Perspectives on Translational Genomics and Public Health in India

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Key Words

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Abstract

It is now recognized worldwide that anticipation and prevention of diseases have significant advantages for the health and healthy ageing of the population. Early recognition of the disease in a vulnerable population such as in children aged <5 years and adults aged >60 years enhances our preparedness for any eventualities and future burden of the diseases to society. It is also recognized that current public health practices alone cannot bring about the desired outcome. When tackling public health-related issues, such problems must be recognized and state-of-the-art principles and innovations from genomic sciences, information technologies, and medical specialties must be encompassed and embraced. These will enhance strategies for preparedness and provide us with a better understanding of how to identify, manage, and control disease burdens. The ever expanding landscape of genomics research also includes experimental and computational approaches for effectively utilizing DNA sequence information. From these perspectives, the intricacies of Mendelian single gene disorders are the least challenging compared to intricacies of multi-dimensional host factors for infectious diseases or complex disorders

such as cancer. The concepts of public health in India are on firm footing; however, integration of contemporary advances to implement public health principles into practice has neither been attempted nor impacted on disease burden or our preparedness to prevent eventualities. At the same time, translational genomics is gradually paving the way for personalized medicine. Principles of personalized medicine remain to be fully understood and practiced despite the pharmacogenomics-based future of drug development, and treatment has not been as exciting as the advances in genomics we are witnessing today. The relevance, importance, and translational impediments of these advances will be discussed.

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Introduction

The completion of the Human Genome Project (HGP) provided us with an array of genomic tools for a better understanding of risks, disease progression, and improved clinical management. The post-HGP era facilitated several significant scientific innovations towards the

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improvement of human health through the use of genomics and family history for diagnosis, prognosis, and effective clinical interventions [1, 2]. This has also ushered a new era of 'personalized translational genomics' focusing more on causes and consequences of as well as possible interventions for polygenic disorders, such as cardiovascular disease, diabetes, cancer, schizophrenia, obesity, and many more, catering not only to the needs of individual patients but also benefiting whole populations [3, 4]. Today, translational genome research is not just limited to understanding the variations that occur in an individual's genome but also extended towards its manifestation in the expression, its translation to basic metabolic machinery, and its impact on the metabolic profile to understand the disease biology. However, the challenge remains to bridge the gap between genomics and public health by giving a physician, in a globally accepted language, all the information collected through 'omics' and information technologies to improve diagnosis and treatment, thus reducing health care costs and improving health outcomes.

In many countries, several challenges exist in order to bridge the gap between genome medicine, translational research, and public health, and in India, these are:

- 1 Etiological heterogeneity of the common diseases.
- 2 Lack of clear understanding of the possible underlying gene–gene and gene–environment interactions.
- 3 Requirement of large clinical and population-based cohort studies for meaningful translation of genomic information into clinical practice and personalized medicine.
- 4 Scarcity of advanced bioinformatics analysis support for the integration and translation of diverse information and data into new knowledge and its application for clinical practice.
- 5 Lack of trained health professionals for genetic counseling and creating awareness on genetic testing across socioeconomic strata.

India, one of the most populated countries in the world, with several ethnolinguistic groups, presents a significant challenge to implement translational genome-based medicine due to its genetically heterogeneous population [5, 6]. Apart from geographical and linguistic divisions, the Indian population has been diversified by caste and religion with a variable degree of endogamy [7]. There is also a very high report of consanguinity in some communities, resulting in genetic disorders in clusters with founder mutations [8]. Among the reported genetic disorders in India, Down syndrome, thalassemia, hemophilia, and muscular dystrophy are the most frequent in

