Personal Genomics In Clinical Medicine: It Is Not In The Future Anymore

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The decade following the International human genome sequencing initiative, which drew the blueprint of the human genome, has seen tremendous advancements that has made genomics fast, cost-effective and therefore in some terms equitable [1]. These approaches which enabled the improved scale, cost effectiveness and therefore its utility and implementation has been popularly dubbed Next Generation Sequencing (NGS) approaches [2]. NGS approaches has the potential to tremendously revolutionize clinical medicine, as imaging has revolutionised clinical medicine almost a decade ago.

One of the major applications that has found popular clinical utility has been for the precise diagnosis of genetic diseases. Genetic diseases are uncommon occurrences in clinics. Though individually rare, the total number of individuals suffering from one of the 7,000 odd genetic diseases known to human is quite significant. It is estimated that in a country like the United States of America one in every 10 individuals suffer from a rare genetic disease. The total number of individuals suffering from genetic diseases worldwide is estimated to be 300 million. Conservative estimates suggest that India is home to over 70 million people suffering from genetic diseases, and approximately a tenth of the global numbers [3].

Briefly genetic diseases can be caused by errors in the nuclear as well as the mitochondrial genomes. The nuclear genome is encoded in 23 pairs of chromosomes in the nucleus. This genome encompasses approximately over 3 billion alphabets of four nucleotides (A,T,G and C) and is present in two copies, one each inherited from our parents. The mitochondrial genome, by comparison is quite small and resides in the organelle called mitochondria, which are entrusted with the production of energy in the cell. They are otherwise called the powerhouses of the cell. The mitochondrial genome has just over 16,000 nucleotide bases and a circular chromosome. Despite its small size, mitochondrial genetic defects are quite common, approximately 1 in every 2000-5000 live births, resulting in a spectrum of diseases known as mitochondrial diseases.

The errors can range from chromosomal abnormalities to single nucleotide changes. Chromosomal abnormalities have been possible to identify, thanks to well utilized approaches for karyotyping and fluorescent in situ hybridisation and very recently chromosome microarrays. While detection of
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single nucleotide changes in genes have been quite difficult, costly and with poor diagnostic yield till very recently, the advent of NGS has seen the revolutionization of their detection, thanks to unbiased approaches like whole exome and genome sequencing approaches.

The next section describes the clinical utility of NGS using a real-life case example.

A middle aged family from a village in western India consulted a dermatologist at a medical college department in Pune. Two kids born out of a non-consanguineous marriage had scale like appearance of the skin, and after multiple consultations with doctors in local hospitals were unable to arrive at a definitive clinical diagnosis. A consultant prescribed the family karyotyping, promptly revealed a chromosomal duplication, in the apparently normal father and both kids. However this did not provide any clue to the disease. The family was desperate to have a normal kid. The smart dermatologist promptly diagnosed the condition as Lamellar ichthyosis, a genetic disease inherited in an autosomal recessive manner.

Cases like this offer a peek into the general situation of genetic diseases in India. While it is widely emphasized that "prevention is better than cure", it has not been widely practiced for such diseases. Firstly two affected kids point out to a systematic lack of counseling, genetic testing apart. The cost burden on the family for treatment of the kids with retinoids is approximately around 50,000 INR per year, which is a significant amount for a majority of individuals, especially from rural India. In practical sense appropriate counseling would have avoided the second pregnancy and would have significantly reduced the burden of disease in family and the antecedent costs.

The doctor put the kids on retinoids, to which the kids reacted well. After further counseling the doctor explained the possibility of genetic testing with the family.

Lamellar ichthyosis, as mentioned earlier is inherited in an autosomal recessive manner. Appropriate genetic testing using conventional approaches would ensue sequencing of 9 genes (Richard and Sherri. 2014) totalling to approximately over 101 pathogenic variations spread over 400 exons. No prioritization of variants could be possible because no basal data on the common variants in the Indian population was available in literature. The case was referred to CSIR Institute of Genomics and Integrative Biology (CSIR-IGIB) under the GUaRDIAN initiative for sequencing as part of the ongoing research programme.

What is GUaRDIAN?

