Utilizing Pharmacogenomics (PGx) to Improve Patient Care in Long-Term Care Facilities

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FidaLab

THE GREATER GOOD

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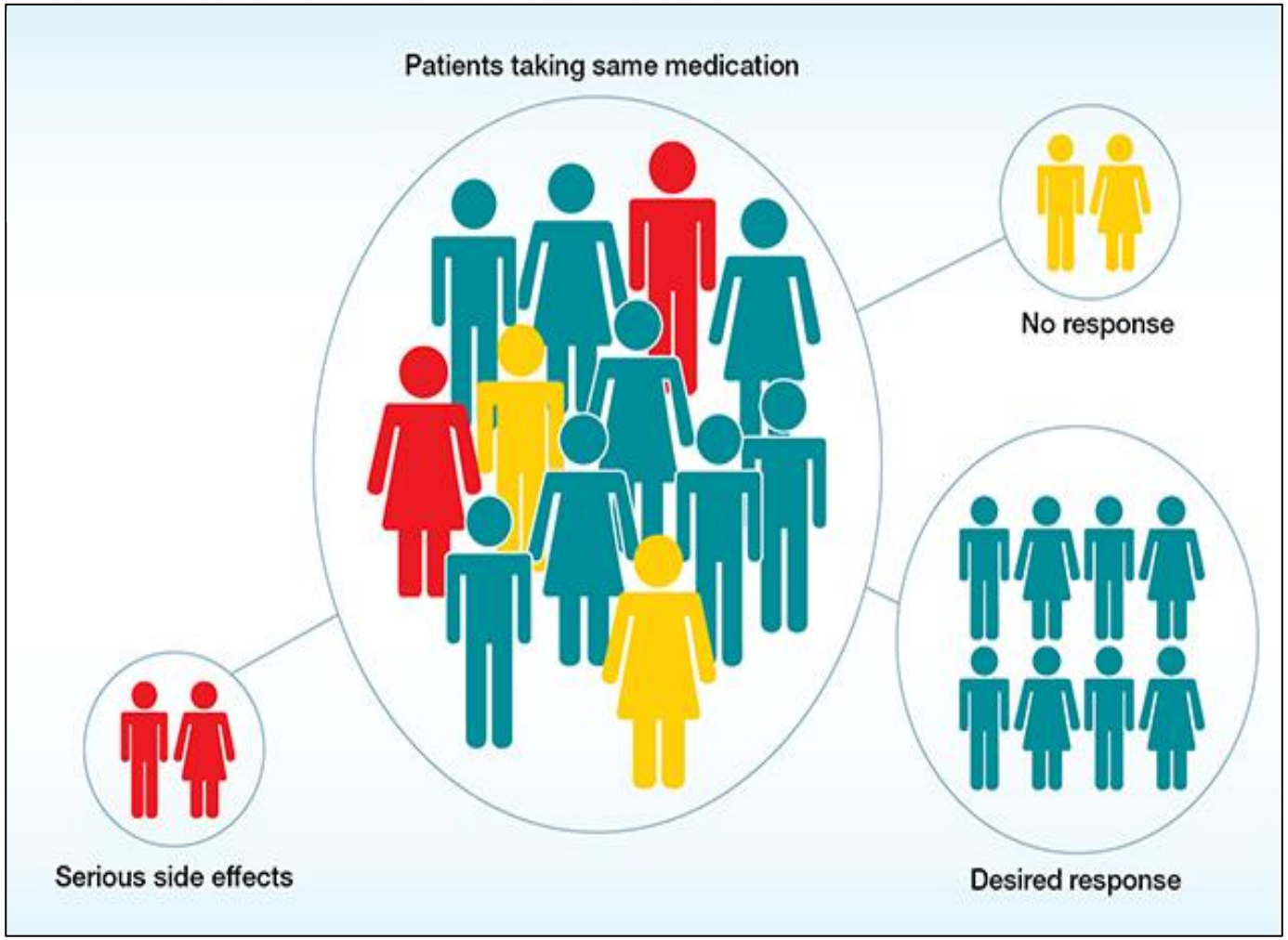
What is Pharmacogenomics (PGx)?

