have the same passion for trekking as me. Here are some of their experiences.





Sneh: "Located around 125 kilometres from Bengaluru, Ramanagara is a perfect getaway from the bustling cities, breathe in the fresh air away from the stifling city crowds and revel in the peacefulness of the mountains. Enriched with a history connecting it to the famous Hindu stories of Mahabharata - the Pandavas and their mother Kunti, after whom the village and the rocky hills have been named, this trek becomes even more appealing and fascinating.

The trek starts from Kunti Betta base, a trail through the rocks, boulders and shrubbery growth that lies towards the base of the hill. The night is pretty exciting as you sit next to the bonfire sharing stories, it's a breathtaking visual to feel the height unravelled when the dawn sets in, the difficulty level is a bit higher for first timers but it is definitely a next door getaway for rugged adventurers. Light weight-baggage, trekking shoes, chilly breeze, lush bouldering mountains, night sky, and twinkling stars accessorize your making it a thumbs up adrenaline rushers...."





Susan: "Avalanche forest, Ooty is 30Km further from Ooty and is an amazing forest area. I and my group had the pleasure of trekking way inside the forest and pitching our tents in the camp site which was in the middle of the forest. There was a mixed feeling of anxiety and excitement. Anxiety because there were only 4 people who knew the trekking trail way inside and out from the camp site and so in case of wandering away from the group, means we are lost in that thick forest. And excitement because there were adventurous activities that we were going to do along with our friends. We got to do kayaking, archery, abseiling and gorge walking. These were so helpful in making ourselves to go past our fears and limitations. Our fear of water and heights were challenged to its maximum. But there was a joy in overcoming them. The beautiful Avalanche lake where we did the kayaking was surrounded by mountains and tall trees. Sitting in the kayak you would want nothing more than staying in that place forever, away from the regular busy city life. We also did a night trekking with just the stars leading our path and some of us were lucky enough to see shooting stars. Sleeping inside the tent was another exciting thing. We could see shadows of wild boars and creepy crawlies near our tents. Surely there were tiger roars heard, probably they were enjoying a surplus meal in the dark of the night. It was cold inside the tent still we slept because of the long tiring activities we did everyday. Returning back there were lessons that were learned. Learnings that the best team player is the one who walks with the slowest and weakest person in the team, including them and helping them in the strenuous way and also that if we do not take up challenges we will never know how best we can perform. It was one of the best experiences of life reminding me personally again that we need just the basic necessities of life to be happy. The rest everything complicates our lives. Simple life is the most content life"

From our Colleague

Exercise at workplace

by Malaichamy Sivasankar, Genome Analyst



The ergonomics process identifies and controls risk factors related to the workplace. Stretching and warm-up exercises is one of the elements which is crucial to reduce the fatigue caused by long hours of work. But this does not replace an ergonomics improvement process – they enhance it.

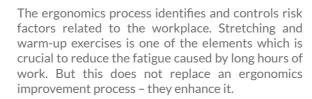


Ergonomics is the science of designing the workplace to fit within the capabilities and limitations of team members. The goal is to make sure the work fits the worker, thereby reducing injury risk and promoting safety, productivity and quality of work.



Sitting at a desk or computer or standing at your work station for extended periods of time can cause muscle tension, stiffness and strain in the neck, arms, wrists, hands, back and legs. Inactivity or being sedentary increases the pressure on spinal discs by about 40 percent more than standing. As a result, the pelvic muscles become tight and when a person stands after sitting for long periods of time, the body is off balanced, causing stress to bones and muscles.

"Benefits of stretching at workplace," include:







It is recommended to take short stretch breaks at least once per hour. Taking frequent, shorter breaks where you can regularly relax and stretch your muscles is preferable. If your job is system based, you should try taking a 5 minute break every 30-40 minutes spent on the computer. Spontaneously stretching any area of the body that feels tense will also help reduce pain and stress on your muscles.

