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Minireview

Pharmacogenomics enhance Value of Safety to Prescription Drugs: Toward a Post-genomics Era for Personalized Medicine and Patient Care

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Abstract

Despite numerous safety regulations and a robust methodology for the testing of pharmaceuticals before and after market entry, key safety issues, such as toxicity and side effects, represent some of the major health problems with the use of various pharmaceuticals. Presently, medical errors are at a bottleneck in health cost, a factor being drug errors in medicines if they cause intolerable or dangerous side effects. As our understanding of pharmacogenomics and genetics has increased its application in clinics and preventive medicine, we have come to understand that genetics and genomics play an important role, in not only how medications function for different variations in people, but also how metabolism variance responsible for causing symptomatic toxicology can be seen. In a post-genomics era, public health is moving towards preventive health care, such as reducing medical cost in various human diseases, and defining medical risks, including misuse or overuse of drugs pertaining to genetic polymorphisms that can cause disease initiation. This short review will discuss the prevalence of genetic variation in drug toxicity, will explore some current Omics-derived methodologies used to understand its application, and predict its responses due to drugs safety based on variable genetics spectrum in personal health care. Moreover, it will make provisional guidance while consulting patient with drug complications due to its similarity versus genetic variance result in inconsistency of functional effectiveness Regarding the use of omics technologies and their application platform, it could be new avenue to improve pharmacological tolerance and reduce medical cost owing to complicated issues likely medical errors and drug errors in patient care.

Background

It is well known that the third most prevalent cause of death in the United States is iatrogenic causes, or in layman's terms, medical error increasing with health care costs [1]. The overwhelming majority of these medical errors are pharmaceutical adverse interactions or adverse drug events [1, 2]. In the United States, there is a well-regulated process for how pharmaceuticals enter the market and their safety is tested. The Food and Drug Administration (FDA) supervises a robust testing process which includes three phases of clinical trials prior to market entry, extensive review by a panel of professionals, and most importantly for the scope of this paper, extensive nationwide phase 4 training which involves pharmacovigilance and pharmaco-epidemiological assessment for risk management [3]. This is a process which involves nationwide reporting of adverse events, identifying and describing safety signals or alerts, the development of case reports and series, data mining to produce product-event combinations, conducting pharmaco-epidemiologic studies, the creation of registries and surveys, and finally the development of a pharmacovigilance plan [3].

For example, the estimated cost value of medication error were assessed using 2004-2016 data in a hospital setting to evaluate primary care. The outcome in assessment indicated that postoperative infection Pressure estimated $569 million in the general population group, and ulcers in elderly population group estimated $347 million [4].

A potential health intervention factor to prevent medical cost from skyrocketing is to consider the impact of medical errors including drug errors; it was reported that 432 FDA- approved indication reflect drug similarity, such as Look-alike, sound-alike (LASA), which may cause harmful health conditions in people, increasing medical care costs [5, 6].

These are all measures which are designed to improve the reporting, management, calculation, mapping, and ultimately to respond to pharmacological adverse events and the prediction and prevention of more events. One of the reasons that the post-market surveillance is so important is because of the fact that not every person responds to medication in the same way. Post-market surveillance is done with a much larger population,

so simply by increasing the number of people, we are able to discover genetic polymorphisms that affect the metabolism of certain drugs and the predilection for certain ethnicities to respond in different ways to drugs. The inherent risk involved in this is high and is one of the reasons that post-market pharmaco-epidemiologic surveillance is so critical.

Problem and Objectives

Post-market surveillance has demonstrated repeatedly that not everyone responds to medication the same way or is best optimized for treatment with a standardized regimen. But what if we could avoid the adverse events and effects of post-market surveillance? Now, in the age of genomics, is it possible for us to use genetic information on polymorphisms to predict how people respond to medications, instead of waiting for adverse events after the fact? These are the objectives studied in this paper.