- Pharmacology + Genomics
  - Pharmacology: Science of how drugs work
  - Genomics: Science of the human genome
- Use a person's genome to choose the optimal drugs and drug doses for individualized medication prescription
- Precision medicine

Traditional Treatment (Trial and Error Method)

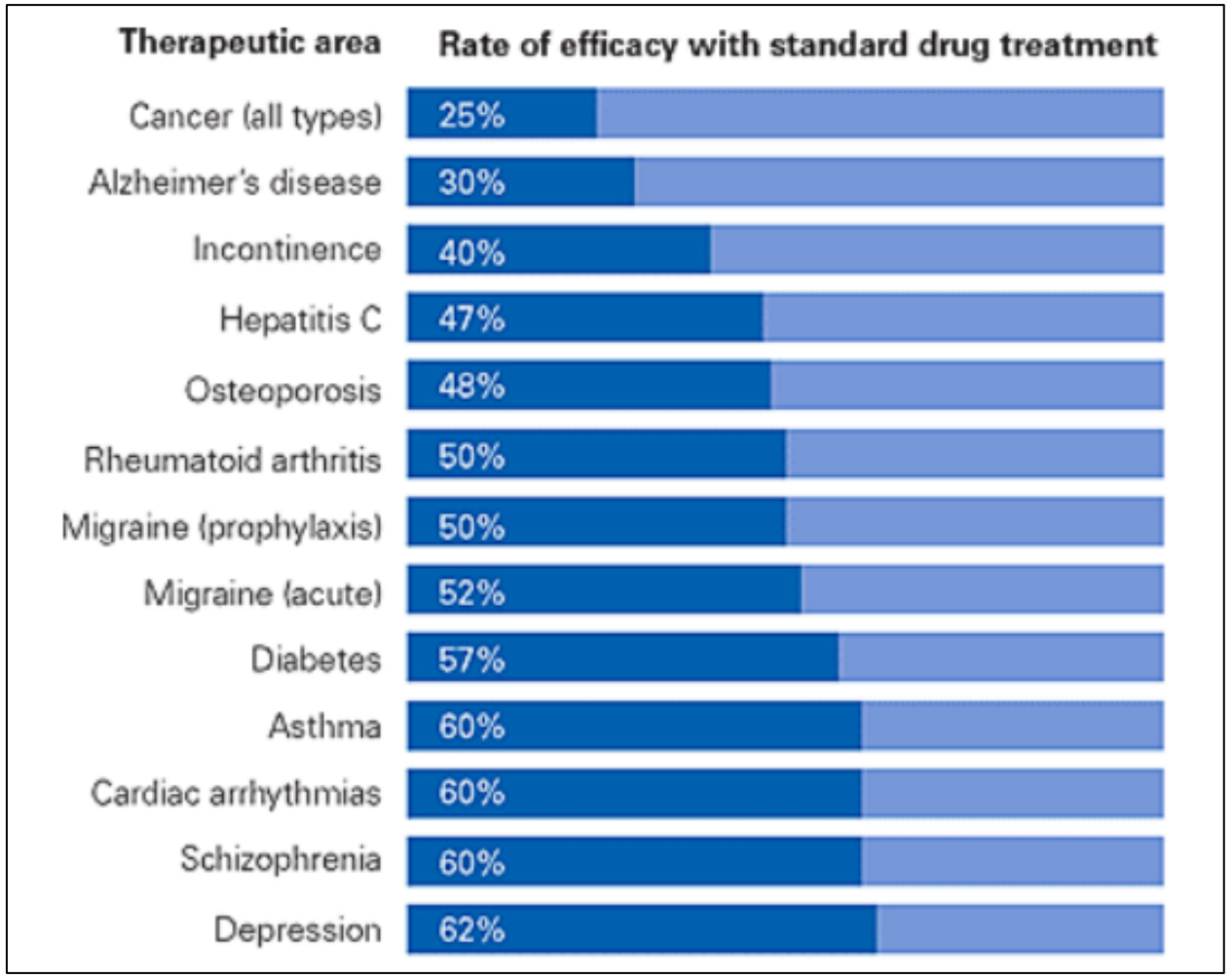
Same prescription



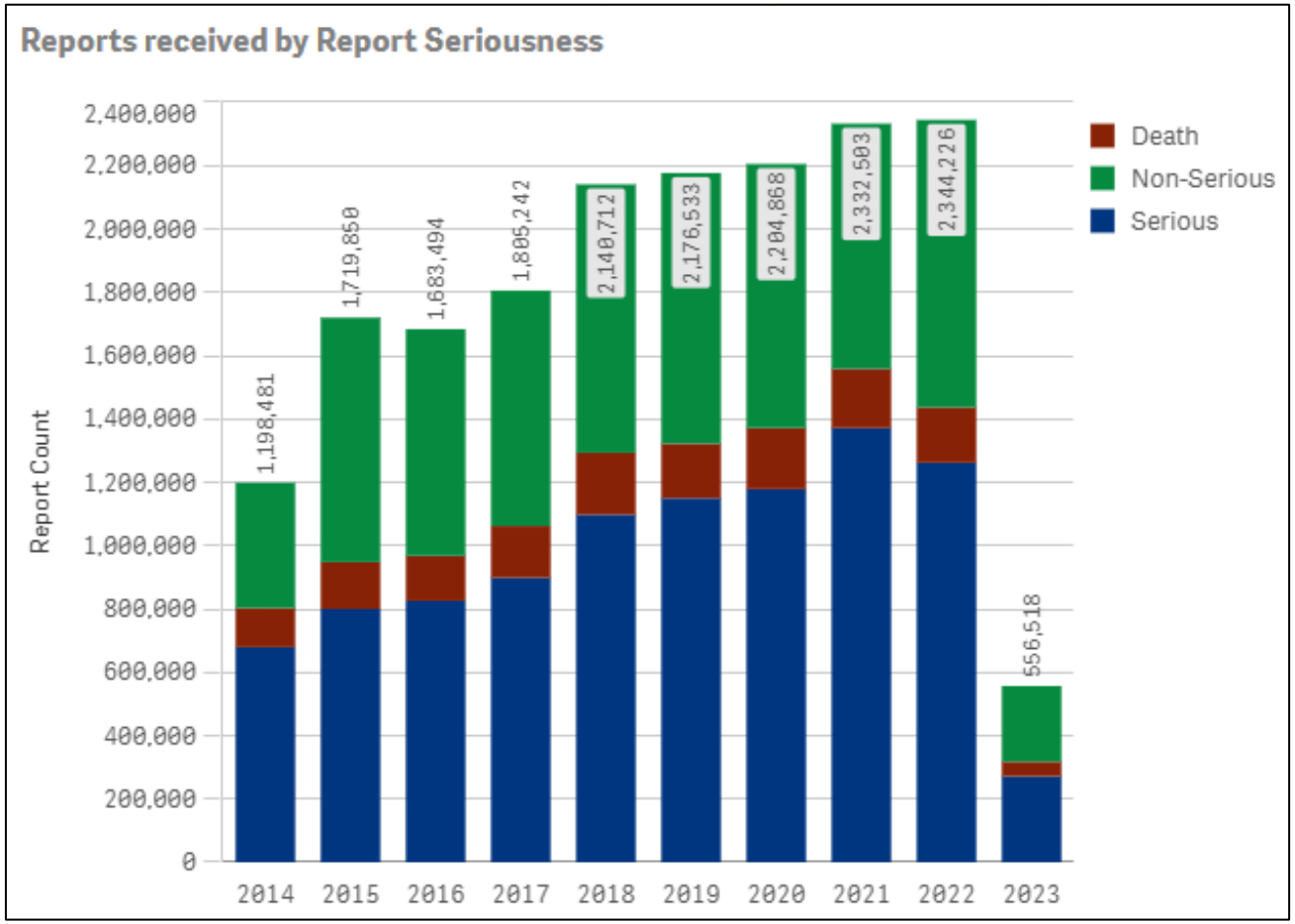
Traditional Treatment (Trial and Error Method)

Standard dose

Traditional Treatment is inefficient



Adverse Drug Reactions (ADRs)



2014-2023
Total reports: 18,162,427
Death: 1,545,544
Serious: 9,533,829
Non-Serious: 7,083,054

FDA Adverse Events Reporting System (FAERS) Public Dashboard - FDA Adverse Events Reporting System (FAERS) Public Dashboard | Sheet - Qlik Sense