urban areas [9–11], which is largely due to the availability of appropriate medical services. To date, there is no complete treatment for Down syndrome and muscular dystrophies, while treatments for hemoglobinopathies and other disorders are beyond reach for the common population [12]. Over the last decade, increased awareness and more practices in the area of molecular genetics, cytogenetic, biochemical genetics and, more recently, genomic technologies have immensely helped to provide affordable diagnosis of several genetic disorders; however, this process has been slow and the services are not readily accessible, especially in rural areas. Prenatal diagnosis of lethal, incurable, and chronic disabling genetic diseases will provide assurance of having an unaffected child for high-risk parents, further reducing the socioeconomic burden of affected children. One of the major challenges in India is the lack of knowledge and general indifference in the majority of the population, including medical professionals, the public at large, and government bodies, to the potential benefits of application of genomics to the field of genetics for public health. Although the high cost of genetic tests and the lack of their accessibility are a major hindrance, the lack of exposure to medical genetics/genomics in medical education and trained personnel in the specialty is also proving to be the major obstacle in the Indian scenario. The primary role of genetics in public health lies in the recognition and prevention of disease but, currently, not necessarily its cure. Therefore, it needs to be taken up as a public health measure for the prevention of lethal genetic disorders, malformations, cancer, and other debilitating disorders.

Over the past two decades, the government of India has initiated several focused genome-based research and development programs for rapid diagnosis, prognosis, and translation of monogenic and polygenic genetic diseases with the aim to develop cost-effective disease management. The majority of the research on cost-effective rapid diagnostic tests and interventional strategies for various genetic disorders are financially supported by the Task Force on Human Genetics, Genetic Research Center (GRC) under the Indian Council of Medical Research (ICMR), a national body governed by the Ministry of Health and Family Welfare, Indian Union. Government agencies that fund research and translational research on monogenic, polygenic, and infectious diseases are, among others, the Department of Biotechnology (DBT), the Department of Science and Technology (DST), and the University Grants Commission (UGC). Some of the notable programs that have been supported by the GRC and ICMR Task Force in recent years are the development of

a new diagnostic method for hemoglobinopathies, a large-scale population-based screening program for thalassemia carrier status, and a study on the effectiveness of genetic counseling [13, 14]. These activities are primarily aimed at integrating cutting-edge state-of-the-art genetic services into India's health care system.

In the past few years, concerted efforts from genome biologists, geneticists, and biotechnologists supported by government agencies and private bodies have achieved a significant improvement in the development of advanced protocols and tools for genetic screening for inborn errors of metabolism, prenatal testing for birth defects, and chromosomal disorders, as well as screening of the adult population for various genetic markers, including those for cancer and cardiac diseases. More recently, several laboratories have undertaken an evaluation of clinically relevant variations in genes of drug-metabolizing enzymes and their relevance to drug effects in clinical practice. The outcomes of such studies have not only reinforced the need to discover and practice pharmacogenomics in the clinics but also to add more data of clinical relevance [15]. However, much needs to be done to evaluate strategies for a better management of genetic disease and public health in India. The relevance, importance, and translational impediments of these strategies will be discussed.

Genetic Disease Burden in the Indian Population

With a population of over 1.21 billion people, India represents about one sixth of the world population. The Indian population consists of a number of endogamous groups, which contributes to the burden of recessive diseases [16, 17]. Among them, the congenital and hereditary diseases are predominantly reported in urban areas. In the urban Indian population, congenital malformations, birth defects, and genetic disorders constitute about the third most common cause of mortality and morbidity [9, 18–23]. This high prevalence is primarily attributed to the high birth rate, decrease in infant mortality rate, consanguineous marriage, and the lack of experienced health care professionals, trained geneticists, and counselors in India. Since the last decade, there has been a significant decrease in infant mortality attributed to infectious diseases and malnutrition in India. However, the rate of mortality due to birth defects has remained the same. It has been estimated that almost half a million infants were born with malformations, with more than 20,000 reported cases of Down syndrome [24, 25]. The most common

