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Review Article

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Is it Possible to Prescribe Right Drug for Every Patient?

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Introduction

Around the world, doctors prescribe drugs by trial and error. After determining the diagnosis, a doctor prescribes one of the drugs from several 'suitable' drugs. When the drug creates unbearable side effects, another drug is often prescribed to address them. If the side effects are severe or the patient is not responding to the drug, another drug is selected with the hope that it may be the 'right one'. Trial and error prescribing of drugs is frustrating and costly practice of medicine.

Examples of drug's side effect

Source of diagram unknown

Contrary to what pharmaceutical companies expect and doctors hope, a drug works well for only 30-70% of patients. In other words, a wrong drug is prescribed to 30-70% of the patients.

Why?

Drug makers submit safety and efficacy data of a drug to be approved by the FDA in the US based on the statistical average of studies covering a relatively small group of patients. In practice, there is no 'average' patient. We are all different. Even the siblings are different. Look at their visual appearance: the color of eyes, hair, facial features, and often even heights. This is because of genetic variations we inherit from our parents. This mutation is throughout our body including in the genes in our liver, which produce enzymes to metabolize most of the drugs. Thus, the drugs can be excreted through say, kidney.

When a doctor prescribes a drug to a patient who has a slow or inactive inherited gene, the drug will not clear fast enough as expected by pharmacokinetics for an average patient. Repeated doses of the drug will make the drug start accumulating in the body. Every drug is toxic. Every drug has side effects. Increased toxicity and side effects may lead to a high risk of Adverse Drug Reaction (ADR) for this patient. ADR is the 4th leading cause of death in the US and in Canada. One patient dies every 4 minutes in the US alone. It is like a large plane full of 350 people crashed each and every day year after year.

Facts about ADR in the US:

- Over 2,000,000 hospitalized every year
- Over 125,000 deaths a year [1].
- Over 350,000 Nursing Home ADRs a year
- Average Medicare patient is on 5-8 drugs, some as high as 20+ drugs a day
- Over 11+ drugs have 96% chance of ADR
- Blood thinner Coumadin/Warfarin used to control thrombosis is responsible for 3 out of 10 (33%) emergency room visits among seniors [2].
- The cost to insurance companies to address ADR is $136 Billion a year, more than total cost of cardiovascular and diabetes care [3-5].
- Physician Liability: The Next Big Thing for Personalized Medicine? [6].
- The cost to insurance companies to address ADR is $136 Billion a year, more than total cost of cardiovascular and diabetes care

ADR is an American, and probably the world's healthcare crisis much bigger than opioids overdose. This ADR is by drugs prescribed by doctors and taken as directed.
And, it is avoidable.

Solution

A simple yet brilliant disruptive Pharmacogenetics (PGx) test can predict, before a doctor even prescribes if the drug is 'just right' for the patient or it is 'too hot' or 'too cold' like in Goldie Lock story.

In conjunction with pharmacokinetics and pharmacodynamics, PGx is the study of how drugs are metabolized by hepatic genes and their mutants.

PGx affects drugs and pro-drugs differently. The drugs are metabolized to be eliminated by the enzymes produced by the genes.

Precision prescribing of drugs is part of personalized medicine so that doctors can prescribe medications appropriate to the patients,

based on their genetic makeup.

A very high level of polymorphism is observed among drug metabolizing genes like Cytochrome 450 (CYP450) supergene family. Patients can metabolize a drug at faster or slower than normal speed. So, some patients eliminate the drug too rapidly before it has a chance to work properly, while others have hard time eliminating it from their body leading to high risk of drug overdose leading to ADR.

Regulatory Guidelines

The FDA has been providing genetic labeling of new drugs as well as number of existing drugs like blood thinner warfarin. The FDA Tabel of Pharmacogenomics Biomarkers in Drug Labels lists over 140 drugs. The PGx information especially covers drugs with the highest level of warnings aka Black Boxed Warnings.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) sets guidelines on PGx information as it relates to a drug therapy [7].

The Pharmacogenomics Knowledgebase (www.pharmkgb.org) is also involved in developing guidelines on PGx [8].
PGx testing is ideally suited to guide safe use of drugs in many healthcare areas, like

- Cardiovasculartherapy
- Cancer therapy
- Gastroenterology
- Psychiatry
- Neurology
- Pain management
- Pediatrics
- Anesthesiology
- Dermatology
- Hematologic disorders
- Gerontology
- HIV and other infectious diseases

Drug metabolizing gene CYP2C9 for warfarin and the gene VKORC1 that activates vitamin K complicate the safe use of warfarin, used to prevent blood clots. Many different dosage of warfarin are often attempted by trial and error exposing the patient to high risk of excessive bleeding or increased blood clots.

The FDA, in fact, recommends a PGx test for all patients before prescribing warfarin to allow more precise dosing to avoid serious and possibly deadly ADRs [9].

The HIV drug Abacavir poses severe and life-threatening risk to patients with HLA-B*5701 mutation. The FDA requires a PGx test before prescribing Abacavir (Ziagen or Epzicom).

Side Note: Doctors, how many of you are complying with these FDA guidelines by using a PGx test in your practice?

The risk of ADR increases exponentially as number of drugs patient is on. A patient who is taking 11+ drugs has 96% probability that at least one drug is causing high risk of ADR.

A PGx test plays a key role in polypharmacy among elderly patients by avoiding ADRs particularly from drug-drug reactions.

How is the PGx test conducted?

To order a PGx test, a doctor needs to collect a blood or more in commonly collect epithelial cells by scrubbing oral epithelium both of buccal cheeks with sterile cheek-swabs. The swabs are sent to a PGx testing laboratory which processes sample for sequencing. Make sure to include a list of all drugs patient is on including drug/s you plan to prescribe. Old Sanger technique of sequencing of genes has been mostly replaced by more efficient Next Generation Sequencing (NGS) technique. PGx testing laboratories are CLIA certified and expected to provide 100% specificity and sensitivity of the sequencing.