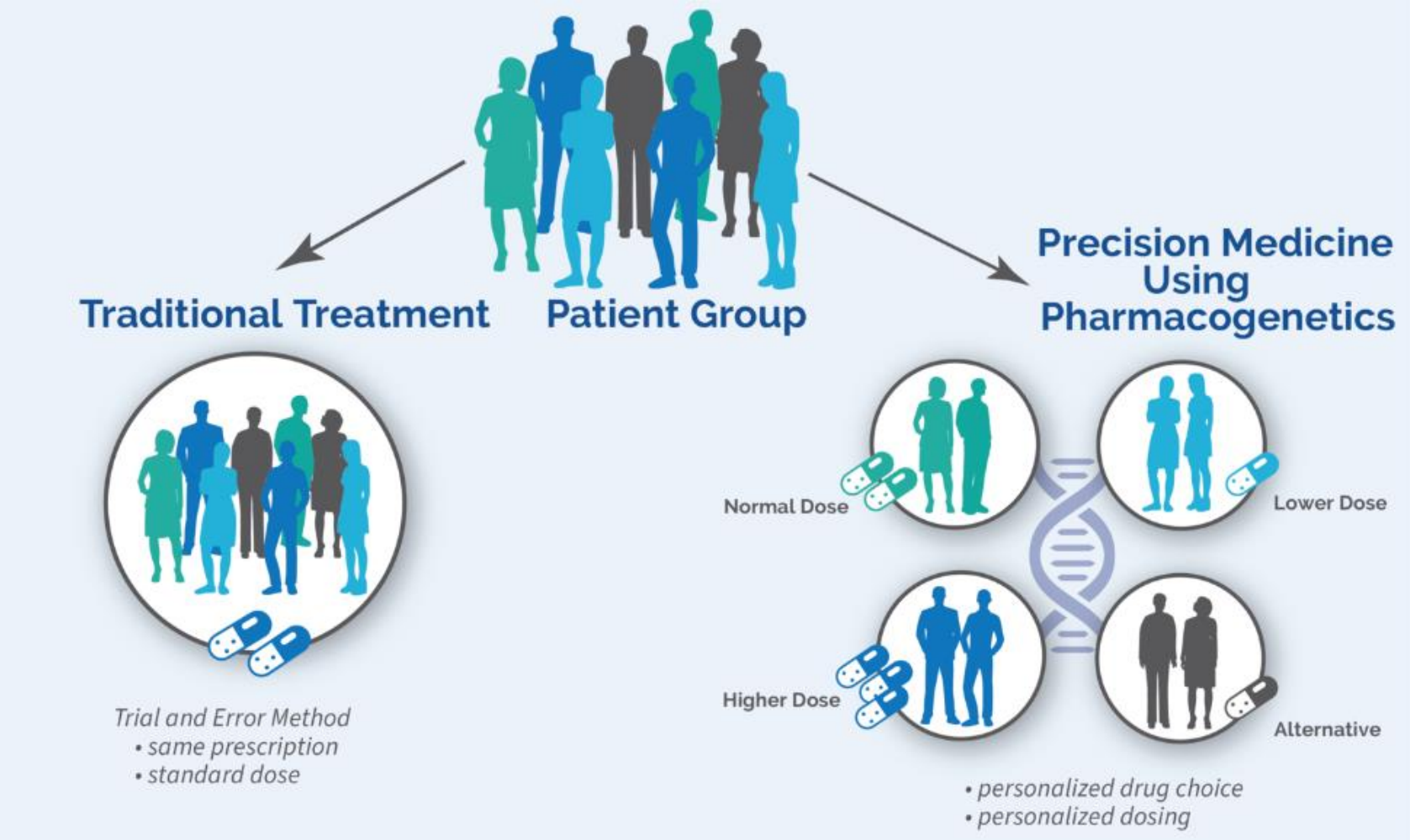
Polypharmacy is a Major Public Health Crisis

- 27-59% in home-dwelling elderly
- 38-91% in LTCFs residents

Consequences of Polypharmacy

- Adverse Drug Effects
- Drug-drug interactions
- Medication Non-Adherence
- Prescribing Cascades
- Risk of Hip Fracture
- Risk of Fall

How does PGx help?



PGx can Significantly Reduce ADRs

Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study

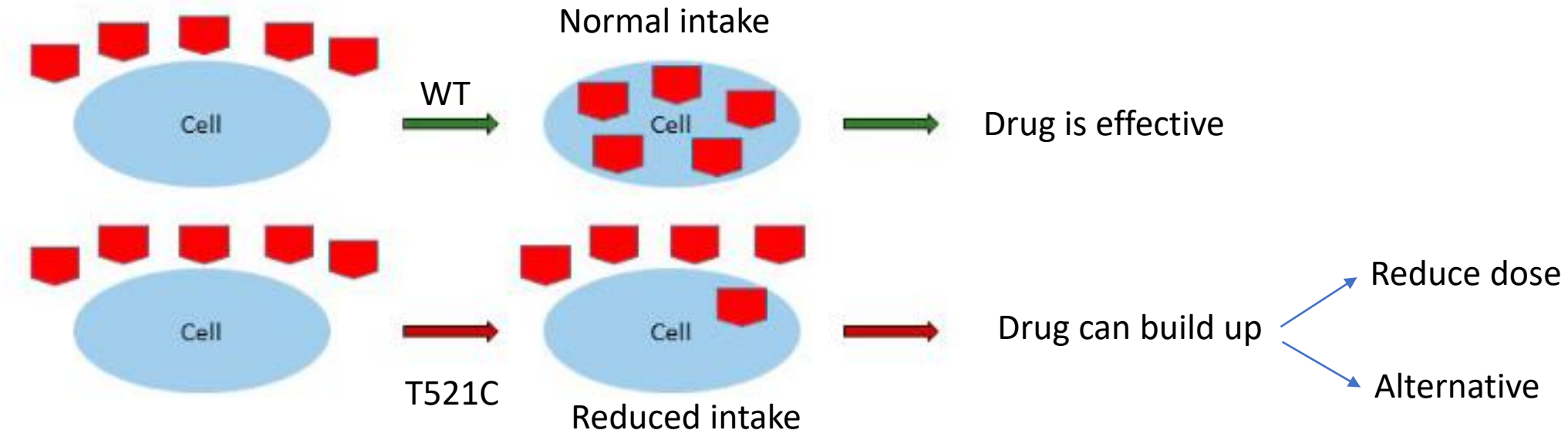
PGx test
-12-genes panel of 50 germline variants
-Actionable variant
-Index drug

