Stratified Medicine: Will it be the Future of Medicine?
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ABSTRACT
The art of predicting the results of any drug treatment has always been a topic of interest among the scientific community across the globe. Many diseases have been attributed to gene defects, giving rise to a whole new field of pharmacogenomics within the domain of clinical pharmacology. Stratified medicine is the science of associating such diseases with genetic defects and predicting the efficacy or toxicity of a particular drug treatment. The article provides an overview of how stratified medicine got evolved and its current and future clinical implications. It also explains how “companion diagnostics” play a crucial role in the success of stratified medicine along with its complex economics, pricing and reimbursement issues.

Key words: Stratified Medicine, Biomarkers, Companion diagnostics, Health Economics.

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BACKGROUND
Response to any treatment in the general population shows wide variations in terms of efficacy and toxicity of the drugs. Further, most of the drugs are known to have major/minor side effects or adverse effects. In this scenario, the ability to predict the outcome of a therapy would not only result in a decrease in the morbidity and mortality, but also reduce the financial burden to patients.1 Genetic studies over the years have given us the clue to this variability in drug efficacy. Many diseases across all therapeutic fields have been attributed to gene defects. It has also been shown that defective genes play a major role in regulating pharmacokinetics of a drug, giving rise to a whole new field of pharmacogenomics within clinical pharmacology.2 The science of associating diseases with genetic defects, and the consequent pharmacokinetic variations, forms the basis of “Stratified Medicine”. It involves grouping or stratifying patients based on their genetic makeup and clinical biomarkers, so as to predict the efficacy or toxicity of a particular drug treatment. This article briefly summarizes the clinical utility of stratified medicine, how it is affecting the pharmaceutical industry, and its relevance in the Indian healthcare scenario.

INCEPTION OF STRATIFIED MEDICINE
The foundation of stratified medicine was laid back in 1960s with the discovery of the estrogen receptor (ER) and subsequently its modulator drug-Tamoxifen.3 Initial work in stratified medicine involved identifying biomarkers for a disease and targeting them with drugs. The push for stratified medicine came with advancement in molecular biology and genome sequencing. Scientists were now able to link genetic defects with pharmacogenomics and drug development gave rise to this new field of stratified medicine.2 Diagnostic biomarkers are used to identify the presence of a pathological condition e.g. cellular and molecular pathology identification of cancers, troponin-I for myocardial infarction, etc.,2 whereas predictive biomarkers, which are more relevant to stratified medicine, help in grouping of patients, and linking these groups to treatment outcomes, drug efficacy or toxicity. For e.g., the anticancer drug Trastuzumab (Herceptin) shows a better efficacy in HER2, a biomarker for Herceptin efficacy, in positive breast cancer patients than in HER2 negative patients,4 or mutation in HLA-B*5701 predicts hypersensitivity reaction to Abacavir.4 Identification of predictive biomarkers and development of assays to measure them has led to rapid advancements in stratified medicine.2

Clinical applications
Oncology
Most of the clinical applications of stratified medicine are in the field of oncology. One of the initial successes of stratified medicine is the development of the anticancer drug Trastuzumab (Herceptin). 20-25% of breast cancer patients, who did not respond to standard chemotherapy regimens, were found to have high levels of a circulating protein Human Epidermal Growth Factor Receptor 2 (HER2). These patients were found to respond to Trastuzumab, which is a humanized monoclonal antibody against the HER2 receptor. Further, patients with no circulating HER2 were found to not have any benefit from treatment with the drug. Diagnostic assays using Immunohistochemistry (IHC) and Fluorescent in-situ hybridization (FISH) techniques have been developed to detect circulating HER2. These tests are now used as precursors to starting chemotherapy.5 Oncotype-Dx is a Gene Expression profiling (GEP) test widely used in the US for predicting relapse in hormone receptor (HR) positive and lymph node negative breast cancer patients. It is a Reverse-Transcrip-tase PCR test which detects levels of 16 oncogenes and 5 control genes in tumor cells, using which a Recurrence Score (RS) is calculated. Two cutoffs of the RS determine whether the patient is at a low, intermediate or high risk of relapse. Based on this score the decision of supplementing hormone therapy with adjuvant chemotherapy can be taken by the physicians.6

