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Review Article

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.[1] 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 biomarkers for the disease, and develop diagnostic assays to detect the same. At the same time, knowledge of these genetic defects and biomarkers showed targets, against which new drugs could be developed. The interplay of genetic defects, biomarkers, pharmacogenomics and drug development gave rise to this new field of stratified medicine.[2]

Biomarkers in stratified medicine

The National Institutes of Health (NIH) defines biomarker as 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.'[3] They are substances which may be identified from blood, body fluids or tissues, using biochemical, radiological or molecular testing.[4]

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.[6] 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 HER 2 receptor. Further, patients with no circulating HER 2 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.[8]

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-Transcriptase 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.[9]

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.[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.[12] Patients with KRAS mutations have shown resistance to treatment with Cetuximab, an anti-Epidermal Growth Factor Receptor (EGFR) drug.[12] 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.[13] Thus ct-DNA shows promise as a predictive biomarker for melanomas, ovarian, breast and colon cancers.[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.[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. Over time, well defined therapeutic and prophylactic regimens of antiepileptic drugs have been established in this therapeutic area. However, most antiepileptic drugs are associated with debilitating side effects and adverse events. These can range from mild dizziness, drowsiness, movement and behavioral abnormalities[14] to life threatening adverse events like Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis Syndrome(TENS).[15] Widely used antiepileptic drugs carbamazepine and phenytoin are both associated with incidence of SJS/TENS. Genetic studies have shown the incidence to be associated with HLA-B*1502 polymorphisms, which are more common in people of certain ethnicities. Defects responsible for SJS/TENS following carbamazepine therapy are more common in Han Chinese, Thai , Indian and Malaysian population;[16] whereas those following phenytoin therapy are more common in the Asian population.[17]

Defects in HLA-A*3101 predispose to cutaneous necrolysis following treatment with carbamazepine, commonly seen in Han Chinese, Japanese and European Caucasians. However this doesn't have much clinical use due to the relatively less severe nature of the reaction.[18] Therapeutic regimens for Multiple Sclerosis have been well tested over the years, with results varying among different drugs and patient groups. Some of the most effective drugs have a greater incidence of adverse effects. Alemtuzumab, one of the most promising drugs has a higher risk of autoimmune thyroiditis. Incidence of autoimmune thyroiditis is higher in patients with high levels of IL-21.[19] As treatment of Multiple Sclerosis has to be continued for a long period, using biomarkers like IFN-beta to predict the efficacy of treatment can help in making the treatment cost effective and safe.[20]

Various biomarkers and genetic mutations have been shown to be instrumental in development of Alzheimer's disease. However, in absence of effective preventive treatment they are of limited clinical use. However the knowledge of these genetic defects can lead to newer drugs for treatment and prevention of Alzheimer's Disease and other dementias.[15]

Other diseases

With more research into genomics, many new genetic defects usually represented by Single Nucleotide Polymorphisms (SNP), which are responsible for drug efficacy, are being discovered. They are potential targets for newer medicines, many of which are in the pipeline. Other significant research include genetic defects in allele CYP2C9, which affect the efficacy of sulphonylureas in Type 2 Diabetes Mellitus[21] and polymorphisms in CYP2C9 along with VKORC1, which is responsible for variability seen in dosing of Warfarin.[22]

Companion diagnostics

As new research is linking biomarkers with treatment efficacies, there is a growing interest for diagnostic assays which can detect and quantify these biomarkers. Hence, pharmaceutical companies collaborate with the diagnostics industry to come up with these diagnostic kits. Once developed, the kits have to be approved by the regulatory authorities before they can enter the market, which has an implication both on time, as well as money involved. To reduce the time taken before a particular diagnostic assay become available, diagnostics are now being developed simultaneously along with the drug or 'co-developed', and are aptly called as 'companion diagnostics' or 'theranostics'.[2] As a result, both generally get approvals and enter the market at similar times.[23] For instance, assay for HER2 (*Hercept* Test) was developed simultaneously with the drug Trastuzumab (Herceptin), and both got US approvals in September 1998.[24]

Developing a companion diagnostic for a drug also has an added advantage during the clinical trials. Patient stratification using the diagnostic can be done early during the trial itself, leading to a better patient selection. This in turn can reduce the duration and cost involved in the trial.[25] 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 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.[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 *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.[5] 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.[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 would 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.[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.[25] 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.[27] 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.[25] 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.[28]

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.[28] Adding to it, few cost-effectiveness analyses (CEA) for stratified medicine interventions exist ,and most have led to inconclusive results.[29] 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.[28]

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.[30] The additional cost has to be covered up from the hospital budget, thus providing hospitals with no incentive for backing the diagnostics.[28] This shows that 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.[28]

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.[28] The presence of ethical issues in stratified medicine gives its assessment a multi-criteria dimension unlike that of traditional pharmaceuticals.[23]

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 abroad for these specialized diagnostics. As some of these tests mandate freshly collected sample, accessing these tests is a difficult proposition for even those who wish to pay.[11]

Expecting the Indian government to help in supporting stratified medicine is an unrealistic dream with only 4% of the national budget being allocated for public health. Almost all resources of the National Health Ministry go towards setting up of health centers in rural areas, immunizations and the health programs for tuberculosis, malaria, AIDS, etc. Primary health care in 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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