Study population
-2017-2020
-6944 patients
    3342 study group
    3602 control group

Outcome
-30% reduction of adverse drug reaction (ADR)

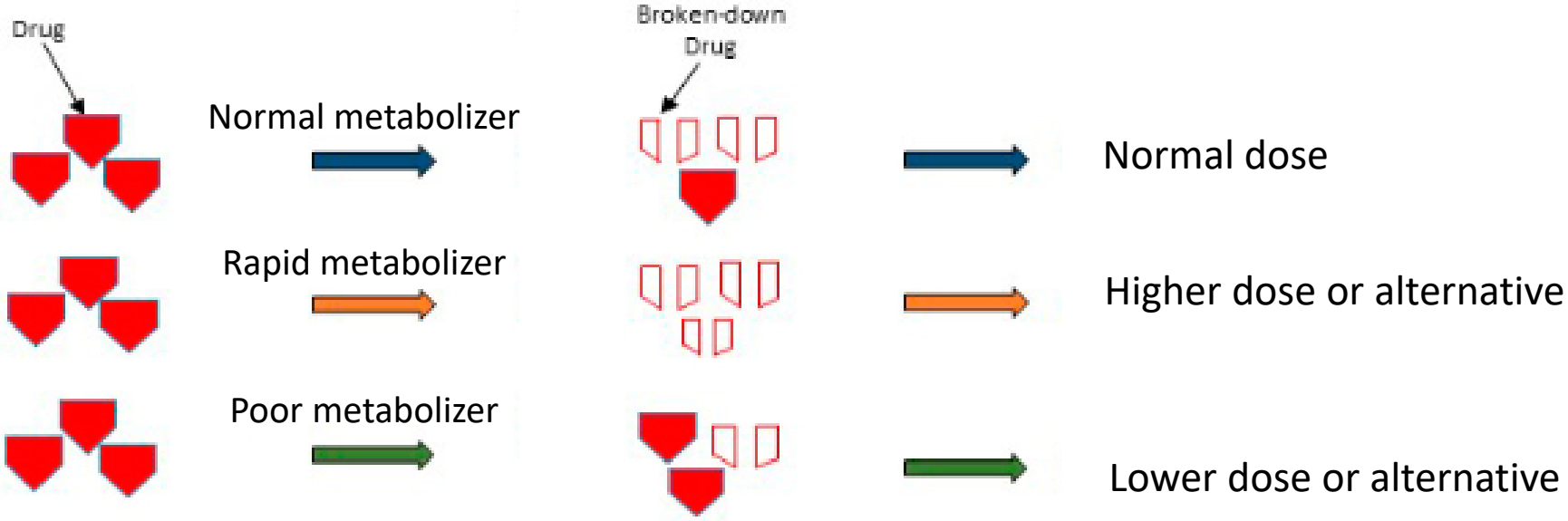
PGx Example 1: Drug transportation

