Personalized medicine and Pharmacogenetics (PGx)

Roberto Solis

Human Genome Project

Yesterday

- The National Institutes of Health (NIH) and the Department of Energy joined with international partners in a quest to sequence all 3 billion letters, or base pairs, in the human genome, the complete set of DNA in the human body. This concerted, public effort was known as the Human Genome Project.
- In 1953, James Watson and Francis Crick described the double helix structure of deoxyribonucleic acid (DNA)
- The Human Genome Project's goal was to provide researchers powerful tools to understand the genetic factors in human disease, paving the way for new strategies for their diagnosis, treatment and prevention.
- In April 2003, researchers successfully completed the Human Genome Project, under budget and more than two years ahead of schedule.

Human Genome Project

Today

- The Human Genome Project has already fueled the discovery of more than 1,800 disease genes.
- As a result of the Human Genome Project, today's researchers can find a gene suspected of causing an inherited disease in a matter of days
- There are now more than 2,000 genetic tests for human conditions.
- These tests enable patients to learn their genetic risks for disease and also help healthcare professionals diagnose disease.
- Pharmacogenomics is a field that looks at how genetic variation affects an individual's response to a drug.
- Pharmacogenomic tests can identify if a breast cancer patient will respond to the drug Herceptin, if an AIDS patient should take the drug Abacavir, or the individual correct dosage for the blood-thinner Warfarin.

Human Genome Project

Tomorrow

- Individualized analysis based on each person's genome will lead to a powerful form of preventive, personalized and preemptive medicine.
- By tailoring recommendations to each person's DNA, health care professionals will be able to work with individuals to focus efforts on the specific strategies — from diet to high-tech medical surveillance — that are most likely to maintain health for that particular individual.
- Based on a deeper understanding of disease at the genomic level, we will see a whole new generation of targeted interventions, creating more effective drugs with fewer side effects.

A Texas testimonial

"[I] just had to thank you for recommending that new gene test for medications. My dad, Dewey Young who is 88 years old, took your test on 4/14/2016. Weeks later, he was admitted to the hospital and was having a heart attack. After receiving 3 stints due to 100% blockage of the "widowmaker", we had experienced a terrible week of adjustment to six different types of medications. The reaction was so bad he had to go back to the original hospital for a drug "tune-up". I remembered that we had just taken your test and asked to receive the results and sure enough, for example, he was struggling with a medication by the name of Metoprolol and it was right on your potentially impacted medication list. I was so proud to have this report because after life saving heart procedures and 5 weeks in the hospital all of our problems came down to medication. I am a advocate of this test and have since had both my husband and myself tested. I believe when hours make a difference in life or death we need every tool possible to make the right decision. Please know I am happy to expand on our hospital story and great recovery due to the knowledge your tests gave us.
Regards,
Chairman of the Board – Hospital"

"With wide open flow to the heart, right meds, he is Superman! He is home commanding his man cave!"

What is Pharmacogenetics?

* **Pharma** = drug or medicine
* **Genomics** = the study of genes

Personalized medicine tailored to YOUR genes

Pharmacogenetics in action

* Imagine if you've had a heart attack and your doctor prescribes a medication that lowers your risk of having another. Taking into account different factors such as your weight, age and medical history, your doctor might prescribe a blood-thinning drug to help prevent blood clots from causing another heart attack.
* Without testing, neither you nor your doctor knows exactly how you'll react to the medication.
* Pharmacogenomics speeds up that trail and error. Before you take a single dose of medication, you can test your DNA to see how likely you will respond to the medication.

Real World Scenarios of Testing

* Scenario 1

-Do you know if your patients stent failures were attributed to poorly metabolized Plavix?

* Scenario 2

-Do you know if your patients anti-depressants will inhibit metabolism of their blood pressure medication?

* Scenario 3

-Do you know if your post-op patients' tramadol dosage is correct?

*Genetic Testing increase patient satisfaction?