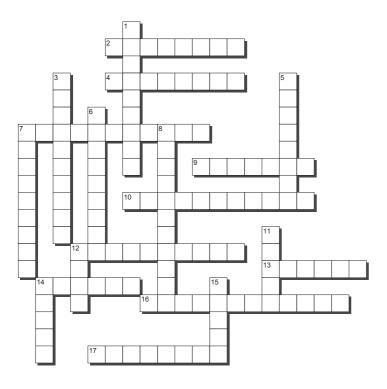
- Reduced risk of cumulative trauma disorders, such as rotator cuff injuries, tendonitis, tennis elbow and "Blackberry" thumb
- ✓ Reduced workplace stress
- ✓ Improved worker productivity
- ✓ Frequent stretching keeps a proper blood and nutrient supply to the working muscles and tissues throughout the workday and prevents fatigue and discomfort and reduces the risk of MSD injuries while reducing stress and increasing energy
- ✓ It stimulates the formation of synovial fluid in the joints, which acts to make the joints easier to move, thus reducing pain and stiffness

Making sure your team members are physically fit is essential in order to promote a healthy and safe work culture

Employee connect

Genomics puzzles

1. Mendel puzzle



[Across]

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

[Down]

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

2. Find the word

Genetics and Adaptations

| S | P | N | R | М | 0 | P | D | 0 | E | 0 | G | Α | I |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| c | D | S | S | Ε | G | G | 0 | G | S | P | 0 | L | P |
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| 0 | Т | D | R | R | D | Ε | Т | S | 0 | Т | Z | Z | P |
| М | U | Ε | Ε | I | I | S | R | I | М | P | S | 0 | E |
| E | R | Ε | Т | N | Т | N | Α | P | 0 | Α | S | Ε | S |
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| Z | I | В | Н | Ι | Т | P | Т | Α | I | Α | М | P | U |
| Т | Ε | Н | 0 | R | М | I | S | Α | E | D | F | Т | N |

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CHROMOSOME
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Photo feature













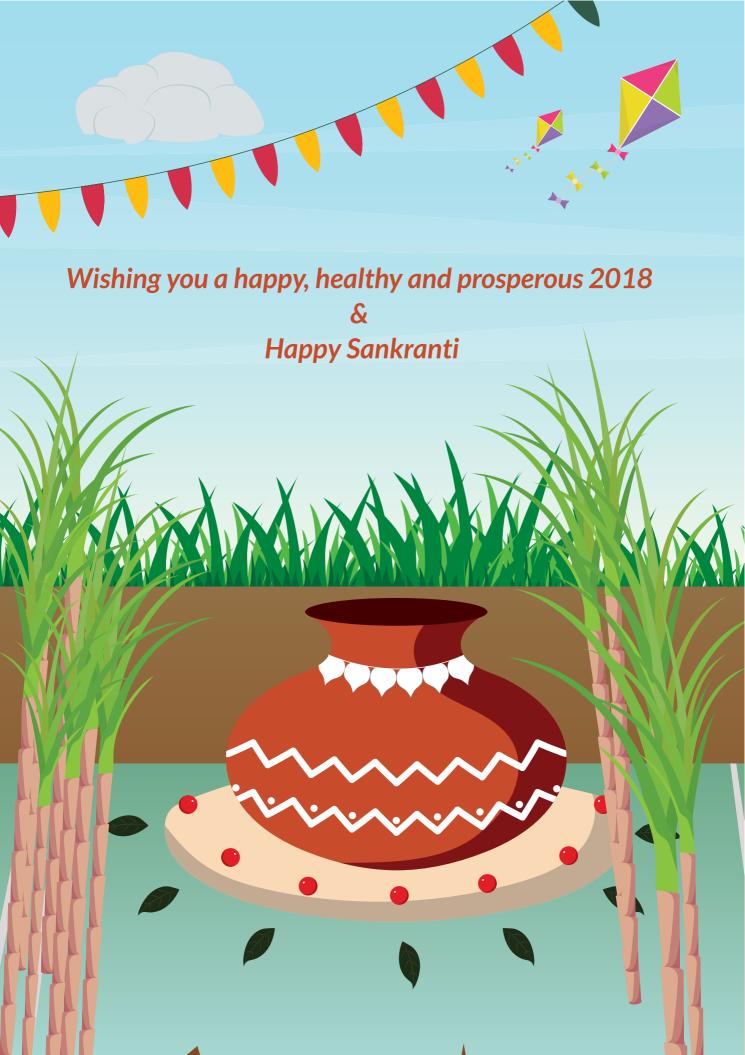














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