Review

Pharmacogenomics, Theranostics and Personalized Medicine - the complexities of clinical trials: challenges in the developing world☆

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ABSTRACT

While the potential for the application of pharmacogenomics and theranostics to develop personalized healthcare solutions is enormous, multiple challenges will need to be addressed to get there. Understanding the complex interactions and detailed characterization of the functional variants of individual ADME (Absorption Distribution Metabolism Excretion) genes and drug target genes is needed to demonstrate clinical utility, using both a bottoms-up as well as a top–down approach. Clinical trials need to be designed appropriately so as to identify not only individual but also population variations. The impact of non-genetic and environmental factors, epigenetic variations and circadian rhythms on an individual's response need to be assessed to make pharmacogenomics clinically indicated. More advanced algorithms and appropriate study designs need to be developed to allow this pipeline to grow and to be used effectively in the clinical setting.

Another challenge lies in the value proposition to the pharmaceutical industry. Fearing the impact of the slice and dice approach on revenues, companies are going slow on developing pharmacogenomic solutions; yet many are hedging their bets, amassing huge amounts of single nucleotide polymorphisms (SNP) data. They are being used as predictors of drug efficacy and safety to zero in on subpopulations that are at risk for either a bad response or no response in clinical trials, supporting the *Fail fast*, *Fail cheap* approach. In addition, the growth of theranostics is impeded by the fear that the approval of both the diagnostic and the drug would get delayed. Education of the health care provider, payor, regulator and the patient is also required and an exercise of change management needs to occur.

Countries such as India should exploit the joint benefit of the reduced cost of tests today, complemented by a large and a highly genetically diverse population.

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1. Introduction

Pharmacogenomics has been described differently on various occasions as an area of fevered speculation, intense hype, the path-breaker of the future — and probably all of them are partly true. In a world that is becoming increasingly individual centric, patients are demanding

individualized therapy, with safer and more guaranteed outcomes. To quote Sir William Osler, "If it were not for the great variability among individuals, medicine might as well be a science and not an art" (Frueh, 2005). Pharmacogenomics and theranostics are paving the way for personalized medicine. While the global pharmaceutical market is approximately worth $825 billion, up to 40% of the medicines that individuals take every day are not effective, resulting in losses of up to $400 billion (India accounts for 20% of the world population, but shares only 2% of the global pharmaceutical market, primarily for generic drugs) (Banerjeee, 2011). Even more worrisome is the fact that phase II success rates are as low as 18%, with 20% of medications failing in the case of cancer chemotherapy and 23% in the case of patients with diabetes in phase II trials. The failure rate went up to about 50% in phase III, with 60% drugs failing due to a lack of efficacy and 21% failing due to safety concerns (Gitig, 2012). Notably, the number of drugs receiving approvals in India (by the Central Drugs Standard Control Organization) per annum following the conduct of clinical trials has decreased from 60 in 2009 (http://www.taxindiaonline.com/RC2/inside2.php3?filename=bnews_detail.php3&newsid=15712) to 28 in 2012 (http://cdsco.nic.in/listofdrugapprovedmain.html). In addition, several medicines have known side effects, and side effects are considered to be between the fourth to the sixth biggest cause of avoidable deaths and costly hospitalization in the US (Lazarou et al., 1998). The teratogenic risks in human pregnancy of over 90% of drug treatments approved in the USA in the last decade are yet to be determined (Banerjeee, 2011). Patients often invest in medications that not only do not yield results owing to the way individuals respond differentially to different drugs, but may also often suffer from severe and in some cases irreversible side effects as a result of the same.

Ten percent of FDA approved drugs (approximately 200 drug labels) carry pharmacogenomic information in their labels (Zanger, 2010) and metabolizing enzymes account for 80% of drugs which have pharmacogenetic data in their label (Brandi et al., 2012). More than 650 drug-related variants have been identified for their clinical relevance (Banerjeee, 2011).

2. Clinical trials and factors impacting response to therapy

Various factors impact a patient's response to a drug. These include not only his genotype, but also non-genetic and environmental factors, including sex, age, diet, lifestyle, and even the intestinal microflora. Epigenetic changes can influence expression patterns in a time-, environment- and tissue-dependent manner. Circadian rhythms also markedly change gene expression patterns of many ADME genes (over 300 have been identified to date) thereby affecting pharmacokinetics and drug response in a time-dependent manner (Zanger, 2010). Some well-known food–drug interactions, such as those of grape fruit juice, as well as black tea with the Cytochrome P450 enzymes or vitamin K rich foods such as broccoli and spinach with warfarin, can significantly impact a patient's response to drugs (Webb, 2010).