Review of Current Toxigenomics, Pharmacogenomics, and Metabolomics

Even without genomic evidence, hypertensive regimens have always been specialized to different populations based on how they respond to different medications. The JNC 8 report which outlines appropriate treatment for hypertension in American patients recommends that black patients be started on a different drug regimen than white patients because of how responses vary [7]. There are many other examples of how genetic variance determines the response to different pharmaceuticals:

Tardive dyskinesia response

Tardive dyskinesia is an irreversible, disfiguring, and life-altering complication of long-term usage of antipsychotics. Antipsychotic medications act on the neural dopamine, serotonin, and alpha receptors responsible for many autonomic brain functions in order to cure diseases like schizophrenia and bipolar disorder. In patients who have been taking antipsychotic medications for many years, a small subset develop tardive dyskinesia, which involves irreversible tics of the facial, neck, and shoulder muscles that do not remit with stopping the offending agent. Psychiatrists had noticed that tardive dyskinesia was present more common in families, which was proven to be genetic by studies in 2002 [8]). First, they noticed that tardive dyskinesia incidence was correlated with the presence of polymorphisms on the serotonin 2A receptor gene. Then, by conducting genetic analysis of patients with and without tardive dyskinesia, they demonstrated that this polymorphism was correlated with the incidence. The implication here is that, had the prescribing psychiatrists been able to conduct genetic testing on this particular polymorphism beforehand, they may have pursued treatments for schizophrenia that were not antipsychotics, or have supplemented some antipsychotics with other psychotropic medications.

Dopamine D4 receptor variants

Tardive dyskinesia is not the only illness that can be directly correlated to genetic polymorphisms. Since the early 90's, a wealth of genetic information specifically targeted to psychiatric disorders and medications has been reported to such a large extent that genetic polymorphism testing is considered essential for prescribing psychiatric medications. Genetic variants in the dopamine D4 receptors were found to bind with variable intensity to the psychotropic drug clozapine, indicating a potential reason for its atypical pattern of success in treatment [9].

CYP variants

The cytochrome P450 system is a group of proteins tasked with much of the breakdown of toxic molecules as well as pharmaceuticals that enter the body. The cytochrome system (CYP) is also one of the places where genetic variability correlates directly with how drugs are distributed in our bodies. One excellent example for illustration is the CYP 2D6 subfamily of proteins, not CYP 2C9 to pharmacokinetics about diclofenac nonsteroidal analgesic drug [10], which are some of the most highly polymorphic proteins across ethnic communities [11].

Certain subsets of variants, dubbed poor metabolizers, have a 2D6 complex less active than other ethnic variants. Compared to other variants, slow metabolizers at 2D6 suffered from an overdose of the hypertension medication nortriptyline at the same doses per weight of patients who were not slow metabolizers. In contrast, there are also ultra-rapid 2D6 metabolizers such that when they were given the same doses of codeine as non-rapid metabolizers, they ended up undergoing an initial overdose of codeine, which much more side effects and no significant therapeutic benefit [11]. Fascinatingly, although the cytochromes affect metabolism of all drugs, one of the biggest areas of research correlating genetic variation in CYPs and response to treatment have been in the field of psychiatry. Since CYP variants were first discovered, an explosion in the amount of data available to assess the toxicity and efficacy of psychotropic drugs with omics testing has occurred [12]. Variants in 2D6, as covered above and 2C19 are essential to the dosing and monitoring of tricyclic antidepressant drugs, which are metabolized by those two cytochromes with varying efficacy depending on the allelic variant. 2C19 variants must be dosed individually with certain antipsychotics and selective serotonin reuptake inhibitors, and when 2D6 variants are found, they must also be tested for variance of the other CYPs. These guidelines are well established in the psychiatric literature and offer further evidence of the importance of omics.

Clopidogrel resistance

Clopidogrel is an anticoagulant medication that forms part of the mainstay of treatment for many diseases such as heart attacks and strokes. However, there are large variations in the clinical utility of clopidogrel that were recently explained by polymorphisms in the CYP system responsible for converting clopidogrel to its active form [13]. Some variants are associated with increased enzyme function, causing premature breakdown of clopidogrel and an inability to improve the anticoagulation in patients.