Most laboratories provide a color-coded PGx test report in few days. First section of the report usually comments on the drugs patient is on and covered by the gene-panel ordered. If a drug is in a red box, the gene responsible to metabolize the drug is slow or inactive. The drug may put patient at a higher risk of ADR and should be replaced by another therapeutically equivalent drug for which the patient has normal functioning gene.

If the drug is in a blue box, the gene is ultra-fast and the dosage of the drug is usually increased. Remember, a pro-drug is affected by a gene in reverse as it is first converting it into an active drug. So, instead of increasing a dosage of drug for an ultra-fast metabolizer, a pro-drug should not be prescribed to ultra-fast metabolizer. That's why the FDA banned prescribing Codeine to children and lactating mothers who have an ultra-fast CYP2D6 gene [10,11].

Many PGx laboratories provide screening of small panel of genes at a time, e.g. psychotropic, cardio, pain, oncology panels etc. In long run, it may be wiser to order a PGx test with maximum genes available for sequencing. For example, most of cardio patients may also be on anti-depressants or painkillers prescribed by another doctor. A doctor may not know how those drugs are impacting the patient if only cardio panel is ordered. There are now PGx tests available to sequence over 50 genes covering over 300 drugs. A PGx test is good for the lifetime.

Clinically actionable PGx data

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed by The PharmGKB and the Pharmacogenomics Research Network. CIPIC is entrusted to help develop updated pharmacogenomics clinical practice guidelines [13].

A PGx test report provides clinically actionable data by utilizing guidance of several sources [14-16].

"Personalized medicine stands right at the center of [the health care] revolution, with the science enabling greater precision that not only can improve the lives of patients, but can also create efficiencies within the health care system by delivering the right treatment to the right patient atthe right time." — Stephen J. Ubl, President and CEO, PhRMA

Who pays for the PGx Test?

In the US, insurance companies including Medicare and 17 State Medicaid as of the time of writing are adjudicating the PGx test. This number is growing rapidly. Please check the Medicaid of your State for an updated status.

PGx reduces Healthcare cost

1. A Mayo Clinic Study of 3,000 patients showed reduction in hospitalization of cardio patients. PGx test data were used prior to treatment with warfarin [17].
2. More than 800 patients were genotyped for warfarin and clopidogrel dosing in the initial phase of the program (a number that has since increased to more than 1,500) at UI Health. Hospital readmission rates due to drug-related complications within 30 days decreased by 77 percent, and within 90 days by 68 percent, Nutescu said, resulting in an estimated cost savings of $2,043 per patient- nearly $600,000 annually at UI Health [18].
3. Breast cancer therapy guided by a commercially available PGx test was able to achieve a cost savings of $2,256 per patient, as a result of the reduction in the use of chemotherapy [19].
4. When treatment with panitumumab (Vectibix) or cetuximab (Erbitux) was limited to patients with metastatic colorectal cancer whose KRAS gene was not mutated, an annual savings of $604 million among all patients was achieved [20].

Potential liability?

The FDA approved first PGx test in 2005, yet most of the doctors are not even aware of the utility of a PGx test in their clinic. The FDA strongly recommends a PGx test before prescribing one of over hundred drugs, and requires a PGx test before prescribing one of 54 drugs, yet most doctors do not know that [12]. Other points for doctors to consider [21].

- Failure-to-warn claim
- Learned intermediary doctrine
- Duty to disclose risks to relatives of patients, or to re-contact with patients to convey new insights

"There is a potentially large pool of prospective plaintiffs who could bring lawsuits alleging that a physician's failure to recommend genetic testing for relevant variants before prescribing a drug contributed to a patient's death or adverse effect" [22].

PGx could be turning ADRs from 'natural risk' to 'medical risk' that can and should be preventable; hence a 'liability risk' and a patient may look for compensation in the courts [6].

What are the benefits to doctors?

1. Eliminate prescribing drugs by trial and error.
2. Avoid ADRs and reduce unnecessary pain and suffering of patients and their relatives.
3. The Right Drug for Every Patient right from the start [22,6].
4. PGx helps you to comply with the FDA's recommendations and requirements, thus reducing unforeseen liabilities.
5. Better patient adherence/compliance to treatment.
6. Reduce patient interruptions and complaints about unpleasant side effects from the drug you just prescribed. It's not uncommon for a doctor to spend 5-6 hours a month handling these concerns.
7. PGx reduces overall healthcare cost by avoiding drugs which need to be replaced within a few days. Or worse, prescribing another drug/s to address unwanted and painful side effects of the first drug.

"The power in tailored therapeutics is for us to say more clearly to payers, providers, and patients: 'this drug is not for everyone, but it is for you.' That is exceedingly powerful." John C. Lechleiter, Ph.D. Former Chairman, President, and CEO, Eli Lillyand Company.

Personalized medicine's advocates include representatives from every corner of the health care system, including clinicians, providers, insurers, industry, the patient advocacy community, and academia. These stakeholders all recognize that personalized medicine offers an extraordinary opportunity to improve the lives of patients in the U.S. and elsewhere [13].

The potential advantages of personalized/precision medicine, based on the knowledge of pharmacogenomics, are profound. There is no doubt it will eventually become the standard of care [23].

"If you knew about this genetic information and did not act on it, you would not be practicing good medicine." St. Jude Children's Hospital The time is now. There is no need to wait any longer. Make PGx test as a part of your standard of care.

Empower yourself to prescribe The Right Drug For Every Patient with confidence. It is a win for everyone [24,6].

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