malformations reported in several multi-centric studies were musculoskeletal disorders as well as neurological and neural tube defects [26–29]. The overall prevalence of neural tube defects in the Indian population is estimated to be 4.5 in 1,000 total births [30]. Among the monogenic disorders, thalassemia and sickle-cell disease are common in the Indian population [31–33]. About 7,000–12,000 babies are born with β -thalassemia major and more than 5,000 cases with sickle-cell disorder in India [31, 34–35]. In the past two decades, clinical studies from government and private medical centers on metabolic screening of newborns highlighted the four most common disorders: methylmalonic acidemia, hyperglycinemia, homocystinuria, and maple syrup urine disease [36–38]. Research is also focused on diagnosis of dysmorphology and its genetic causes. Van der Knaap disease, calpainopathy, recessive forms of osteogenesis imperfecta, progressive pseudo-rheumatoid arthropathy of childhood, and Handigodu disease are some of the conditions relatively common in some parts of the country [39–42]. Chromosomal aneuploidy, microdeletion syndromes, birth defects, familial cancer, and associated monogenic syndromes were also commonly referred to genetic studies and genome analysis.

Noncommunicable diseases account for nearly half of all deaths reported in the Indian population. Among them, cardiac diseases reported for 52% mortality followed by chronic obstructive pulmonary disease, various cancers, and diabetes mellitus. The projection shown in previous studies suggests a steep increase in the burden of noncommunicable diseases [43–45]. Due to the rapid rise of heart disease, stroke, and diabetes, the impact is to the tune of 237 billion dollars during the years 2005–2015 (WHO) [46].

Translational Genomics: Present Status

India is the second largest population in the world, has a significant socioeconomic disparity, and is experiencing an increasingly high rate of infectious and chronic diseases. In an emerging economic country like India, the import of expensive technologies and therapeutics is becoming difficult due to the enormous costs. In order to address these issues, India is trying to implement biotechnological advances in the field of medicine. One such effort is the Indian Genome Variation consortium (IGVDB, <http://www.igvdb.res.in/>), which has developed a large-scale Indian population-specific database of genomic diversity to facilitate various aspects of pharmacogenomics

and personalized medicine. The technological advances in the field of human genome research for the diagnosis, prognosis, and therapeutic outcome coupled with the declining cost of genome sequencing are facilitating the use of these technologies in clinical practice. Since there are no comprehensive written guidelines for genome analysis, more and more industries are offering such services. However, the implementation of translational medicine is hampered by the dissemination of information and lack of evidences to show a decreased disease burden and improved clinical outcome. Other challenges include the quality of the genomic data from the laboratories, the management of genomics information and its association with specific diseases, and the awareness among health care professionals and patients to use the genomic information and policies for data sharing. Therefore, efforts are needed to (a) reach harmonization of service practices for reliability, (b) increase awareness among patients and health care providers, (c) develop mechanisms to share data, (d) develop mechanisms to manage affordability, and (e) implement the right practices.

International Landscape

Several international agencies, such as the European Alliance for Personalised Medicine (EAPM), the European Association for Predictive, Preventive, and Personalized Medicine (EPMA), EuropaBio, the Genomic Medicine Alliance (GMA), the International Rare Disease Research Consortium, the Global Alliance for Genomics and Health (GA4GH), and EuroGentest, are involved in population-scale genome sequencing and analysis for pharmacogenomic application, developing new diagnostic and therapeutic strategies and professional guidelines for diagnostic DNA sequencing [47]. It has been predicted that, in the next 3–5 years, there will be considerable gain in the availability of molecular diagnostic resources, particularly in the area of pharmacogenomics, identification and detection of pathogens, genetic counseling, and electronic medical records with the goal of enhancing the clinical decision support. Towards this, several projects were implemented involving whole-exome or transcriptome sequencing in cancer genomics and pharmacogenomics [48]. Moreover, a number of projects focused on geographical priorities [49, 50]. In the United Kingdom, one such large effort is to sequence 100,000 whole genomes by 2017, focusing on NHS patients with cancer, rare genetic disorders, and infectious diseases ([http://www.genomicsengland.co.uk/the-100000-genomes-](http://www.genomicsengland.co.uk/the-100000-genomes-project)