Patient Selection

* New patients that need to get a baseline for an effective medication management program
* Patients on multiple medications
* Patients taking a prodrug [P] (Codeine, Tramadol, Plavix, Tamoxifen)
* Patients with history of substance abuse, cancer or psychiatric disorders
* Patients on opioids that say they need a higher dose or when prescribed drugs do not show up in urine drug tests
* When a patient has unexplained symptoms or current medications aren't effective

Why PGx Testing?

* Providing efficient healthcare to patients
* Diagnosing cause for drug related side effects
* Assisting healthcare providers select the most efficient drug dose for their patient
* Avoiding therapeutic failure
* Minimizing side effects and toxicity
* Achieving optimal therapeutic response
* Eliminating trial and error on patients
* Defining how patients respond to drugs based on their genetic makeup, the right drug, right dose, right now.

How does PGx Testing prevent Adverse Drug Reactions

* It can inform you if Plavix will not work for a patient. If Plavix does not work patient is at risk of having a stroke or a heart attack.
* What happens if a patient that is new to Warfarin is on a dose that's too high? Cerebral hemorrhage (brain bleed), GI bleed
* What happens if a cancer drug doesn't work for the patient? Potential cancer relapse and financial toll
* What's the risk to a patient if they are sent home after being discharged on new meds? Risk of ADR's and readmission.

Stats and Key points:

* Better Medication Therapy
* Adults. Geriatrics. Pediatrics.
* 42% of patients taking pain medication get no relief.
* Patients carrying low-function gene variants, have a 350% to 800% risk for major cardiovascular events.
* 25% of patients on prescription medication report adverse events.
* The most common ADRs occur from opioids, selective serotonin re-uptake inhibitors (SSRIs), beta-blockers, ACE inhibitors, and NSAIDs.
* Improved patient adherence and compliance.
* Knowing a patient's genotype has been shown to increase the likelihood of patients adhering to a prescribed regimen.