Simvastatin and SLCO1B1 gene

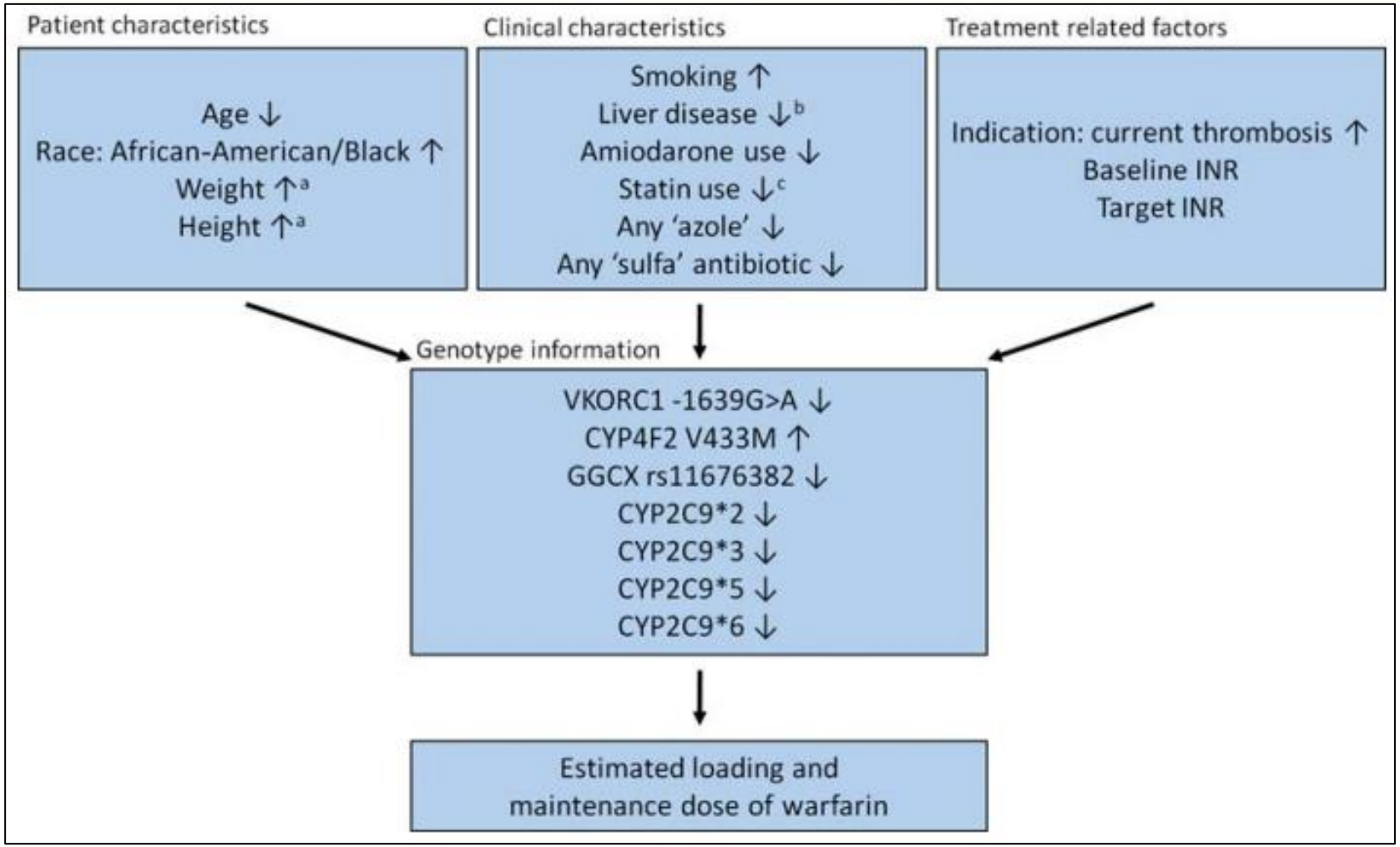


PGx Example 2: Drug Breakdown

Amitriptyline and CYP2D6 and CYP2C19 genes



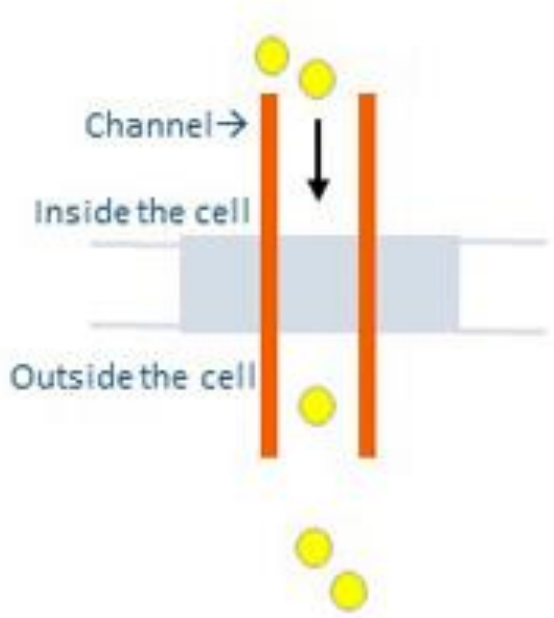
PGx Example 3: Warfarin Dosing Algorithm