GUaRDIAN is the acronym for Genomics for Understanding Rare Diseases India Alliance Network. GUaRDIAN is a consortium of clinicians and researchers, presently encompassing over 20 clinical and research centers in India, and is one of the largest networks in the field in the country. The consortium aims at using cutting edge genomics technology to enable identification of genetic variations in diseases and enable clinicians arrive at precise diagnosis for rare genetic disease.

Any clinician, department or clinical center is welcome to be part of the consortium. Interested participants should be willing to be part of and contribute to the general cause and follow the common standards of the community. You could find more information on the consortium at URL http://guardian.meragenome.com.
Enter next generation sequencing. The family was promptly taken up for exome sequencing. The sequencing revealed a single nucleotide mutation in TGM1 (Transglutaminase 1) gene confirming the diagnosis of Lamellar Ichthyosis [4]. Further screening of the family revealed both parents were carriers for the mutation, while both kids were homozygous for the mutation. Counseling and discussion with the dermatologist was advised.

**What is exome sequencing?**

Exome sequencing is a methodology which involves capture of genomic loci which encode for proteins (exons) followed by high throughput sequencing. A comprehensive overview of the technology and its utility is reviewed by the authors [5]. From the first report of its utility in 2009, exome sequencing has now become the mainstay in aiding clinical diagnosis of genetic diseases. The quick adoption of the technology has been largely due to the cost, ease of use and interpretation and coverage/comprehensiveness in terms of covering a large proportion of the protein coding genes. It also offers a value for money compared to the still costly whole genome sequencing, which is yet to be widely adopted in clinical settings due to the cost, complexity and analytical issues.

The family came back to the clinic a few months later. The kids’ mother was pregnant again. The case was referred to a consultant who offered amniocentesis and prenatal testing for the mutation. The fetus tested heterozygous for the mutation. Months passed, and a baby angel with normal skin was delivered early December 2015.

This example offers a few pointers and learning points. (i) Genomics has the potential to reduce the health care costs, and avoid preventable morbidity through technology, thus making lives more productive. (ii) Whole genome/whole exome sequencing for genetic diagnosis is now available in India, and is rapidly revolutionizing the diagnosis of rare genetic diseases. (iii) Molecular diagnosis of the disease would enable a desperate family to have a normal child, unaffected by the disease. (iv) Identification of the mutation would enable the drastic reduction in costs for prenatal testing and carrier screening, thus making it affordable and provide equitable access. (v) The reduction in cost has made access to the genomic technology quite equitable, with potential to benefit a larger number of people for whom it can make a real difference.

To enable the wide utility of genomic technology in clinical settings and help families suffering from genetic diseases and clinicians who see and care them a collaborative research framework was initiated by the Council of Scientific and Industrial Research (CSIR), called the Genomics for Understanding Rare Diseases - India Alliance Network (GUaRDIAN) [6]. This network today has over 60 clinical collaborators from over 20 centers across the country, making it one of the largest genetic networks of its kind in India. The network collaborates with clinicians like you who come across families suffering from rare genetic diseases, and would badly need a molecular diagnosis. If you would come across a family suffering from rare genetic disease, please feel free to contact us and refer them to the programme. The genomic analysis is performed free of cost to the patient.

Personal genomics was perceived to be an elitist concept till very recently. When our groups sequenced the first human genome in India [7], it was not uncommon for people to question the utility of such an expedition which was of-course expensive and considered egalitarian [8]. Little did people realize that the cost of genome sequencing was on a slippery slope, and was expected to reach the common man in a decade or so. The expedition paved way for the development of expertise in the area that benefits the country through infrastructure and expertise to handle genetic diseases in everyday clinical setting.

The drastic reduction in costs and advances in technology is slated to bring the cost of genome sequencing even further, and revolutionize clinical medicine, not only in the spectrum of rare genetic
diseases, but also fields as varied as oncology, microbiology and the likes. It is not too futuristic to think someday every individual would have access to his genetic blueprint which would enable clinicians to access relevant genomic information to enable prescription of the right drug, at the right dosage, and avoid potential preventable harm through prediction of adverse drug events to specific drugs or formulations [9].

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6. Available at: http://guardian.meragenome.com/