Another commercially available molecular test is the MammaPrint test. It is a 70-gene signature test using microarray technology. Its applica-
tion is in prognosticating and predicting cancer relapse and metastasis in hormone receptor positive or negative, lymph node negative breast cancer patients.\textsuperscript{10,11} One of the most extensively studied oncogenes is the KRAS gene. Mutations in this gene have been associated with colorectal, pancreatic, lung and many other cancers.\textsuperscript{12} Patients with KRAS mutations have shown resistance to treatment with Cetuximab, an anti-Epidermal Growth Factor Receptor (EGFR) drug.\textsuperscript{13} Tumors undergoing apoptosis/ necrosis release tumor cells into the bloodstream, which contain circulating tumor DNA (ct-DNA). Studies identifying KRAS mutations in these circulating fragments of DNA have helped identifying which patients would not benefit from therapy involving Epidermal Growth Factor Receptor (EGFR) blockade.\textsuperscript{13} Thus ct-DNA shows promise as a predictive biomarker for melanomas, ovarian, breast and colon cancers.\textsuperscript{2}

**HIV**

Abacavir is a nucleoside reverse- transcriptase inhibitor used against HIV. It has a once a day dosage schedule, relatively few drug interactions and a favourable long term toxicity profile making it a preferred 1st line anti-retroviral drug. However, severe hypersensitivity reactions occur in patients carrying the HLA-B*5701 allele, limiting its use in certain populations which carry the particular gene. Adverse effects range from fever, constitutional symptoms, gastrointestinal and respiratory symptoms which worsen with continued use of the drug, making it imperative to discontinue treatment.\textsuperscript{6} Early detection of the gene defect can facilitate starting an alternate anti-retroviral regimen, thus preventing development of resistance to the drug.

**Neurology**

Epileptic disorders are among the most common neurological diseases seen in all populations and across all age groups. Overall, seizures can be of numerous etiologies and can range from mild dizziness, drowsiness, movement and behavioral abnormalities to life threatening adverse events like Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis Syndrome (TENS).\textsuperscript{15} Several case studies show that if stratification is done before clinical trials, the time taken for regulatory approvals is much less, as compared to stratification done during clinical development or post marketing. A classical example of this is development of Zelboraf ( vemurafenib: Roche, Basel, Switzerland) which is an inhibitor of oncogenic, V600-mutated BRAF kinase, along with the Cobas 4800 (Roche) BRAF V600 mutation test. The drug received approval after just 4 months of submission and within 5 years of initiating human trials.\textsuperscript{24} Hence, pharmaceutical companies are now moving in favor of companion diagnostics with the idea of earlier entry and acceptability of a drug into the market.

**Economics of stratified medicine**

Stratified medicine brings with it new and novel concepts which promise more efficacious medicines for the patients. However, for any stratified medicine approach to succeed, an economic study of the feasibility is a must. As per Trusheim \textit{et al}, in order to be economically feasible, there needs to be a significant variation in efficacy or safety of the drug within different groups in the population. Also, the benefit derived from finding the optimal sub-populations should outweigh the costs involved.\textsuperscript{17} The pharmaceutical industry seems to have seen value in the economic feasibility of stratified medicine, as is evident from the fact that 30-50% drugs in the development pipeline are linked to biomarkers.\textsuperscript{26} However, in bringing out the new drugs, the pharmaceutical industry needs to move away from the established business models designed to serve the traditional pharmaceuticals and aimed at a wider population. Stratified medicine targets only a niche population and hence need development of smarter business models and value systems. It also represents the convergence of two business models, that of the drug and the diagnostic, before market authorization. Economic studies indicate that structure of the clinical trials and determining at which stage the convergence of the two business models should happen, are the most defining factors in successful implementation of stratified medicine.\textsuperscript{25}
In ideal scenario, the diagnostic should be validated before starting clinical trials. In this case there is no risk of the diagnostic failing during development, which would be detrimental to the pharmaceutical company as the therapy would have no value in the market without a stratifying agent. Also, phase 2 attrition during clinical trials, which is a big challenge to the pharmaceutical industry, can be minimized by better selection of patients early in the trial. The cost incurred in trials would also be reduced by smaller, better defined clinical trials. Biomarkers can serve as the surrogate end points in the trials, thus reducing the time involved. Thus, converging these two business models early in the phase of drug development is a win-win situation for the pharmaceutical company. However, developing diagnostics early in the clinical trial is more risky to the diagnostics company, given that many drugs fail during phase 1 and phase 2 of trial. Hence, not many diagnostic companies are willing to invest in co-development of the diagnostic early in the clinical trial. Also, the diagnostics are undervalued by the payers and reimbursement authorities as the value assessment of diagnostics is more cost based instead of being value based, as is for pharmaceuticals. Hence stratified medicine also calls for new value assessment systems, other than those developed for traditional pharmaceutical drugs, since the process in development of these “niche-buster” drugs is lengthy, expensive and highly uncertain.

