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Pharmacogenomic Tests for Safe, Efficient and Cost-Effective Pain Management

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Chronic pain is one of the most significant public health problems and is a major contributor to healthcare costs in the United States. Opioids are the most commonly prescribed treatment for chronic pain. However, due to the risks associated with opioid therapy, the Centers for Disease Control and Prevention (CDC) has published guidelines (CDC Guideline for Prescribing Opioids for Chronic Pain, United States, 2016) to improve the safety and effectiveness of pain treatment by opioid medications. Inter-individual variability in opioid response is a major concern associated with this class of medications. A significant proportion of patients are unable to attain optimum pain relief with opioid treatment, while others suffer from serious opioid-induced adverse events and/or are prone to developing medication dependence. In addition to age, gender, weight, and race, genetic factors are important regulators of patients' responses to opioid treatment. According to the National Institute on Drug Abuse (NIDA) and the American Society of Addiction Medicine (ASAM), 50 percent of opioid addiction cases are related to an individual's genetic factors (Meshkin, 2015). These factors include genes that modulate opioid metabolism (pharmacokinetics), opioid receptor signaling (pharmacodynamics), and the pain perception pathway. Variability in these genes not only affects patients' pain relief response but also influences their likelihood of developing adverse drug effects and drug addiction. In Figure 1, we illustrate the impact of genetic variability on opioid response and some downstream consequences. Genetic tests that predict patients' likely response towards opioid therapy (pharmacogenomic testing) help physicians select the optimal drug therapy for a specific patient. An optimal therapy is one that maximizes therapeutic benefit, improves patient adherence, and minimizes the chances of adverse drug reactions.

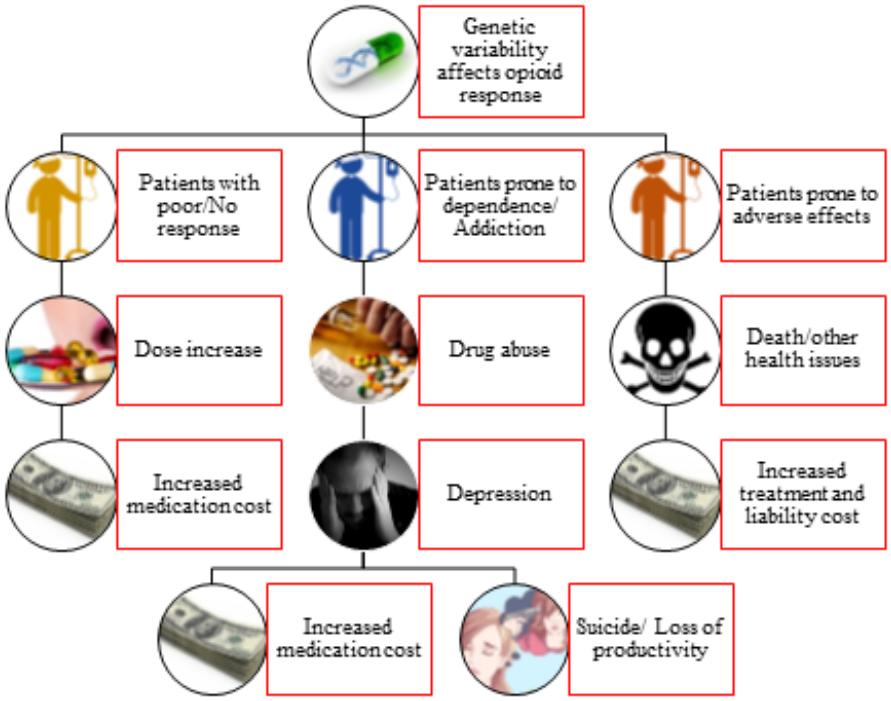

Figure 1. Influence of individual's genetic variability on opioid response and further downstream consequences.

