



Purpose

The purpose of this review is to explain the precision medicine initiative and the implications it has for pharmacogenetics and pharmacogenomics.

Summary

Current advances in pharmacogenomics have accelerated our ability to understand the reasons behind varied response and efficacy of drugs across individuals and provide a platform to customize therapeutic approaches to the treatment of diseases based on an individual's unique genetic makeup. Two examples of the application of pharmacogenomics include knowledge about the deleterious effects of standard congenital myasthenic syndrome treatment approaches on the progression of the slow-channel type (SCCMS). Knowledge of all genetic variance of SCCMS will provide clinicians with immediate knowledge for treatment and bypass the deleterious impact that the most effective treatment for the majority can have on this minority subgroup. The second example involves an understanding of variants for genes that code for codeine to morphine metabolism and the high risk for death using normal doses of codeine in children who may be ultrafast metabolizers. While some of the genetic variants are known, many are not and the FDA has used this information to release a warning against the use of codeine in children until a reliable means for identifying ultrafast metabolizers has been found.

Implications

The ability to prescribe, design and implement customized therapies for individuals with disabilities, especially in those conditions that are heterogeneous, will improve clinical and quality of life outcomes dramatically, and prevent unnecessary harm or even death to individuals with a genetic contraindication. Precision medicine using pharmacogenomics is far improved above using the trial and error one-size-fits-all approach. Precision medicine will provide physicians with the justification needed to challenge insurance company denials of specific types of prescriptions or therapies and ultimately improve the speed in which relief and treatment and the prevention of side effects can occur.

Precision Medicine and Pharmacogenomics

by JG Andrews, MK Galindo, SA Rice

Introduction

At the beginning of 2015, President Obama launched the "Precision Medicine Initiative" emphasizing approaches towards the ability to personalize medicine based on individual variation to better improve outcomes. This is a big change from the clinical trials approach that controls for all individual variation and recommends treatment based on how it works on average for the population without accounting for biological, social and environmental differences that affect us all. While the concept of personalizing treatment approaches based on biological difference is not new, the completed mapping of the human genome in 2003 has changed our perceptions of our genome. We have learned a lot of new information regarding the many variations in the human genome that cause differences in our individual responses to the environment, stress and medical interventions.

The National Institutes of Health (NIH) is poised to launch a consumer interactive national cohort of at least one million people that will contribute data about lifestyle, environment and genetics to aid in generating new ways to advance our ability to design interventions that are "precise" to an individual. This NIH big-data cohort approach to precision medicine is called "All of Us" and is expected to begin recruitment next year. Other approaches to precision medicine involving genetics include improvements in management of disease through advances in the fields of pharmacogenomics and pharmacogenetics.

Pharmacogenomics

Pharmacogenomics is the technology of assessing how differences across the genome can affect how individuals respond to medications. Pharmacogenomics eliminates a one-size-fits-all clinical trial approach in developing and prescribing therapeutic drugs. Present pharmaceutical clinical trials evaluate the effect of medications based on the response to medications in large group trial participants. Pharmacogenomic information identifies markers in the human genome that will make individuals more or less responsive to medications and more or less susceptible to medication side effects. Pharmacogenomics involves variants in the genome that do not cause disease or deleterious conditions but simply affect how inserting an environmental influence, such as medication, into the body can generate disparate responses across individuals. Pharmacogenomics can also determine treatment response based on disease causing variants of heterogeneous conditions.

Pharmacogenomics in choice of medication: Congenital Myasthenic Syndrome (CMS)

CMS is a heterogeneous neuromuscular disorder involving genetic mutations in at least 20 different genes that leads to disruption in protein synthesis important for neuromuscular function. CMS is typically diagnosed based on clinical findings and because there are a variety of different mechanisms that can cause the syndrome, the differentiation between CMS subtype is often based on response to treatment. For the majority of CMS subtypes the most beneficial treatment includes preventing the breakdown of a neurotransmitter called acetylcholine through the prescription of anticholinesterase inhibiting drugs. Therefore, in the absence of genetic confirmation of subtype, anticholinesterase-based medications are the first line pharmacologic approach for CMS. Patient monitoring of symptoms determines if the therapy is effective or the child requires an alternative approach. Unfortunately, for approximately 30 percent of patients with CMS, treatment with an anticholinesterase can cause a significant deterioration in function for the infant or child.

This is an important example of how a treatment that is beneficial for 2/3 of a population who have a medical condition, is detrimental to the remaining 1/3 of the individuals with the same condition. Precision medicine research and interventions will avoid this “trial and error” approach and predict who will respond to a medication and who should avoid the same medication

Pharmacogenomics affecting variation in response to medication

Codeine is an opioid used in the management of mild to moderate pain and typically contraindicated for individuals who have shown to be allergic to it. Overdose of the medication can cause

decreased responsiveness, increased risk for aspiration and decreased drive to breathe deeply. Individuals have different genetic variants that can classify them as either ultra-rapid or poor metabolizers for codeine and morphine. Ultra-rapid metabolizers have an overactive variant of an enzyme called cytochrome P4502D6. They metabolize codeine and morphine more rapidly and more quickly, making a higher dose of medication rapidly available within the body under normal dosing regimens. The large dose of available morphine in an individual's body is associated with a decreased drive to breathe and ultimately death. Recently, the FDA issued a warning due to the number of deaths associated with children who are ultra-rapid metabolizers of codeine that died after using the medication for post-surgical pain. The FDA recommends that codeine be avoided in children until we have the capacity to screen for all possible genetic variants of cytochrome P450 and other enzymes associated with medication metabolism.

Implications

The implications of precision medicine go far beyond the molecular confirmation of a diagnosis. Research in pharmacogenomics can provide critical information about the genomic variations that affect response to current pharmacologic treatment recommendations and future interventions. Understanding the individual variation and the implications for drug response, metabolism and drug elimination will replace the trial and error approach to treatment of diseases and will allow us to streamline care based on the individual's genomic data.

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