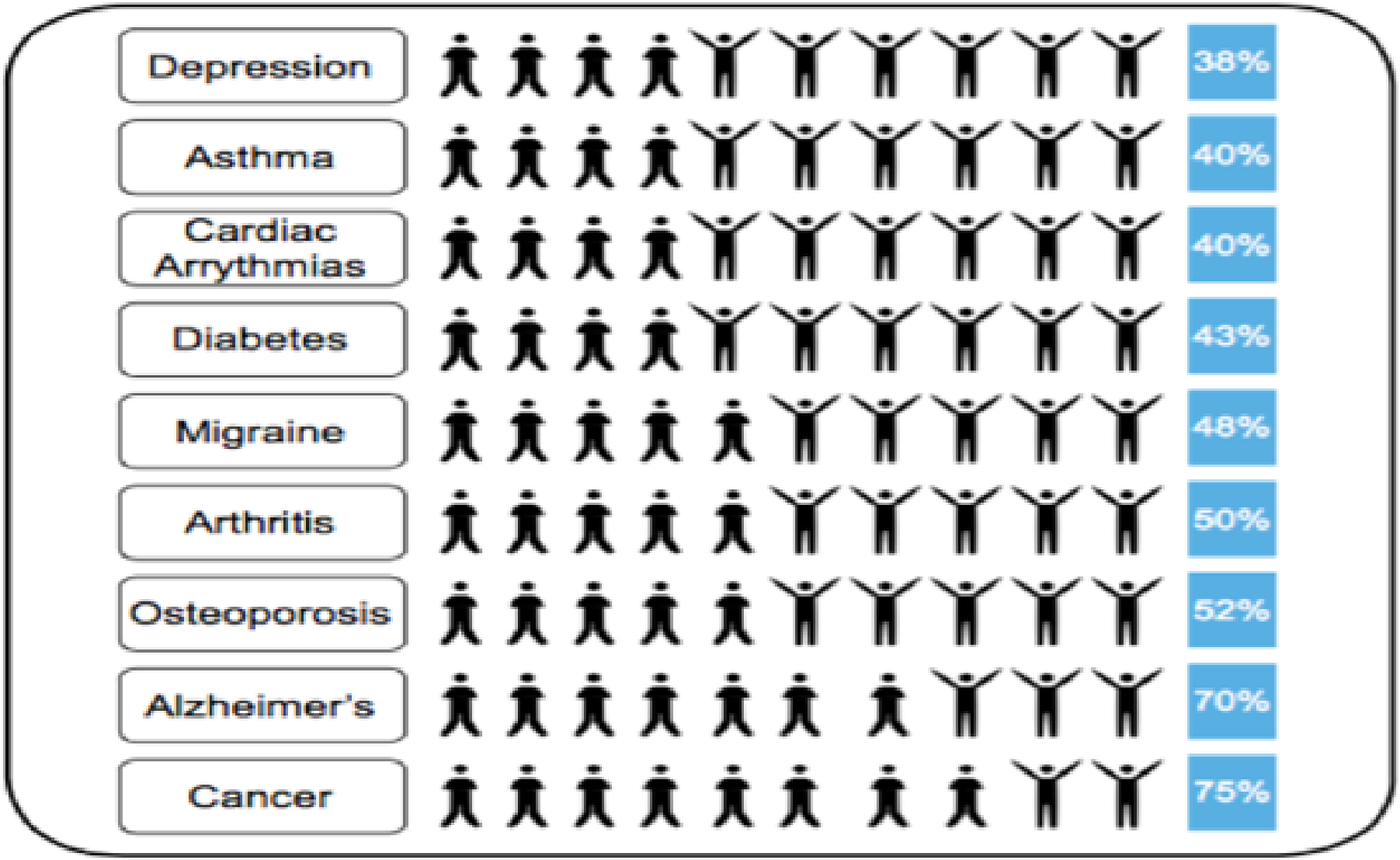


Figure 1. Percentage of patients for whom drugs are ineffective. (Source of data: Spear, B.B., Health-Chrizzi, M.,&Hff, J. (2001) Clinical application of pharmacogenomics. TRENDS in Molecular Medicine., 7(5), 201-204).

Continued Stats:

* An estimated $136 billion is spent on treating ADRs annually. Prescription opioid analgesics are among the most common causes of ADRs
* Up to 30% of patients have a genetic opioid metabolic defect. This results in 100,000 deaths and $2.2 billion adverse drug events per year.
* 3 out of 4 patients are at risk of an adverse drug event
* In the US, prescriptions of medications is at all time high

Types of Metabolizers

PGx Cardiovascular Panel

Potentially Impacted Medications				
Category	**Class**	**Standard Precautions**	**Use With Caution**	**Consider Alternatives**
Cardiovascular	Angiotensin II Receptor Antagonists	Irbesartan (Avapro)		
	Antianginal Agents	Ranolazine (Ranexa)		
	Antiarrhythmics		Mexiletine (Mexitil) Propafenone (Rythmol)	Flecainide (Tambocor)
	Anticoagulants	Apixaban (Eliquis) Dabigatran Etexilate (Pradaxa) Fondaparinux (Arixtra) Rivaroxaban (Xarelto)	Warfarin (Coumadin)	
	Antiplatelets	Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)		Clopidogrel (Plavix)
	Beta Blockers	Carvedilol (Coreg) Labetalol (Normodyne, Trandate) Nebivolol (Bystolic) Propranolol (Inderal) Timolol (Timoptic)		Metoprolol (Lopressor)
	Statins	Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor)	Atorvastatin (Lipitor) Fluvastatin (Lescol) Lovastatin (Mevacor) Simvastatin (Zocor)	

PGx Pain panel

Category	Class	Standard Precautions	Use With Caution	Consider Alternatives
Pain	Fibromyalgia Agents	Milnacipran (Savella)		
	Muscle Relaxants	Carisoprodol (Soma) Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin) Tizanidine (Zanaflex)		
	NSAIDs	Ketoprofen (Orudis) Ketorolac (Toradol) Nabumetone (Relafen) Naproxen (Aleve) Sulindac (Clinoril)	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Indomethacin (Indocin) Meloxicam (Mobic) Piroxicam (Feldene)	
	Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Methadone (Dolophine) Morphine (MS Contin) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Dihydrocodeine (Synalgos-DC) Fentanyl (Actiq) Hydrocodone (Vicodin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)