PGx Example 4: Mutation Type

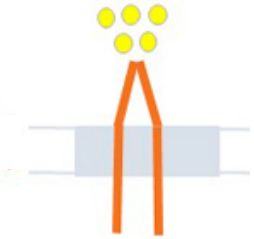
Ivacaftor and Cystic Fibrosis

Healthy individual



Normal CFTR protein

CF patient



Deformed CFTR protein

No CFTR protein made

PGx Example 4: Mutation Type

Ivacaftor and Cystic Fibrosis

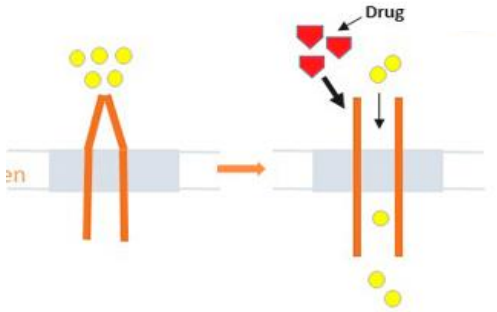
Cystic Fibrosis Patients

↓

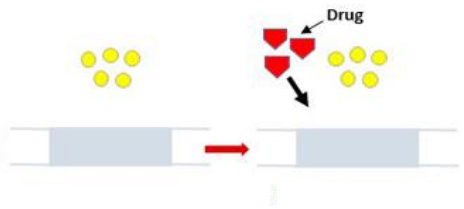
Test for CFTR mutation

Gating mutations ↙

Protein production mutations ↘



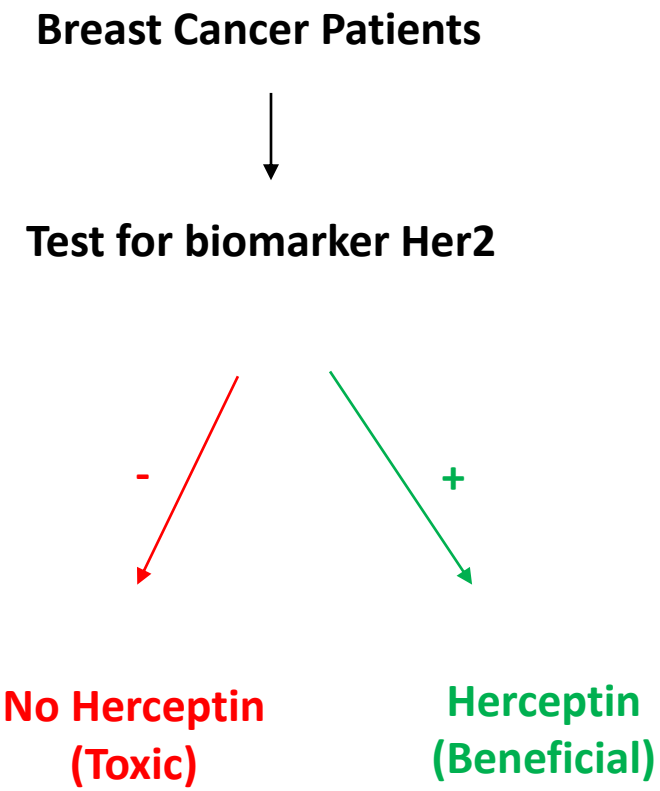
Ivacaftor works



Ivacaftor does not work

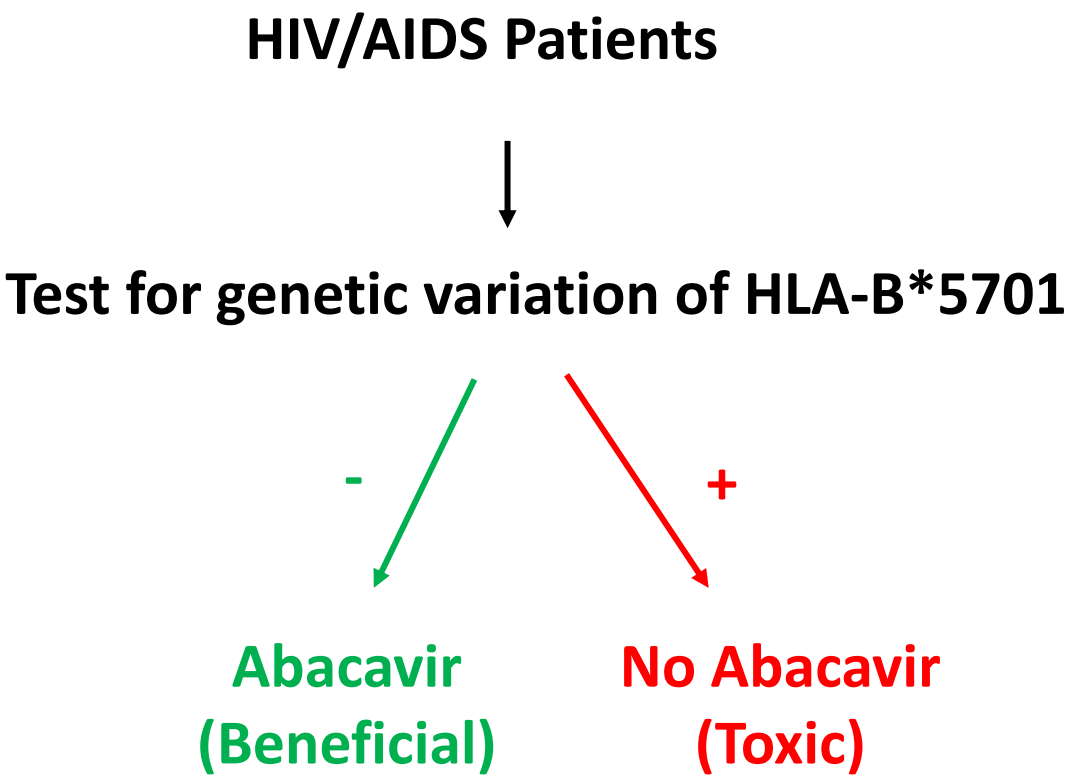
PGx Example 5: Targeted Therapy

Breast cancer and Herceptin



PGx Example 6: Genetic Variation

HIV/AIDS and Abacavir



PGx and OTC

Ibuprofen and CYP2C9

Genotypes	Activity Scores	Phenotypes	Therapeutic Recommendations
CYP2C9*1/*1	2	Normal metabolizer	Initiate with approved recommended dose
CYP2C9*1/*2	1.5	Intermediate metabolizer	Initiate with approved recommended dose
CYP2C9*1/*3 CYP2C9*2/*2	1	Intermediate metabolizer	Initiate with lowest recommended dose for shortest duration. Consider other risk factors such as age, hepatic impairment, CYP2C8*3 for ibuprofen. Titrate to clinical effect with close monitoring of adverse effect such as elevated BP or kidney dysfunction
CYP2C9*2/*3 CYP2C9*3/*3	0.5 0	Poor metabolizer	Initiate at 25%-50% of starting dose, or use alternative NSAIDs not metabolized by CYP2C9 (ASA, ketorolac, naproxen, sulindac)

***1: WT**
***2: Reduced activity**
***3: loss of function**

PGx and OTC

PPIs and CYP2C19

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation
CYP2C19 rapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *Helicobacter pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
CYP2C19 normal metabolizer	Normal PPI metabolism; may be at increased risk of therapeutic failure compared with CYP2C19 IMs and PMs	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *H. pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy
CYP2C19 intermediate metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy
CYP2C19 poor metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy

PGx and Polypharmacy

NCT02428660, J Manag Care Spec Pharm. 2018;24:1250-1259

- Medication Therapy Management - MTM
- MTM + Clinical Decision Support Tool (CDST) – CMTM
- CMTM + PGx – PGxMTM

- PGx helped identify more serious drug therapy problems (DTPs)