[project](http://www.genomicsengland.co.uk/the-100000-genomes-project)). Other European countries are also undertaking such efforts, like Belgium through its Belgian medical genomics initiative (BeMGI), which encourages clinicians and researchers to use genomic technologies in translational genomics (www.bemgi.be). Similarly, the Estonian government has sanctioned a pilot program of sequencing 5,000 Estonian genomes and the development of the Estonian Biobank (www.geenivaramu.ee/en). In Israel, the Clalit health system provides medical colleges with sequence-based panels for assessing somatic and germ line changes for cancer risk and therapeutic response by testing for founder mutations (<http://www.clalit-global.co.il/en>). The newly developing comprehensive cancer centers in Australia use genomics-based cancer research in patient care. Some of these data are available through ClinVar or dbGaP, containing genotype and phenotype correlations (www.ncbi.nlm.nih.gov/clinvar). In Canada, the Genomics and Personalized Health Competition (GAPH) funded 17 projects in an effort to understand the role of genomic medicine implementation in patient care with the help of 19 biotechnology-oriented companies (<http://www.genomecanada.ca/en/portfolio/research/2012-competition.aspx>). In Japan, several genomics-focused biobanks have been established, consisting of genomic variation databases and conducting studies for clinical efficacy and utility of genomic medicine in clinical practice (<http://www.src.riken.jp/english/project/person>).

In addition to these programs, highly focused pilot studies were also executed before implementation of full-scale programs on disproportionate disease burdens. For example, at Luxembourg's Centre for Systems Biomedicine, experts in neurobiology and pathway analysis in community-driven annotations generate a genetic and molecular interactive map in Parkinson's disease (www.en.uni.lu/lcsb). The interactive map will consist of genomic sequencing data for early diagnosis and stratification of patients. Similarly, PersonalizedOMIC Lattice for Advanced Research and Improving Stratification (POLARIS) is a pilot project in Singapore involving sequencing of transforming growth factor- β to evaluate the genetic risk for stromal corneal dystrophies (<http://research.singhealth.com.sg/Pages/polaris.aspx>).

Thailand's Ministry of Public Health and Ramathibodi Hospital are focusing on Stevens-Johnson syndrome/toxic epidermal necrolysis and launched a 'pharmacogenetics card' consisting of patient's HLA variant information, predicting the risk of contracting Stevens-Johnson syndrome/toxic epidermal necrolysis and specific drugs. Electronic Medical Records and Genomics (eMERGE)

network (<http://www.genome.gov/27540473>), the Pharmacogenomics Knowledgebase (PharmGKB, <https://www.pharmgkb.org>), the Implementing Genomics in Practice (IGNITE) network, the GAPH, IRDiRC, and GA4GH are some of the databases that contain genomic or translation medicine information [47]. However, such efforts need to be implemented in the Indian scenario.

Recently, several genome research projects have been initiated from low- and middle-income countries. Some of the major genome analysis programs include Human Heredity and Health in Africa (H3Africa), the Qatar Genome Project, and the Mexico National Institute of Genomic Medicine (INMEGEN) [51].

The Indian Scenario

There are lessons to be learned and examples to be taken from worldwide efforts on translational genomics. However, these need to be tailored to the needs of the Indian population. While the Indian population is riddled with disorders of all types and magnitude, we will limit this discussion to genetic disorders, although infectious and tropical diseases are equally life threatening and a scourge to the population. The burden of emerging, re-emerging, and periodic outbreaks of diseases is also a serious threat. Considering that there are 4,635 anthropologically well-defined human populations, which includes 532 tribes and 72 ancestral tribes with a total population density of 1.21 billion people [7], India faces the challenge of diverse genomic structures. With the majority of Indian societies being endogamous with rigid social customs, the distribution of genetic variations is not always universal but depends on local cultural practices. A high prevalence of specific disorders is also recorded in pockets of communities, which requires in-depth study. Genetic services in India have started as small genetic units in medical schools in some of the major cities, testing for neural tube defects and hemoglobinopathies as well as screening for mental retardation as initiated primarily by the ICMR in the early 1980s. These services have expanded enormously over the last three decades, and at present, the majority of the medical hospitals attached to schools have clinical geneticists and basic researchers working together on various genetic disorders through molecular investigations. Medical genetic services are currently available sporadically in different parts of the country, and some of the clinicians also practice clinical genetics independently. Genetic sonograms, prenatal diagnosis coupled with molecular and cytogenetic analy-