In pharmacogenomic studies, it is important to study not only the individual SNPs, but haplotypes (statistically associated SNPs or co-located alleles) as well, making the HapMap an important element in the diagnosis of disease. The human exome, representing only 1% of the human genome, accounts for approximately 85% of disease causing mutations (Dolled-Filhart et al., 2012). With both the speed of molecular discovery increasing exponentially (in parallel with the costs), one may feel that we are at the brink of finding the solutions to all our problems.

Next-generation rapid sequencing (NGS) technology is likely to bring the cost of sequencing the human genome from $2.7 billion, to potentially $ 1000 and global pharmacogenomic testing of an individual could cost less than $ 100. Interest in pharmacogenomic profiling for drug dosing and drug selection is expected to grow as awareness increases and costs decrease. Currently, the National Human Genome

Research Institute (NHGRI) Genome Sequencing Program estimates that its per-genome cost is $7666. Illumina, whose HiSeq DNA sequencing systems produce the bulk of the human genome sequence reads, is offering the same for as little as $4000 in bulk, while Complete Genomics is charging $5000 or less. The $10 million Archon X Prize competition scheduled to occur in September 2013, requires a team to produce 100 human genome sequences in 30 days or less, at a maximum cost of $1000 per genome sequence (with an error rate of at least 100 kb and at least 98% completeness). While we may thus reach the $1000 genome target in the near future, the criticality however lies not only in sequencing the genome, but in interpreting the data — leading to the '$1000 genome–$1 million interpretome' paradox (Perkel, 2013).

Global revenues from clinical trials are expected to reach $32.73 billion in 2015 and to exceed $65 billion by 2021 (India and China show a Compounded Annual Growth Rate of more than 20%) (http://www.visiongain.com/Report/973/Pharma-Clinical-Trial-Services-World-Market-2013-2023). A study across 12 leading pharmaceutical companies from 1997 to 2011 demonstrated an average spending of $5.8 billion per drug (Mapes, 2012) and trials account for nearly 60% of the drug development cost. The Associated Chambers of Commerce and Industry in India (Assocham) has reported that almost 100 global and local pharmaceutical companies are conducting clinical trials in India, resulting in revenues of close to $1.6 billion. With close to 150,000 people enrolled on the same, the norms for the conduct of these trials are going to become stricter in the near future. Diseases such as malaria, chicken guniya, tuberculosis, kala azar (visceral leishmaniasis) and head and neck cancer are more prevalent in India and trials need to be conducted to develop therapies to meet the needs of specific strata of populations (http://www.business-standard.com/article/economy-policy/govt-tightening-clinical-trial-norms-112080602002_1.html). An increasing number of these will be pharmacogenomic trials, involving biomarkers and companion diagnostics.

2.1. Factors impacting the design of pharmacogenomic trials

Various factors need to be kept in mind while designing pharmacogenomic trials. It is desirable to choose a genetically homogenous population as far as possible, as differences in ethnicity may impact the response to the drug. Appropriate population stratification is thus important. While several disease associated biomarkers have been identified, it is desirable to assay some markers that are not associated with the disease to maintain a negative control as well. Irrespective of the type of trial, the biomarker should be evaluated for predictability and clinical validity. Methodological bias is also an important consideration, especially in the case of retrospective analyses/meta-analyses, and the use of a centralized measurement facility for evaluating biomarkers is desired; alternatively pooled datasets based on predefined criteria need to be carefully selected to reduce some types of bias. It is also desirable to use the drug of the same brand to avoid the confounding effects of variable bioequivalence (Brandi et al., 2012).