PGx Psychotropic panel

Category	Class	Standard Precautions	Use With Caution	Consider Alternatives
Psychotropic	Antiaddictives	Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave) Naltrexone (Vivitrol)		
	Anti-ADHD Agents	Amphetamine (Adderall) Dextroamphetamine (Dexedrine) Lisdexamfetamine (Vyvanse)	Dexmethylphenidate (Focalin) Methylphenidate (Ritalin)	Atomoxetine (Strattera)
	Anticonvulsants	Carbamazepine (Tegretol, Carbatrol) Eslicarbazepine (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal) Perampanel (Fycompa) Pregabalin (Lyrica) Rufinamide (Banzel) Tiagabine (Gabitril) Topiramate (Topamax) Valproic Acid (Depakote, Depakene) Vigabatrin (Sabril)	Fosphenytoin (Cerebyx) Phenobarbital (Luminal) Phenytoin (Dilantin) Primidone (Mysoline) Zonisamide (Zonegran)	
	Antidementia Agents	Galantamine (Razadyne) Memantine (Namenda)	Donepezil (Aricept)	
	Antidepressants	Citalopram (Celexa) Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Escitalopram (Lexapro) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Nefazodone (Serzone) Sertraline (Zoloft) Vilazodone (Viibryd) Vortioxetine (Brintellix)	Amoxapine (Amoxapine) Fluvoxamine (Luvox) Maprotiline (Ludiomil)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)

PGx Sample Report

Codeine (Codeine) Evidence Level: **Actionable**

Non-Response to Codeine (CYP2D6 *4/*4 XN Poor Metabolizer)

Greatly reduced morphine levels are expected and the patient may not experience adequate pain relief when taking codeine. Avoid prescribing codeine and consider alternative opioids other than tramadol or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

Clopidogrel (Plavix) Evidence Level: **Actionable**

Increased Response to Clopidogrel (CYP2C19 *17/*17 Rapid Metabolizer)

Clopidogrel can be prescribed at standard label-recommended dosage. Individuals with the *17 allele may have an increased risk of bleeding while taking clopidogrel.

Escitalopram (Lexapro) Evidence Level: **Actionable**

Insufficient Reponse to Escitalopram (CYP2C19 *17/*17 Rapid Metabolizer)

Monitor plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.

Esomeprazole (Nexium) Evidence Level: **Informative**

Insufficient Response to Esomeprazole (CYP2C19 *17/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 50-100% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 50-100%.

Safety Announcement

* The U.S. Food and Drug Administration (FDA) has added a *Boxed Warning* to Plavix, the anti-blood clotting medication. This label warns patients who may not effectively metabolize the drug (i.e. "poor metabolizers") and therefore will not receive the full benefits of the drug.
* The **Boxed Warning** in the drug label will include information to:
* Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
* Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.

Continued..

* Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.
* Plavix is given to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease. Plavix works by decreasing the activity of platelets, making platelets less likely to form blood clots.
* For Plavix to work, enzymes in the liver (particularly CYP2C19) must convert (metabolize) the drug to its active form. Patients who are poor metabolizers of the drug, do not effectively convert Plavix to its active form. In these patients, Plavix has less effect on platelets, and therefore less ability to prevent heart attack, stroke, and cardiovascular death.
* It is estimated that 2 to 14% of the population are poor metabolizers; the rate varies based on racial background.

Anticipated benefits of Pharmacogenetics:

* **More powerful medicines -** Pharmaceutical companies will be able to produce therapies more targeted to specific diseases, maximizing therapeutic effects while decreasing damage to nearby healthy cells.
* **Better, safer drugs -** Recovery time will go down and safety will go up. The likelihood of adverse reactions will go down or will be eliminated altogether.
* **More accurate methods of determining appropriate drug dosages -** Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics -- how well the body processes the medicine and the time it takes to metabolize it.