Benefits of Pharmacogenomic Tests

Improve treatment efficacy and safety- Genetic variability has been reported to influence patients' pain perception and their sensitivity towards pain medications. Because of this variability, some patients respond poorly or do not respond at all to the prescribed dose of pain medications. Some patients may develop serious, even life-threatening side effects at relatively low prescribed doses. For example, respiratory depression, one life-threatening opioid-induced adverse effect, is the major cause of opioid-related deaths. According to the Centers for Disease Control and Prevention (CDC), more than 14,000 people died from overdoses involving prescription opioids in 2014.
As a specific example, codeine is a commonly prescribed opioid pain reliever and cough suppressant. It is normally metabolized into morphine by the enzyme CYP2D6. Some individuals (called ultra-rapid metabolizers) carry an extra copy of the CYP2D6 gene and process codeine into morphine more quickly than normal. This can result in their blood morphine levels increasing above the recommended safe limits. High concentrations of morphine can cause a person's respiration to shut down.

There have been multiple reported cases of children treated with codeine who have died of morphine-induced respiratory depression due to variability in their CYP2D6 gene. In these children, their ultra-rapid CYP2D6 metabolism resulted in a morphine overdose from a seemingly innocuous dose of codeine, ultimately resulting in fatal respiratory depression. (Ciszkowski, 2009) (Kelly, 2012). In another report, a nursing infant died after ingestion of high levels of morphine from his mother's breast milk. The mother was taking codeine and was also found to be an ultra-rapid metabolizer for CYP2D6 (Koren, 2006).

After witnessing such cases, the U.S. Food and Drug Administration (FDA) has announced a new black box warning against codeine use for management of pain in children. Codeine is one of nearly 150 FDA-approved drugs with federally mandated pharmacogenomic information on the labeling. By adopting pharmacogenomic tests in clinical practice, physicians can tailor their prescriptions according to their patients' genetic makeup and hence improve the overall safety of the treatment.

Cost benefits– According to the National Institute on Drug Abuse (NIDA) the total number of opioid medications prescribed in the United States has increased by about 2-3 fold in the past 20 years (Figure 2). Opioid drugs are commonly used for pain management in the case of workplace injuries, with roughly 30% of worker's compensation claimants under opioid therapy (Dembe, 2012). Patients who don't experience the desired pain relief from opioid treatment due to genetic factors are likely to take higher doses in the hope of obtaining a better response, which can eventually lead to drug abuse and addiction. The U.S. societal costs of opioid abuse were estimated to be $53.4 billion in 2007 (Birnbaum, 2011). Moreover, there are indirect costs associated with opioid dependence in addition to the cost of the medication itself. One such cost is the depression often induced in opioid-dependent patients. Chronic use of opioids alters brain chemistry, resulting in depression-like psychiatric conditions. Management of depression by antidepressant drugs not only adds another layer of prescription costs but also negatively influences patients' working performance. Loss of productivity, costs related to medical complications, and criminal justice expenses are some of the indirect costs associated with opioid dependence that poses an increasing economic burden for society. And as the incidence of opioid abuse and addiction is on the rise, this burden is likely to increase in the future.