sis, and management of various genetic and nongenetic disorders are routinely performed [52]. Similarly, technologies such as copy number variations (CNVs), exome sequencing, targeted resequencing, as well as microarray and metabolome analysis are also sporadically but increasingly being practiced for the diagnosis of prenatal disorders, complex diseases, and various types of cancers among many others [53, 54]. Moreover, geneticists also provide genetic counseling services to the patients. Diagnostic facilities are available as a part of the genome analysis unit or independently, comprising cytogenetic, molecular, and biochemical genetics diagnostic tests, using contemporary technologies. In addition, there are private laboratories specialized in providing medical diagnostic services. However, most of the facilities with high-throughput genome analysis technologies are confined and affordable to few people living in the cities and are beyond reach for the larger population.

Translational Genomic Studies in India from a Clinical and Laboratory Perspective

The prevalence of most of the disorders in India does not deviate significantly from that in other countries. Approximately 2% of newborn cases are reported to have single gene and chromosomal disorders, while around 3% of couples have risk of having children with recurrent conditions. Approximately 30% of serious chronic conditions and over 1,400 common single gene disorders are often associated with possible genetic variants. To cater to the increasing demand, efforts are underway to establish centers that provide genetic and genomic services as well as a centralized diagnostic facility serving multiple hospitals. For clinical service involving multiple hospitals, especially in resource-limiting scenarios, it has been proposed to have a minimum of 1 medical genetics expert, more than 1 genetic counselor, as well as supporting staff. Laboratory service should be mandated to provide state-of-the-art technologies in the area of genetic and genomic tests and their analysis.

In India, health services are provided to the general public by the Government of India via the Ministry of Health and Family Welfare and by private sectors by various corporate organizations. India, Asia's third-largest economy, spends approximately 1% of its GDP on health care in comparison with China (3%) and the United States (8.3%). Moreover, the state governments also manage the health budgets separately. India provides free or highly subsidized health care service to economically de-

prived groups through various health care programs implemented via secondary and tertiary hospitals and primary health centers for urban and rural populations [53]. These centers are often associated with doctors and health professionals trained at medical schools who conduct both medical and basic research. In India, the Ministry of Health and Family Welfare under the Central Government is primarily involved with the planning and delivery of health care services. However, the executions of these programs are managed by state governments [54]. Due to budget insufficiency, only 25–30% of the population is able to access this system. The majority of health care is provided by corporate/private health services to cater to the need of the population. In urban areas, super specialty hospitals provide state-of-the-art medical care, which is primarily accessed by the economically privileged population. Medical care in India is either funded by individuals or through the employer, and medical insurance has begun to take shape. Both the Medical Council of India and the National Board of Examinations are involved in developing guidelines for medical practitioners and courses in medical institutions.

The major issue has been that the spectrum of variations/mutations in defective gene(s) is not uniform across the population for the reasons described above, and this lack of consistent hotspots demands integration of contemporary genomic technologies. These activities require integration of state-of-the-art genomic solutions into India's health care system.

Major Hurdles in Translational Genome Medicine in India

The slow progress of translational genome medicine in India requires a boost to achieve greater heights, and this is not insurmountable. Specifically, the following efforts need to be made: (1) generating public interest, (2) maintaining a large pool of trained health care professionals and counselors, (3) lowering the cost of genome tests and increasing their accessibility to the population across the socioeconomic strata, and (4) creating a population-wide health-based genome registry.