Economic issues from molecule to marketplace

Pharmacogenetics will lead to an overall decrease in the cost of health care because of decreases in:

* the number of adverse drug reactions,
* the number of failed drug trials,
* the time it takes to get a drug approved,
* the length of time patients are on medication,
* the number of medications patients must take to find an effective therapy, and
* the effects of a disease on the body (through early detection).

Future of Medicine

* Predictive: enhanced use of genetic diagnostic markers to predict disease
* Personalized: based upon individualized genetic characteristics, therapy will be individually tailored
* Preventive: utilize patient specific medications to prevent disease
* Participatory: patients will continue to take more control of their health care (e.g. electronic medical records)

Personalized Medicine brings big wins to managed care

According to a recent report from the Personalized Medicine Coalition (PMC), "The Personalized Medicine Report: Opportunity, Challenges, and the Future."

"Personalized medicine aligns extremely well with managed care," says Daryl Pritchard, PhD, vice president, science policy, PMC. "It provides high-value prevention and treatment strategies based on individual patient molecular information."

"Furthermore, as personalized medicine is increasingly recognized as a leading paradigm in healthcare, more patients will be attracted to healthcare delivery systems that promise to practice more effective personalized care."

Managed Healthcare® EXECUTIVE

A new agenda

How will personalized medicine fit into President Trump's proposed healthcare agenda?

Trump has stated that his goals in healthcare reform include bringing costs down while accelerating the pace of biomedical innovation. Personalized medicine provides continued momentum for both goals.

"If the new administration supports value-based care and patient-centered treatment strategies to help improve outcomes and drive down costs, as well as improved clinical trial design to help speed up and reduce costs of the regulatory approval of medical products, then personalized medicine will fit in very well," says Pritchard.

Managed Healthcare® EXECUTIVE

Personalized Medicine Coalition (PMC), "The Personalized Medicine Report: Opportunity, Challenges, and the Future."

Cost Savings

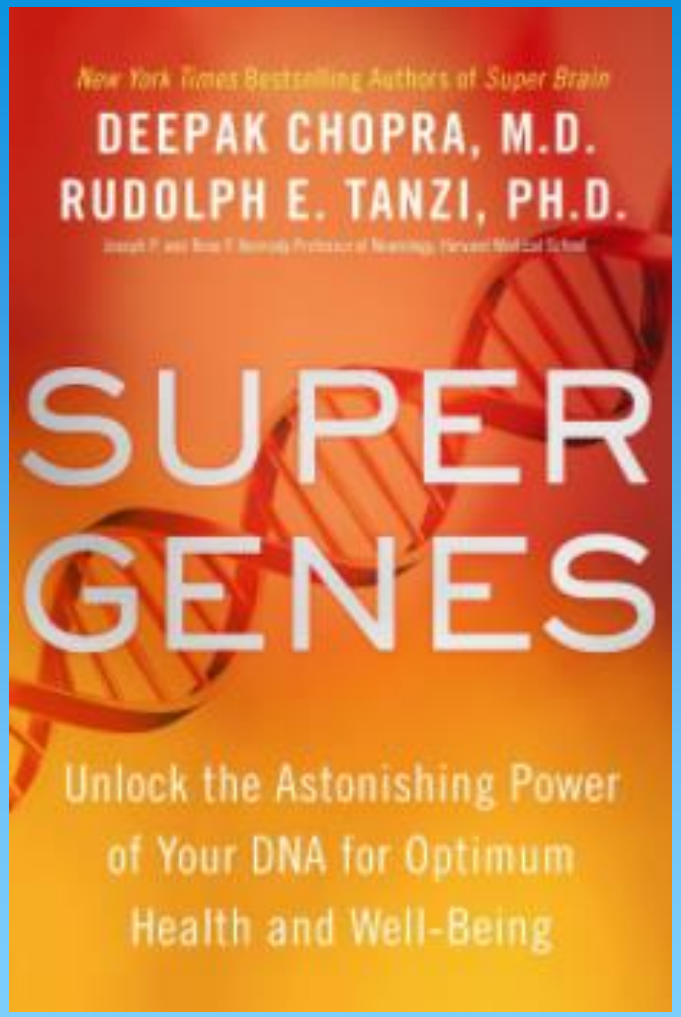
"There are added costs from diagnostic testing and analysis services, but these costs should be more than offset," says Pritchard. "Overall care costs should go down because of money saved avoiding ineffective treatments. Plus, the safety and efficacy profile of these treatments in responders is much improved."

