Personalized Medicine in the Pain World

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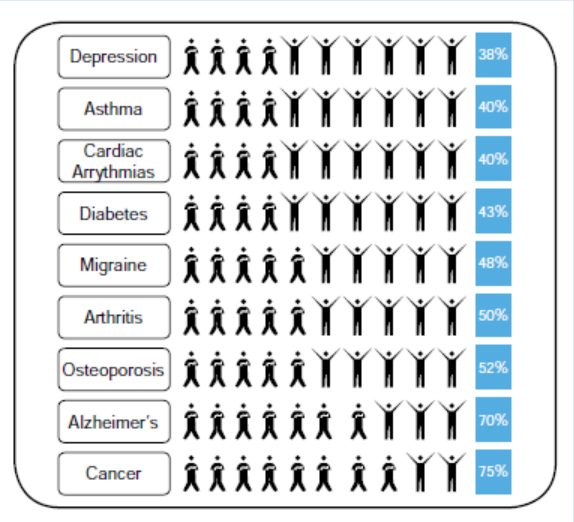
The most important goal of medicine, and health care in general, is to relieve patient suffering.[1] Pain is legion and all humans suffer it's ravages many times in their lives. Some develop chronic pain which is a significant clinical challenge. Pain is the most common reason to see a physician around the world. Interestingly however, the treatment of pain was of little interest for decades and has only recently become its' own established specialty with a specialized literature, training and certifications; the field is only 40 years old. For centuries pain has been difficult to treat and unfortunately, the ability to treat pain hasn't really changed much in the last 40 years.[2] The current approach to chronic pain treatment has been one of trial and error. Little different from other chronic diseases. However, new approaches give hope that clinicians ability to treat patients may become much more focused and individual.

Evidence based medicine (EBM) has become the measure of clinical practice. EBM presupposes that patients fit a pattern, usually a bell curve, of response to therapy. Unfortunately, this approach belies the underlying outcomes of current treatments. Drug efficacy can vary anywhere from 2-100 fold. Drugs are ineffective in depression 38% of the time, migraines 48% and osteoporosis 52%.[3]



Percentage of patients for whom drugs are ineffective. [3]

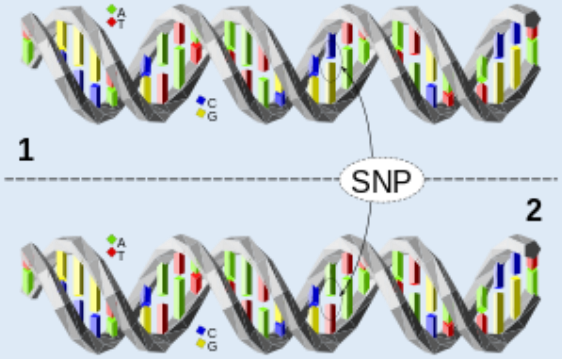
Further, over 50% of patients have the potential for drug-drug interactions that are rarely part of the patient evaluation.[4] However, these drug-drug interactions are only partially determined by a more detailed drug history. Prima fascia all patients do not

respond to drugs the same and this is illustrated in how we treat patients clinically. Clinicians start with a medication, if it works they may increase the dose, if it doesn't work the switch to a different medication. This approach is trial and error, and synonymous to the N=1 "trial".[5] The initial drug used is based on clinician experience, training, and literature. However, we approach patients with only a few dosage strengths and our clinical trials consist of robustly simplified patient populations very different from what is seen in the clinic. Limited dosages, clinical trials as they are currently designed are making an implicit statement that reflects the belief that patients are uniform, respond to the same dosages of medications and should all respond to the same medications. What is needed is a more "personalized" approach.

Patients are individuals, they are "personal" and a personal approach to medicine would be ideal and more effectively relieve suffering. Personalized Medicine (PM, also called "precision" or "individual" medicine) is a new field that identifies specific biological markers to define the best treatments for a given individual patient.[6] When a patient enters a clinic, after a thorough evaluation, history and physical, the approach is to give a medication or therapy and watch the result. There will be either a positive clinical effect, no effect or an adverse effect. It would be a tremendous step forward to be able to predict these 3 groups prior to initiating a treatment: This is the goal of PM. The increased interest in PM is reflected in the explosive increase in publications on this topic. Over the last 30 years' publications in this area have increased over 70 fold, professional organizations have evolved, conferences occur regularly and research has blossomed.

One of the greatest current areas of interest for research and use of PM is adverse drug events or reactions (AEs). Analgesics are among the top 4 drug classes involved in these AEs.[8] There are 2.2 million serious AEs in the United States. They are the 3rd cause of death in the US annually. Additionally, over 100,000 of these are from properly prescribed medications. In a European meta-analysis AEs during hospitalization were found to be around 4%, with one study showing a high of almost 13%.[7] The pain clinician should be well informed as to potential AEs from all the medications they prescribe. However, there is now a tool that may help them better determine the risk of AEs in a given patient. AEs can be reduced by careful medication

prescribing and use, although treatment directed by genetic testing has been shown to much more dramatically reduce AEs in certain populations, e.g., those on warfarin.[9] As the technology improves the ability to predict AEs will also increase.