The impact of variations in the prescribed dose over the duration of the illness would also impact drug response. Metabolic enzymes and transport proteins may be quantitatively and qualitatively different in pediatric/elderly populations (EMEA Guideline, 2011) and interpretations regarding safety and efficacy in such trials need to take due consideration of the same. Drug–drug interactions occurring during multi-drug therapy need to be carefully assessed. The definition of the disease is also important as different variants of the gene may result in different diseases. Thus the statistical power of the trial would depend on the accurate definition of the disease. The sample size should be adequate to account for the effects of genotypes/alleles/haplotypes on the outcome analysis. A larger sample size may be required to assess adverse drug reactions (ADRs), as compared to the attainment of response. When multiple mutations are involved in determining the outcome to be assessed, then a diagnostic test that assesses the phenotype is better than the one that assesses the genotype (Adams, 2008).

2.2. Diagnostic tools: DNA chips, microarrays and biomarkers

Genome-wide (GWA) association studies play a key role in determining biological genotype–phenotype correlations, and diagnostic tools are required to effectively translate these into clinical care, simultaneously addressing multiple confounding factors — and this is where the challenge lies. Challenges from a clinical trial perspective for GWA studies include the small sample sizes resulting from a small population demonstrating the rare ADRs (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC30039490/) (addressed through national and multinational consortia) and the difficulty of replication of results, a lack of rare or even less common (<5%) variants on the microarrays (addressed through NGS or the mapping of the individual's genome), and heterogeneity. Finally, advanced algorithms need to be defined which will allow one to interpret the multifactorial nature of drug response phenotypes, while correlating data from biological gene networks. Complex genetic influences from multiple minor impact genes, entire pathways, or gene–gene and gene–environment interactions could thus be identified (Zanger, 2010).

Variants of drug-metabolizing enzymes impact drug response, meaning that some individuals are ultra-rapid metabolizers and others, poor metabolizers of specific drugs, and the variance directly impacts the bioavailability of a drug and thus both its efficacy and its toxicity. For example, 105 variant alleles of CYP2D6, a class of drug-metabolizing enzymes found in the liver (with one or more point mutations), have been identified (Adams, 2008). DNA chip microarrays, which can screen up to 100,000 SNPs in a few hours, can be used to diagnose these phenotypic variations. The chip developed by Affymetrix for example (DMET Plus) covers 1936 genetic variants (including SNPs and copy number variations) across 231 relevant genes (including a 100% coverage of PharmaADME "Core ADME Genes" (32 genes) and 95% coverage of PharmaADME "Core Markers" (185 variants) (http://www.affymetrix.com/estore/browse/products.jsp?productId=131412#1_1)). The 'Core ADME genes' and 'Core Markers' are basically a list of a list of genes and genetic biomarkers that could be screened using today's technology platforms to identify predictors of pharmacokinetic variability, and thus promise to improve the drug development process by enabling the design of safer and more effective drugs for particular subpopulations. This list was generated by PharmaADME, an industry–academia effort that was launched to develop a consensus, "Core List" of standardized "evidence based" drug metabolizing (ADME) genetic biomarkers that are broadly applicable to many pharmaceutical clinical trials and FDA drug submissions (http://www.pharmaadme.org/joomla/).

Attrition rates in phase II trials have been very high as adequate efforts have not been invested in clinical validation at the start (Haberman, 2009). The economics of trials drives the need to fail fast and fail early (Chew, 2010). Translational research leverages biomarkers across the stages of the clinical development plan from target identification to assessing the effects of hitting this target on the pathophysiological mechanism and on determining how altering this mechanism would affect the clinical outcome — thus defining the likelihood of success of a candidate drug. Translating research from bench to bedside has become a criticality. The most frequently cited success story is that of the HercepTest®/trastuzumab (Herceptin®) combination from Dako and Genentech/Roche for the Her2-positive subset of breast cancer patients. Another example is that of Imatinib (Glivec™, Novartis), a synthetic tyrosine kinase inhibitor, which is used in the management of interferon-resistant chronic myeloid leukemia (CML) and is now, considered as the drug of choice for metastatic and inoperable gastro intestinal stromal tumors (GIST) (Nair, 2010).

At the end of the day, conclusive interpretations based on data drawn from the integration of genomics, proteomics, metabolomics, and epigenetics, and the use of companion diagnostics or theranostics together are going to help define the right target population and this, complemented by the appropriate study design, and a well-executed clinical trial, will help translate research to positive clinical outcomes.