Managed Healthcare® EXECUTIVE

Personalized Medicine Coalition (PMC), "The Personalized Medicine Report: Opportunity, Challenges, and the Future."

Personalized Medicine Testing

- Pharmacogenomics
- Pre-Natal Testing
  -Downs, Edwards, Patau
- ACOG/ACMG Carrier Testing
  -CF, SMA, Fragile X
- Hereditary Cancer
  - Breast, Ovarian, Uterine, Colorectal, Stomach, Prostate, Melanoma, Pancreatic
- Oncology
  -Chemotherapeutics



Super Genes

Deepak Chopra, M.D.
Rudolph E. Tanzi, PH.D.

Pharmacogenomics:

Increasing the safety and effectiveness of drug therapy

AMA Case Study

Pharmacogenomics: Increasing the safety and effectiveness of drug therapy

AMA AMERICAN MEDICAL ASSOCIATION

ARIZONA CERT CRITICAL PATH INSTITUTE

CRITICAL PATH INSTITUTE collaborate · innovate · accelerate

CASE STUDY

Implementing Proactive Pharmacogenetic Testing as a Standard of Care

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Photo courtesy of St Jude Children's Research Hospital

Primary Intended Outcomes

1. Facilitate the appropriate use of proactive pharmacogenomic tests as the standard of care for St. Jude patients.
2. Incorporate clinical decision support (CDS) tools linking pharmacogenetic testing to medication use, and characterize their use in the electronic medical record (EMR).

Relevant PPMI Recommendation(s)

B23. The following characteristics or activities should be considered essential to pharmacist-provided drug-therapy management in optimal pharmacy practice models:

B23f. Adjustment of medication regimens based on genetic characteristics of the patient.

Situation Analysis

Although pharmacogenetics has existed as a discipline since at least the 1950s, the adoption of genetic testing to guide the safe and effective use of medication remains the exception. While there has been considerable progress in the technical ability to perform genomic testing , various barriers exist that limit the adoption of pharmacogenetic tests as the standard of care. Examples of barriers include fragmentation of health care systems, especially for lifetime genetic results, complexity of the underlying laboratory results, and the immaturity of CDS and EMR systems to facilitate point of care use of pharmacogenetic data when making drug therapy decisions. At St. Jude, we are able to overcome many of these barriers to implementing pharmacogenetics. We provide all the medications for our patients, have decades of experience performing pharmacogenetic research, and have an integrated, comprehensive EMR with customized decision support.

