Pharmacogenomics is an exciting field that will fundamentally change how we understand and treat disease and prescribe medication. In this article, we challenge the prevalence of Adverse Drug Events (ADEs) and look at how moving beyond a ‘one size fits all’ approach to medication can improve care, save lives and reduce costs associated with avoidable hospitalizations and ER visits.

Many do not realize that, despite stringent drug guidelines and exceptional healthcare practitioners, preventable medication errors occur regularly. In fact, ADEs are thought to be the 4th leading cause of death in the US.¹

These incidents happen for a number of reasons, many of which are related to a lack of information that could be readily addressed by available technology. For example:

- Information about a patient’s medication history is not available to physicians at the time of prescribing, which leaves room for prescribing a medication that will interact badly with another.
- Decision-support tools showing potential drug interactions or indicating which drugs a patient is insured for (and therefore can afford) are not available at the point of care, which can lead to prescriptions remaining unfilled. About one in ten Canadians do not adhere to treatment because they cannot afford their prescription medications.²
- Prescribing remains a risk-fraught manual process in Canada – prescriptions are either hand-written or printed from an EMR system and faxed or carried to the pharmacy where they are manually re-keyed into the pharmacy management system.

All of these preventable causes of ADEs can, in part, be addressed by extending the reach of digital health systems and facilitating better collaboration among healthcare providers and with patients. At the same time, pharmacogenomics holds game-changing potential regarding how drugs are administered to work with (not against) an individual’s genetics.

The following example, which refers to the 2014 Hawaii Clopidogrel lawsuit, illustrates this.
When proven treatments don’t work

Rudy was a fourth generation fisherman of Polynesian descent who began to suffer from chest pains when pulling in his heavy lines. After six weeks his symptoms prompted him to seek medical attention and he was diagnosed with blockages in his arteries. His cardiologist performed an angioplasty, a procedure that opens the blockage, and inserted stents to keep the arteries open.

Along with the procedure, Rudy was prescribed a six-month course of Clopidogrel, a drug used to prevent clotting. All was well for three months, until he had severe chest pain and was rushed to the hospital. En route, Rudy suffered cardiac arrest and could not be resuscitated. An autopsy revealed a complete artery blockage at the site of the stent. His cardiologist, puzzled by the failure of Clopidogrel, had the pathologist run a post-mortem blood sample to check Rudy’s genetic profile, specifically looking at the genes responsible for the enzyme that converts Clopidogrel into its active drug form.

In Rudy’s case, like 75% of Polynesians, he carried the genes for a slow version of the CYP2C19 enzyme resulting in an ineffective response to the drug. Tragically this test, if run prior to treatment, would have informed his cardiologist to make an alternate drug selection, and in all likelihood, Rudy’s death would have been preventable. Sadly, cases like this are not uncommon.

Startling facts about drug efficacy

The reality is that a high percentage of all drugs prescribed simply do not work for individual patients. In Canada we spend more than $30B, or 15% of our total health care budget on medications many of which are both ineffective and dangerous. For example, 38% of patient prescriptions for depression are ineffective, 40% for asthma, 43% for diabetes, 50% for arthritis and 75% for cancer.

Not all of these medication failures result in death, but the challenge with ineffective medications goes beyond efficacy to safety. Even though medications are prescribed according to stringent guidelines, they still can (and do) result in toxicity.

How is this possible? Lack of efficacy can reflect a complex interaction of factors; however, one important underlying reason is that each individual metabolizes medication differently and can experience vastly different responses. To better understand this, we need to look at how drugs work and how they are metabolized and cleared from the body.
How drugs work

Drug safety and efficacy depends on maintaining drugs in a therapeutic window where the concentration is greater than the minimal threshold of effectiveness and below the level where the drug has toxic side effects. All drugs have therapeutic windows and some are much narrower than others. For example the blood thinner Warfarin is well-known for its narrow window and can reach dangerous levels where patients are at risk of lethal hemorrhage.

The challenge for physicians is that every individual is profoundly different in how they handle medications. Age, gender, weight, kidney function, liver function all matter. But increasingly we are now aware that the genetic make-up of the individual is extremely important. Ninety percent of the population carry at least one genetic variant in the enzymes responsible for drug metabolism. Only 7% of patients have all normal variants across the five most common CYP enzymes in drug metabolism. ¹

In Rudy’s case, approximately 20% of the general population, and up to 75% of Polynesians ³ carry the slow version for the CYP2C19 gene, resulting in the treatment failure on Olopidogrel.

The physician’s challenge: one size does not fit all

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When Paracelsus, a medieval Swiss-German physician credited as the founder of toxicology noted “the dose makes the poison,” he was quite accurate. Therapeutic levels are a balance between the dose ingested and the drug’s absorption, distribution, and especially metabolism and clearance. Most drugs undergo Phase I metabolism in the liver by the Cytochromes P450 (CYPs). These membrane-bound proteins can either:
- activate a drug to its active form,
- convert an active drug to an active or toxic metabolite,
- convert an unexcretable drug to an excretable form or
- inactivate the drug

The activity of the CYPs can be influenced by a number of factors, including other drugs that either induce greater activity or inhibit activity. After Phase I, many drugs will require a further step, Phase II, in order to be safely cleared by the body. Any factor that increases or decreases the function of these metabolic enzymes will affect the concentration of the drug within the therapeutic window and therefore its efficacy and safety.
These variations cause the same dose of medication to result in vastly different drug concentrations ranging from ineffective, to therapeutic, to toxic depending on the individual’s gene expression. For a given drug, a patient’s genetic makeup will result in their ability to metabolize medication to be classified as a poor metabolizer, a normal metabolizer or an ultra-metabolizer.

Further complicating this, multiple drugs will have antagonistic or synergistic effects on the same metabolic pathway. Without understanding these individual and cumulative effects a physician cannot accurately predict how a medication will behave.

Top three inducers of adverse drug effects

ADE's occur for a number of reasons but most come down to three possibilities:

1. **Drug-Drug (DDI) Interactions**
2. **Drug-Gene (DG) Interactions**
3. **Drug-Drug-Gene (DDG) Interactions**

Electronic Medical Records and Pharmacy Management Systems can go a long way to protect against Drug-Drug Interactions. As patients’ records become digitized, information about their medications is more readily available to practitioners. However, it is estimated that one third of preventable adverse drug effects are the result of Drug-Gene Interactions and Drug-Drug-Gene Interactions, which the FDA now recognizes as being as significant as Drug-Drug Interactions and deserving of similar attention. As a result, over 100 product inserts now contain FDA drug-gene guidance.

Beyond ‘one size fits all’

Ten years ago, this genetic information was prohibitively expensive to gather at an individual level, and the best physicians could do was to prescribe drugs in a one size fits all manner with some variation of dosing for age, weight and renal function.

Today, the information required to understand how an individual patient will react to medications is available for under $500 per patient, and this price is declining rapidly. Solid information exists for over 80 different genes that have an effect on drug safety and efficacy.

When applied to populations at particular risk, such as seniors where one in 200 are hospitalized each year as a result of an ADE, pharmacogenomics can reduce hospitalization and ER visits. One study, targeting seniors who were taking three or more medications, reported a 39% reduction of hospitalizations and a 71% reduction of ER visits.

We can improve our use of medications through pharmacogenomics, which in turn will improve care, in some cases save lives, and at the same time reduce healthcare costs associated with hospitalizations, ER visits and other avoidable interactions with the health system. In light of the prevalence of preventable adverse drug events and the potential for personalized medicine to impact patient safety, it begs the question: why are we not embracing its potential and working systematically to eliminate all preventable adverse drug events?