2.3. Leveraging biobanks and databases: collaborating for the future

Biobanks, if linked to Electronic Medical Records, would play a key role in the translation of genotypic–phenotypic data to clinical therapy and thus personalized medicine. Challenges that prevail include informed consent, ensuring patient confidentiality, the issue of donor's rights, the management of incidental findings, the need for interoperability between research and clinical databases, the high-power computing that is required to manage this data, and the related socio-commercial aspects which makes one wonder whether the $1000 genome sequencing will require a million dollar investment for the meaningful interpretation of this data (Davies, 2010). Over a billion dollars have been invested in the past ten years in the biobanking industry, and the global market for biobanks is forecast to reach over $22.3 billion by the year 2017 (http://www.prweb.com/releases/biobanks_cord_blood_banks/stem_cell_banks/prweb8831399.htm).

At least 179 biobanks exist in the US and the Taizhou project in China is expected to cover the entire population of the country (http://www.reportlinker.com, 2009). Kaiser's Research Program on Genes, Environment and Health (RPGEH) attempts to triage genetic, environmental and medical information, to allow for better interpretation of health outcomes and has also resulted in the largest DNA biobank in the US. Similarly, Genethon (Paris) is one of Europe's largest cell and tissue repositories (Scott et al., 2012). Important biobanking projects in Asia include NUS-NUH Tissue Repository, SingHealth Tissue Repository, Singapore, UMCRI Tumour Tissue Bank, Cryocord Premiere stem cell bank, Malaysia, RIKSEN Bioresource center cell bank, Japan; Institutional Tissue Bank Fudan University, China Cord Blood Corporation and China and National Biobank of Korea (NBK). Some of the biobanks in India include NIMHANS, Bangalore (the brain biobank), ACTREC, Mumbai (cancer biobank), ORBO (Organ Retrieval Banking Organization), AIIMS, New Delhi, the National Repository for Cell Lines/Hybridomas, NCCS, Pune and the Mycobacterial Repository, JALMA, Agra (Ravishankar, 2012, http://www.biospectrumasia.com/biospectrum/opinion/1750/biobanking-attractive-prospects-asia).

Companies such as Genset SA (recently acquired by Serono SA), DNAPrint, genomics, deCODE genetics, Genaissance Pharmaceuticals Inc., and Oxagen Ltd., as well as pharmas such as GlaxoSmithKline and Novartis AG invested in building SNP databases. The SNP Consortium has published more than a million SNPs on the web (Branca, 2002). The $120 million Human Genome Project involving 700 scientists from the US, Canada, China, Japan, Nigeria and Kenya recently sequenced the complete DNA material of more than 1000 people from 14 population groups in Europe, Africa, East Asia and the Americas. Scientists have identified 38 million variations in the DNA accounting for about 98% of all the estimated human variation in the world (htttp://online.wsj.com/article/SB10001424052970204707104578090863855010972.html). The Cancer Genome Atlas is an effort to collect more than 20,000 tissue samples from more than 20 cancers, and identify cascades of genetic changes that give rise to tumor growth (http://cancergenome.nih.gov).

The Indian Genome Variation (IGV) Consortium, a government-funded collaborative program among six laboratories of the Council of Scientific and Industrial Research (CSIR) aims to provide data on validated SNPs in over a thousand genes in 15,000 individuals (Dhar and Joseph, 2012). HUGO (Human Genome Organization) the first-ever human genome sequencing project in India, driven by scientists at the Institute of Genomics and Integrative Biology (IGIB), New Delhi has been completed (BioSpectrum http://www.biospectrumindia.com/biospecindia/news/156732/indias-r-d-the-future-forward). The Indian Council of Medical Research (ICMR) has recently set up a new task force on pharmacogenomics to focus on specific research topics in the field of pharmacogenomics and will also work on the development of an 'Indian pharmacogenomics chip' (http://www.thehindu.

com/todays-paper/tp-national/tp-tamilnadu/icmr-sets-up-task-force-on pharmacogenomics/article575518.ece?textsize=small&test=2).

As more and information becomes available, the need for accessibility of information becomes important. Pharmacogenomics Knowledgebase (www.PharmGKB.org) is a publicly available repository for pharmacogenetic and pharmacogenomic data and serves as an interactive tool for researchers investigating how genetic variation effects drug response and has been funded by the NIH (Mc Donagh et al., 2011).