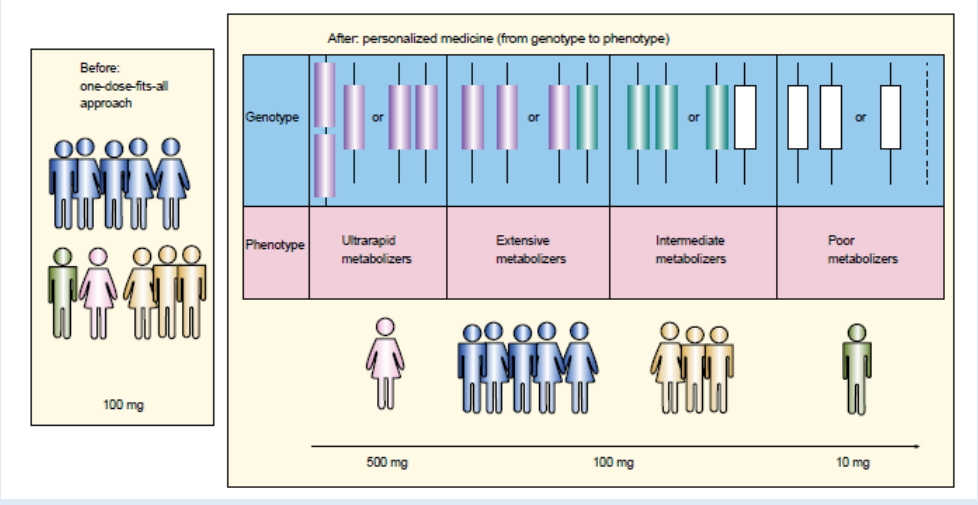
Single nucleotide polymorphisms (SNPs) are not mutations, but rather an area in a given gene where one person has one nucleotide and another has a different nucleotide.[10] The SNPs do change function and are rather common, with 10 million in any given human genome.[11] These SNPs affect drug metabolism, specifically the CYP450 Enzyme system. CYP 3A4, 2D6 and 2C19 affect analgesic metabolism, vide infra. Specific SNPs can result in a patient being an extensive, rapid, ultra-rapid or poor metabolizer of analgesic medications. The result of slower or faster metabolism is a patient that does not respond as expected to a given medication. Increased metabolism can result in a shorter than expected half-life with potential lack of analgesic efficacy. Slowed metabolism can result in toxicity and even death as drug serum levels unexpected increase.

The CYD 2D6 enzyme metabolizes approximately 20% of the drugs taken. This enzyme occurs at very low activity in most Asian populations. They will be "poor metabolizers" and will either not convert pro-drugs to their active counterpart resulting in poor efficacy, or increase the risk for AEs. An active drug that is not metabolized to inactive components can result in toxicity and potential death. PM genetic testing can determine if a patient is an ultra-rapid, extensive, intermediate or poor metabolizer and potentially reduce the risk of poor efficacy or increased AEs. Most NSAIDs are metabolized by the CYP 2C19 enzymes. Codeine is converted to morphine by the CYP 2D6 enzyme. With low activity, this conversion will not occur. Most opioids and antiepileptic drugs all are metabolized by the CYP enzyme system. Again poor or ultra-rapid metabolizers present scenarios that increase the risk of reduced efficacy or increased toxicity and AEs. Studies looking at CYP 2C19 metabolism in twins has shown that there is a correlation with cardiac side effects with

reduced metabolism, especially QT prolongation, e.g., with Methadone.[12] P-Glycoprotein is a carrier protein that removes drugs from the CNS. PGP needs to be activated before it can carry out this function. It has been shown when activation occurs at a heightened level morphine effectiveness is reduced.[13] Establishing the level of activation of PGP can help clinicians in identifying patients who might need dosage adjustments or medication changes. CYP2C9 in involved in the metabolism of Coumadin. It is less active in Koreans than in Sweds, which results in different efficacy at a same dosage.[14] These are some of the examples where PM and genetic testing can be of benefit to patients.

Although frequently related to genetics, other markers may play a role in phenotypic expression, novel biomarkers, Histones, circulating DNA, miRNAs and other proteins and peptides that may predict drug response.[6] These may well be targets in the future for PM. Epigenetic factors have been proposed as being of more importance than genetic factors.[15] Epigenetics is said to be, "a bridge between genotype and phenotype" and in the future will be evaluated as part of a PM profile.[16] Proteomics is another area of research and interest where PM may play a significant role in the future.[17]

There is little "downside" of genetic testing as far as physical risk. There are ethical considerations, and the upfront cost can be significant.[18] However, it should be kept in mind that this testing occurs only once in a lifetime for any given set of genes tested. Additionally, the cost of testing has been decreasing significantly over the last few years. PM is here to stay and pain clinicians should be aware of the potential benefits of this testing. Additionally, the field is expanding dramatically and currently has application in psychiatry, cardiology, oncology and other fields as well as pain. PM provides an additional tool to help direct medical management in pain patients and should be seriously considered to help direct pharmacological therapy.



Representation of one-dose-fits-all approach vs personalized medicine. [3]

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