Pricing and Reimbursement issues
The proposition of designing a therapy with a predictable good outcome has the potential to greatly improve current medical practices and to strengthen the value proposition to pricing and reimbursement authorities. However; stakeholders involved in stratified medicine are dealing in a complex web of legal, regulatory and reimbursement environments which are tailored to deal with pharmaceutical drugs, but not designed for stratified drugs and companion diagnostics. Economic stakeholders in stratified medicine include the pharmaceutical companies, diagnostic companies, the third party payers and hospitals. Pharmaceuticals and diagnostics are both assessed by different regulatory authorities within the health systems. As such, the drugs involved in stratified medicine and the diagnostic accompanying it are assessed separately by two different authorities, instead of taking a holistic view of the combination of the two. The value assessment of pharmaceuticals usually takes a value based approach, whereas that of diagnostics adopts a cost based approach, thus favoring the pharmaceutical industry. But in stratified medicine, the drug has value only if it is accompanied by a diagnostic. The third party payers too view diagnostics with a negative bias, insisting on established clinical utility and/or cost effectiveness of the test, as the cost involved in the test can adversely affect the healthcare budgets. Adding to it, few cost-effectiveness analyses (CEA) for stratified medicine interventions exist and most have led to inconclusive results. In absence of CEA, Budget Impact Assessments (BIA) gain significance for the payers, who expect that application of the test will reduce treatment costs by using effective regimens and having lesser complications of the treatment and hence less utilization of healthcare resources.

Healthcare providers and hospital are more interested in the BIA than the CEA, which for them remains the same as traditional pharmaceuticals. The cost of the stratifying diagnostic, as with other diagnostics, is determined by the DRG (diagnosis related group) fee schedule in the inpatient (hospital) setting and a code-based fee schedule in the outpatient (ambulatory) setting. These are predefined as fixed payment rate per case based on historical cost patterns. No consideration is attributed to the clinical or economic value of the test. The additional cost has to be covered up from the hospital budget, thus providing hospitals with no incentive for backing the diagnostics. This shows there is great need for holistic assessment of the value of diagnostics and reworking of the pricing and reimbursement policies for diagnostics. The current reimbursement policies do not reward the value creation and innovation involved in the diagnostics, thus dissuading diagnostic manufacturers from investing in stratified medicine. Again, the economic implications of stratified medicine cannot be evaluated on Health Technology Assessment (HTA) alone, but have an equally important ethical consideration as well. While the industry gives importance to the economic implications, the regulatory authorities and clinicians are more concerned about the ethical issues arising due to false positive/negative results of the diagnostic test. Any diagnostic test would have a sensitivity/ specificity value which would provide for false positive/negative results. Ethical issues arise when appropriate treatment is denied to a patient due to wrong results of the diagnostic test. The presence of ethical issues in stratified medicine gives its assessment a multi-criteria dimension unlike that of traditional pharmaceuticals.

Indian scenario
In India, where medical insurance is yet to make inroads, stratified medicine faces hurdles of a different type. Only 25% of India’s population is covered under some type of health insurance, either government backed schemes like Mediclaim, ESIS, CGHS or through private insurance companies. With only 1% of the GDP being spent on public health, India has a lot to fulfill in terms of basic health needs before it thinks of investing in the latest frontiers of medicine. Lack of standardization in medical practices and treatment regimens combined with medical malpractices in India, makes the private insurance companies cautious when it comes to reimbursements. For almost 70% of population who pay for healthcare “out of pocket”, accessing the costly diagnostics involved in stratified medicine remains out of bounds. For the miniscule remainder of population, who can afford to pay the price, samples need to be shipped across the country, thus burdening the healthcare system. With only 1% of the GDP being spent on public health, India has a long way to go before we can think of implementing the concept of stratified medicine. It is only the ‘crème de la crème’ of Indian society who might have access to this science which is breaking technological barriers in the developed world.

CONCLUSION
With multiple studies showing efficacy of <60% for many of the established therapeutic regimens across different therapeutic areas, there is need for advancement and acceptance of stratified medicine by the medical community. This however will depend to a large extent on ability of the pharmaceutical companies, biopharmaceutical companies and P&R authorities in bringing down the cost of the diagnostics and drugs. To meet these challenges, newer economic studies, business models and value assessment systems, suited to stratified medicine are a must. So also, stratified drugs have to be viewed as different from traditional pharmaceutical drugs by the P&R authorities and payers, giving its due in terms of value creation and innovation. In India, we have a long wait till the basic health need of majority of the population is met. Stratified medicine may only be a consideration in top tiered medical institutes and hospitals in the country.

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