2.4. Cutting it fine — stratification, a key to personalized medicine

As clinical utility is demonstrated and the benefits of pharmacogenomics start to be realized for both individuals and health care systems, issues of data ownership and multiple commercial implications and other ethical issues arising from clinical applications come into the picture. While the 'slice-and-dice' approach (involving market segmentation as a result of developing personalized therapies) raises obvious commercial concerns in the pharma industry, and also raises ethical issues about racial profiling, this approach obviously stands to benefit key segments of society owing to their genetic differentiation. For example, heart failure rates are high in African-Americans, as they appear to have a much lower response rate to angiotensin-converting enzyme (ACE) inhibitors, the conventional therapy for heart disease. The drug BiDil, was developed to treat congestive heart failure in a defined sub-population (http://www.scientificamerican.com/article. cfm?id=race-in-a-bottle&print=true(9/21/2009). Another example of a selective response of sub-populations is that of "Ancestral North Indians" (ANI), which are genetically close to Middle Easterners, Central Asians, and Europeans, as compared to "Ancestral South Indians" (ASI), which are as distinct from ANI and East Asians, as they are from each other. It has been reported that up to 30 essential drugs are not effective on 13% of Northern India's population (Reich et al., 2009). Community intervention design, in which a region or a hospital performing pharmacogenetic analyses are compared to other region(s) and hospital(s) that are not performing such tests, would also help contribute to such analysis (Brandi et al., 2012). Thus, one could visualize that despite stratification of a huge and a genetically diverse Indian population, each segment would still represent a large enough slice to draw commercial benefits, and yet benefit society as well. The criticality would be to make this affordable to the masses and yet profitable to the industry, especially in a geography where there is very little healthcare coverage.

2.5. Pharmacogenomics — India, a key destination

Various companies globally, including those in India, have started investing in pharmacogenomics, such as Xcode Lifesciences (which uses InDNA technology to provide solutions for lifestyle-related diseases such as coronary, diabetes and obesity using saliva samples, https://xcode.in/), NutraGene (which launched the country's first commercial Type 2 Diabetes Genetic Scan based on a buccal (cheek) swab sample — individual tests cost below Rs7500, and include complimentary genetic counseling, http://www.nutragene.com/), Acton Biotech, Pune (which offers genetic tests to predict response from chemotherapy drugs such as gefitinib and cetuximab), OncQuest Laboratories, Mumbai (which brought Imatinib Resistance Mutation Analysis for chronic myeloid leukemia to the market and has launched several pharmacogenetic tests including those for Irinotecan toxicity, warfarin dosing and Clopidogrel dosing, www.oncquest.net/), TCG Life Sciences, Advinus Therapeutics and Jubilant Biosys, Bangalore. Avesthagen, Bangalore is running the five-year, $32 million AVESTAGENOME Project. AVESTAGENOME is a system biology-based study of the Parsi population (a genetically homogenous population of about 69,000 people) to determine the genetic basis of longevity and age-related disorders (Murarka, 2012). Thus, India is rapidly building therapeutic, diagnostic and infrastructure capabilities in this space, and various companies (http://www.actonbiotech.com/

pharmacogenomics) supporting the same have been established. Ganit Labs is a genome sequencing and translational genomics lab, based out of Bangalore (http://www.ganitlabs.in/), ABC Genomics, based out of Lucknow provides low cost in situ synthesized custom microarrays for all available sequenced genomes (http://www. abcgenomics.com/), Geneombio Technologies, based out of Pune, provides predictive genetics and pharmacogenomic services, including gene based prediction for genetic susceptibility towards major life style diseases such as osteoporosis, insulin resistance and cardiovascular disorders and also undertakes drug toxicity studies based on specific CYP and/or pathway gene analysis (http://www.geneombiotechnologies.com/about-us.php), and Xcelris Genomics (Bangalore), provides "application focused" research in Next Generation Genomics (http://www.xcelrisgenomics.com/). Sandor Proteomics is a contract research and diagnostic center based out of Hyderabad. It focuses on the discovery of biomarkers pertaining to human health and agriculture and has been accredited by NABL (National Accreditation Board of Laboratories) as a diagnostic center for inborn metabolic errors (http://www.sandor.co.in/aboutus-proteomics.html) whereas Sandor Medicaids provides logistics solutions to manufacturers in the medical device and hospital supplies industries that look for a temperature sensitive environment for their products (http://www.sandor. co.in/aboutmedicaids.html). Mitra Biotech, based in Bangalore, is a Indo-US translational biology company focused on developing personalized treatment options for cancer. Jai Health launched Jai-Heart, the first genomic based risk estimation solution for heart disease developed specifically for the Indian, South-east Asian and Middle East population, based on a simple saliva test (Vyas, 2012).