All the above examples were chosen for a specific reason: the genetic variations responsible for causing differential responses to treatment are easily measurable with current genetic testing mechanisms. A discussion of these testing meth-

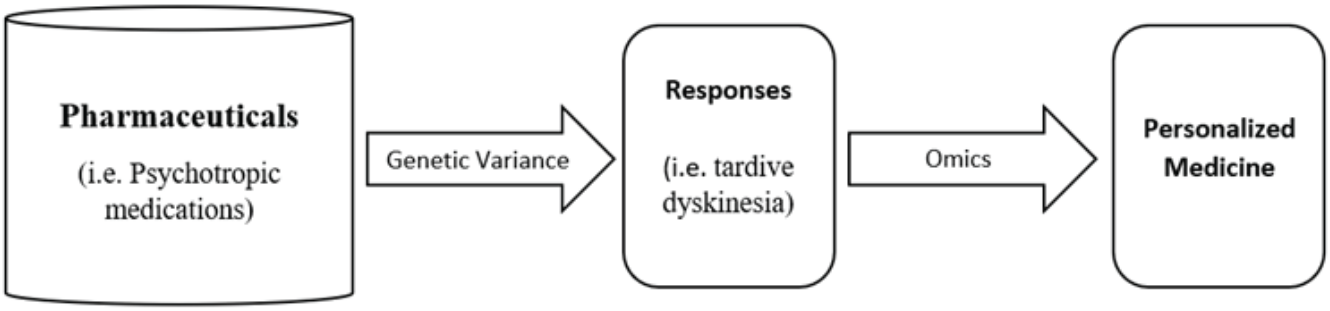

Figure 1. Path to Personalized Medicine

odologies is below, but the point here is that all of the drugs above can be directly influenced with polymorphisms, and there is an incontrovertible direct benefit from doing genetic testing on individuals receiving these drugs, as well as the opportunity to have these tests done. The next question is how we can use omics to predict these patterns and use them to influence our prescribing decisions by incorporating regular genetic testing into our treatment algorithms.

Methodologies

There are several methodologies available to providers for conducting genomic analysis of potential pharmaceutical choices. The most clinically relevant and widely available testing modality is CYP variant testing, with Amplichip as one of the predominant ones. Amplichip testing yields information at all the major CYPs to inform providers of how the patient performs at all the CYP proteins, allowing them to modify their clinical choices [14]. Genotyping panels are another way this is accomplished. There are tests of common genotypes of drug-related polymorphisms available on the market at competitive rates which can be used to predict metabolizers for certain drugs, and this type of testing is much more targeted that whole genome sequencing or exome sequencing.

Another less orthodox way to include genomics is to simply conduct text mining to look for case reports of polymorphisms more common in certain ethnic groups, which can still provide useful clinical correlates without the need for genetic testing. Text mining would simply involve PubMed searches for interactions or toxicity of certain drugs with certain CYP variants, and this would either clue the physician into the need for further genetic testing or reassure them that there is not evidence as yet to suspect genetic variance influencing metabolism [15].

While the above methods are useful for assessing the current literature, each patient remains different and the totality of genetic polymorphisms is still not yet discovered. Therefore the recommendations of the author are not to focus exclusively on genetic testing or mapping, but instead to use a combination of the best tools at out-of-disposal: this is CYP genotyping in combination with therapeutic drug monitoring (TDM). Therapeutic drug monitoring offers the best clinical way to manage how patients respond to drugs. It involves regular repeated monitoring of symptoms and clinical efficacy of the drug which, in conjunction with CYP genotyping, makes sure that the medication is being maximized for this specific patient. This is referred to as personalized medicine, where we take general standards of care and combine them with genotyping and genomics to yield the best possible result for each patient. As is the case with most genomics and omics-based strategies, the new tools are part of the package in treating patients, and not a replacement of a therapy or strategy.

Conclusions

In a pre-genomics era, health care had imposed high cost of drug evaluation due to low efficacy and lack of detection system for determining side effects in health endpoints. The first variances patterned in drug response were described by psychiatrists in wards who noticed certain patterns. Now in the post-genomics era, advanced knowledge about omics-driven health care visualizes how pharmaceuticals can impact patients, significantly expanding the bounds of genetic variation research. Therefore the cost-value of patient care should continue to develop omics technologies. But these technologies do not exist on a silo, and it should be evolving in a multi-dimensional direction. The value of omics-based strategies, as they are in all fields of health care and health management, include a safety issue, which is not to simply provide a piece of information with no relevance, but instead to contribute to the pieces of information designed to make the best possible decisions for patients to improve their quality of life implemented with omics platforms.

Disclosure

No conflicts of interest

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