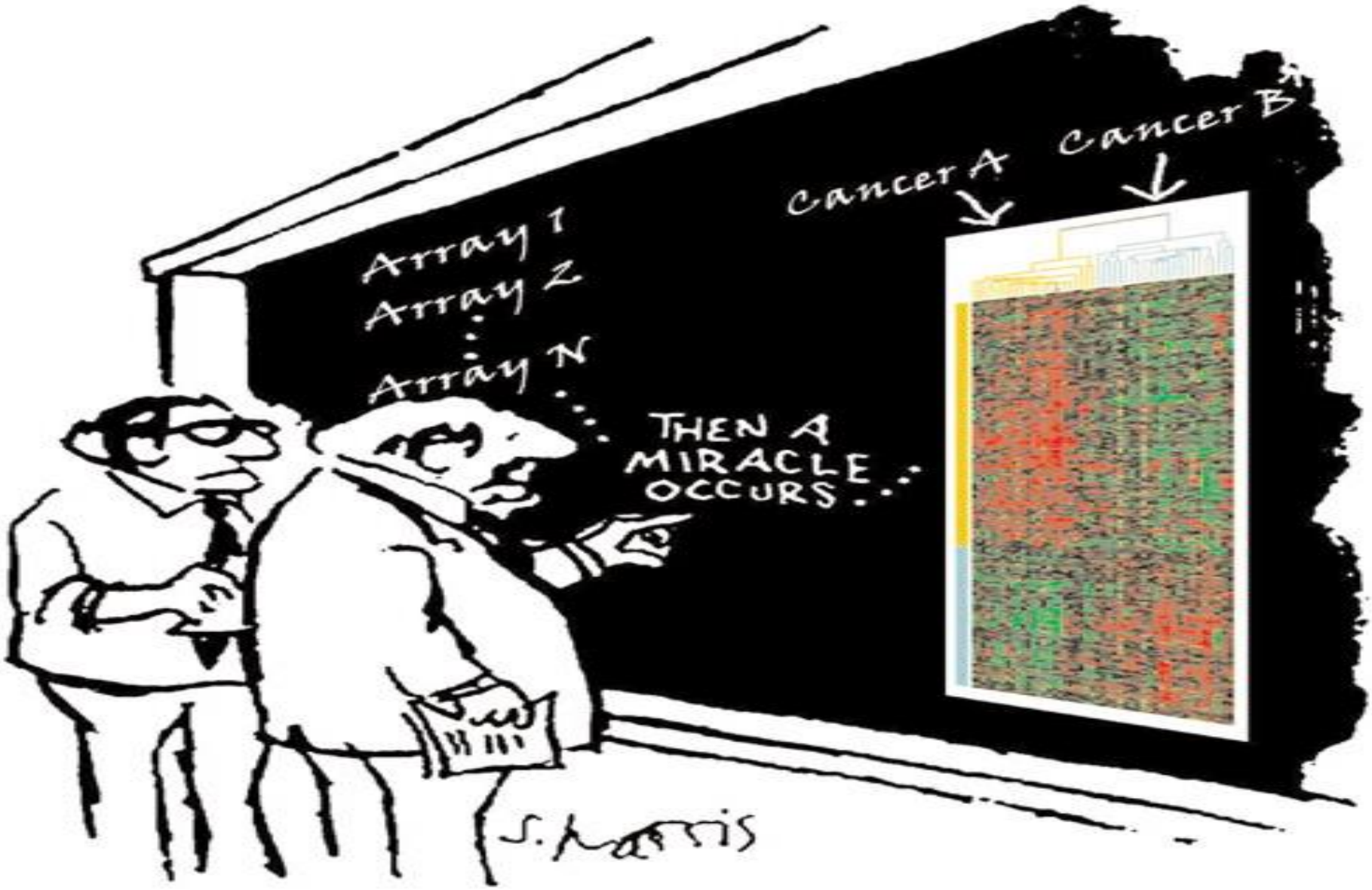
Our philosophy is that pharmacogenetic tests results should be a part of the EMR prior to drug prescribing. If a genetic test is ordered at the time a drug is prescribed, clinicians must wait for the test results, which are often only available after the patient has already started therapy. A preemptive approach allows time for the reporting and interpretation of genetic test results so that

PPMI
PHARMACY PRACTICE MODEL INITIATIVE

Implementing Proactive Pharmacogenetic Testing as a Standard of Care

Sources

* U.S. Food and Drug Administration: Paving the Way for Personalized Medicine –FDA's New Role in a New Era of Medical Product Development; fda.gov
* Coriell Institute of Medical Research: Coriell Personalized Medicine Collaborative; cpmc.coriell.org
* National Human Genome Research Institute-Advancing human health through Genomics research ; genome.gov
* Senator Edward M. Kennedy; Remarks on the Senate's Consideration of the Genetic Information Nondiscrimination Act. April 24, 2008
* *National Human Genome Research Institute (NHGRI)* *http://www.genome.gov/*
* Managed Healthcare Executive – Modern Medicine



"I think you should be more explicit here in step two"

Thank You

"We are in a new era of the life sciences…but in no area of research is the promise greater than in the field of personalized medicine."