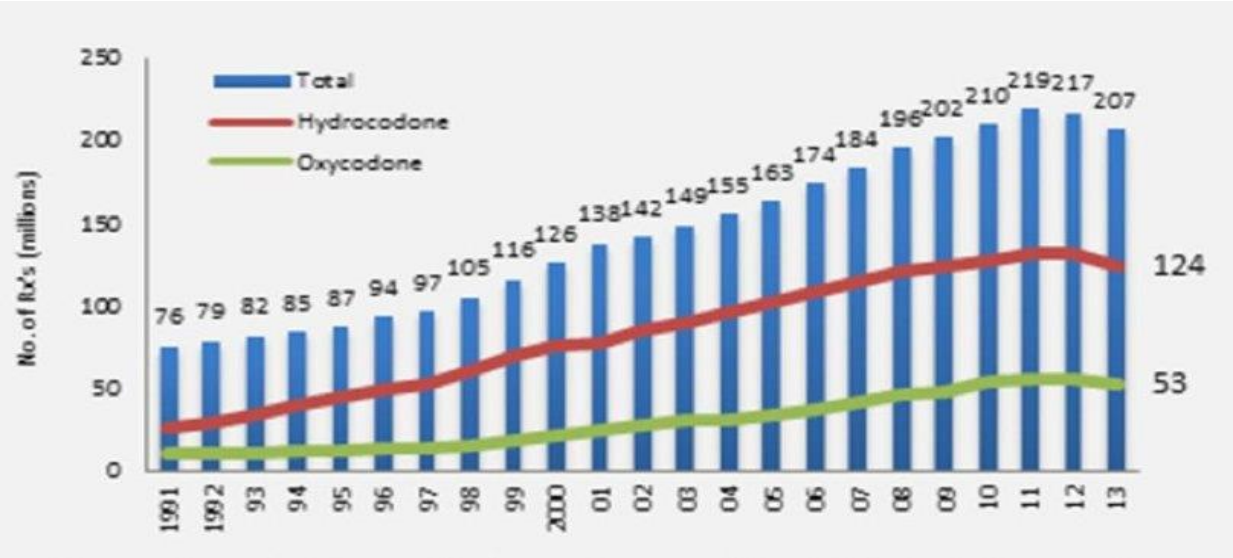

Figure 2. Opioid prescriptions dispensed by US retail Pharmacies. (Data were taken from National Institute on Drug abuse)

Increasing health care costs, the likelihood of adverse drug events and abuse potential related to opioid use all argue for the adoption of better strategies to identify appropriate treatment choice and drug dosing while avoiding negative drug reactions. Pharmacogenomic testing is one such strategy that can help physicians prescribe the right drug in the right dosage based on patient's genetic makeup and hence minimize the overall medication costs either directly or indirectly. Genetic tests offer multiple cost reduction benefits:

1. Patients whose treatment is guided by pharmacogenomic testing will be more likely to experience optimum pain relief from their medications and hence will be more likely to adhere to the prescribed dosage regimen. This will reduce the costs associated with overdosing and unnecessary medications.
2. Such patients will also have reduced chances of experiencing adverse effects, and hence treatment-induced morbidity and mortality. Pharmacogenomic testing thereby decreases hospitalization cost, loss of productivity cost and other miscellaneous medication costs.
3. Ensuring genetically appropriate drug treatment also minimizes the chances of drug abuse and addiction and associated depression, thus decreasing related costs.

These factors, combined with the relatively low cost of performing the test, make pharmacogenomic testing an effective tool in improving adherence to prescribed drug regimens and in reducing overall health care costs. Insurance companies, health care providers, and workers' compensation insurance

providers should adopt pharmacogenomic testing as a predictive tool to prioritize their claims and save money.

Challenges

Despite current scientific advancements in the field, pharmacogenomic testing is not routinely used by most of the clinicians to guide their pain management treatment plans. There are clinical, scientific and regulatory challenges that must be overcome in order to apply genomic information in clinical practice. One of the most common challenges is the lack of sufficient data to prove the clinical validity of pharmacogenomic testing for specific drug/genotype interactions. More clinical trials are needed to prove the utility of these tests in improving treatment safety and efficacy. Additionally, the interpretation of genotyping results is often not entirely straightforward, and there may be many other factors that influence a patient's drug response, i.e. diet, drug's chemistry, drug-drug interaction, etc. Regulatory bodies have been established that are trying to better understand and optimize the use of genetic data in pain management treatment and are working to establish dosage guidelines based on patients' genotype. However, there are still pieces of missing information that need to be addressed. Scientists, health care practitioners, and regulatory agencies need to work together to overcome these challenges and help adopt these tests in regular clinical practice.

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