The basic and advanced laboratory facilities in three major areas of gene-based diagnosis, such as cytogenetics, biochemical genetics, and genomics, require trained professionals as well as advanced instrumentation in clinical research facilities to provide reliable results within a reasonable time. High-throughput tests, such as microarrays and DNA sequencing, demand quality control, a major

requirement for accreditation and monitoring of results [55, 56]. It is also noted that the genetic counselors play a significant role in discussing the utility of the results, interpreting the results, maintaining the confidentiality to protect the individuals, and suggesting necessary action to be taken. Medical professionals are relied on to make decisions, but they are not adequately trained to handle genomic medicine and are already overburdened with clinical practice. The recent increasing trends in self-motivated personal genome analysis and the resulting data are likely to improve the situation. Nevertheless, there is a need to create a new breed of 'genome analysts' to facilitate appropriate clinical translation. Besides, in India most of the genome-based tests are not covered by the health insurance provided by the major companies. This is a major issue, not only in India, but in several countries across the world. In India, there is also a lack in community genetic services due to a paucity of resources [57]. This is compounded by several cultural, religious, and social issues, which play a major role in the management of genetic diseases and birth defects.

Another challenge in translational genome medicine is the implementation of collaborative network-providing clinical and laboratory resources on rare and common disorders reported in the Indian population. This can only be achieved by generating curated clinical databases to be of any benefit. Recently, a few databases on Indian genome variation and genetic disorders have been made available to the public. Among them, the Indian Genetic Disease Database (IGDD; <http://www.igdd.iicb.res.in>), which provides a curated repository of mutation data reporting over 50 different genetic diseases in the Indian populations [58].

Ethical Concerns and Societal Acceptance

In India, ethical issues related to genetics and genomics-based analysis are governed by the 'Statement of specific principles for human genetics research' by the ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2000) and by the 'Ethical policies on human genome, genetic research and services' by the DBT, Government of India (2002) [59, 60]. Numerous challenges exist in implementing a public health genomics program in India, such as lack of appreciation and acceptance by clinicians and individuals due to lack of knowledge, scanty clinical data, general mistrust, and unavailability of utility framework underlying its relevance. Moreover, ethical principles related to public health application need fur-

ther refinement. The major ethical issues raised against implementation are the confidentiality and privacy of genomic information, intellectual property rights, allocation of resources apart from genomics, awareness of the public about the strengths and weaknesses at the population level, cost of genomic tools, and public opinion on individuals' genome information in the public domain as databases and effectiveness of genomic tools to improve the existing gaps. A national bioethics committee, the ICMR, and DBT, Government of India, have formulated policies in ethics involving research using human samples for genetics and diagnostics. Disclosure of the right to know, privacy and confidentiality, privacy/stigmatization/discrimination, autonomy, psychological distress, human dignity, and cost-effectiveness are all to be considered [61]. Moreover, germ line gene therapy and therapy for enhancement, regenerative therapy, biopiracy, and genetic information for warfare are some of the other major concerns pertaining to translational genomics.

Future Directions

Several approaches can be taken to establish public health infrastructure and other public and private networks to support the translation of genomic information to improve public health in India. One such approach is establishing partnership with academic institutions and government health departments, which can explore avenues for genomic research that utilize existing newborn blood spots as well as childhood birth and disease registries in order to generate data on the local population

cluster for genetic risk and disease prevention. Community-based research programs can be initiated with the help of government agencies to bridge the gap between health professionals in the community, academic partners, and public health practitioners. In developing countries such as India, where the economic constraints coupled with an inadequate scientific and industrial base lead to poor capacity to utilize genomic knowledge and technology, the concern for intellectual property rights and high cost of goods and services are the major impediments for the implementation of nationwide public health genomic programs. Moreover, the lack of adequate knowledge and awareness of both the public and medical profession has resulted in neglecting children with genetic disorders and the geriatric population. Vulnerability to commercial exploitation, a lack of quality genetic services, the socioeconomic background of the participants, and family social structure influence the implementation of public health genomic programs in India. These issues remain to be systematically addressed and resolved.

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