However, to realize improved outcomes and cost savings, one needs to implement not only the scientific advances discussed above but changes to health care systems and practice patterns as well. Change management, patient and physician education, competitive pricing, regulations to ensure appropriate informed consent processes, privacy protection concerning the use of genotype information in multiple studies and data ownership, are critical to support the growth of this domain to benefit India. Key institutes, such as the CSIR-Institute of Genomics & Integrative Biology (IGIB), based in Delhi, a premier Institute of Council of Scientific and Industrial Research (CSIR), are also engaged in research on areas such as genomics, molecular medicine, bioinformatics, proteomics and environmental biotechnology.

India has recently established the Translational Health Science and Technology Institute (THSTI) at Gurgaon, Haryana as an emerging health biotech science consortium with the intent of translating science and technology into clinical practice (http://www. clinicalresearchsociety.org/translationalmedicine). Aravind K. Tripathi, senior researcher, Cancer Profiling & Pharmacogenomics Division, Acton Biotech has reported the lack of exposure of molecular biology among doctors, the high costs of these tests as compared to the cost of treatment, longer turnaround times, the lack of bedside technologies, lack of skilled manpower and the smaller market size; and hence the lack of investment in marketing these tests, as some of the key challenges impacting the growth of pharmacogenomics in India (Jahanara, 2010).

Clinical trials in India are regulated by the Drugs and Cosmetics Act 1940, amended 2005, and must also comply with the Ethical Guidelines for Biomedical Research on Human Subjects 2000 (adopted by the Indian Council of Medical Research, ICMR) and the Good Clinical Practices (GCP) 2001 guidelines (adopted by the Ministry of Health). All research proposals for human trials must be approved by an Institutional Ethics Committee (IEC) and must obtain consent from research subjects. Accordingly, each IEC must respect the standard operating procedures stipulated by the ICMR guidelines. The Department of Biotechnology (DBT) mandates that for a pharmacogenomic study to be conducted in India it should be of national relevance, and to meet this requirement, the disease under consideration should have a high prevalence in India. In addition, it is necessary that the drug under consideration should be a widely-used drug for the treatment

of the disease, and the proportion of patients who either do not respond to the drug or do not elicit adverse reactions should be high. While submitting the proposal to the DBT, it is extremely important to assess whether there may be any underlying clinical heterogeneity in the manifestation of the disease and if so, it is important to outline how it would be handled in the study (http://dbtindia.nic.in/uniquepage.asp?id_pk=41).

3. Conclusion

Rare but severe adverse events have been a major cause for drug withdrawals after FDA approval, resulting in losses of up to a billion US dollars for a pharma company. Oncology is one of the most promising therapeutic areas in pharmacogenomics, owing to the enormous tumoral genomic variability. As noted above, the success of pharmacogenomic trials will require a blend of trained clinical workforce, validated genetic tests, payors willing to fund pre-treatment tests, accessibility, and change management. The application of pharmacogenomics and theranostics could well be the key to developing patient-focused, cost effective therapies and truly translating the vision of personalized medicine from a dream to reality, not only in the United States, but also in India and the vast reaches of the developing world where the need for cost efficient and effective therapy is great. The healthcare benefits that can be leveraged even from a stratified approach, wherein patients are segmented based on genotypic/phenotypic variations, are significant, as the net population of India itself is more than 1.2 billion. While defining appropriate study designs and establishing well defined algorithms may seem like tall challenges, evidentiary requirements, like medical advice, continually change, and an important policy issue is what constitutes adequate proof of clinical utility, particularly in the developing world where innovation promises to vastly improved outcomes. Well defined regulations, establishing a skilled work force, educating the patient, healthcare provider and the payor, providing a focus on investment, cost effective solutions and ensuring patient safety and privacy will be key drivers to ensure the full recognition of the potential of pharmacogenomics and the acceptance of the personalized medicine approach in developing countries such as India. Stakeholder collaboration of payors, providers, patients, care delivery institutions, and government may be increasingly important to achieving the shared goals of improved outcomes and cost savings.

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