- Pharmacist recommendations were more readily accepted by a prescriber

PGx and Polypharmacy

NCT02378220, PLoS One. 2017;12:e0170905

- Home health management patients
- No PGx testing
- With PGx testing

- PGx reduced re-hospitalizations and ED visits

PGx and Polypharmacy

Drugs Aging. 2016;33:929-936

- Medication Review
- Medication Review + PGx

- PGx resulted in a 38% increase in medication change
- PGx resulted in ~$1300 medication cost savings per patient per year

PGx and Polypharmacy

Am J Case Rep. 2023;24:e938850

- A case report
- 70-year-old woman
- Polypharmacy
- Multiple Comorbidities

- PGx helped optimize statin-therapy to avoid Statin-associated muscular symptoms (SAMS)
- PGx could have helped initial dosing of warfarin

FidaLab PGx Test

Gene Symbol	Gene Name	Comprehensive	Cardiovascular	Pain	Psychiatry
ANKK1	ankyrin repeat and kinase domain containing 1	√			√
APOE	apolipoprotein E	√	√		
COMT	catechol-O-methyltransferase	√		√	√
CYP1A2	cytochrome P450 family 1 subfamily A member 2	√		√	√
CYP2B6	cytochrome P450 family 2 subfamily B member 6	√		√	√
CYP2C19	cytochrome P450 family 2 subfamily C member 19	√	√	√	√
CYP2C9	cytochrome P450 family 2 subfamily C member 9	√	√	√	√
CYP2D6	cytochrome P450 family 2 subfamily D member 6	√	√	√	√
CYP3A4	cytochrome P450 family 3 subfamily A member 4	√	√	√	√
CYP3A5	cytochrome P450 family 3 subfamily A member 5	√	√		
F2	coagulation factor II, thrombin	√	√		
F5	coagulation factor V	√	√		
HLA-B	major histocompatibility complex, class I, B	√			
MTHFR	methylenetetrahydrofolate reductase	√	√	√	√
OPRM1	opioid receptor mu 1	√			√
SLCO1B1	solute carrier organic anion transporter family member 1B1	√	√		
VKORC1	vitamin K epoxide reductase complex subunit 1	√	√		

FidaLab PGx Test Report

1

Rx Medication Review

a list of prescribed drugs and any gene or drug interactions

2

Drug Guide

a drug focused report by therapeutic category

3

Summary of Genes Tested

a summary of your results for all genes tested.

4

Detailed Explanation of Findings

a more informative view of drug and gene relationships

Rx Medication Review

Prescribed or Contemplated Gene Interactions	Major Drug Interaction	Moderate Drug Interaction
+ alprazolam (Xanax)		✓ + trazodone (Oleptro)
x citalopram (Celexa) DRD2 (rs1079598) C/C Increased Risk of Antipsychotic Weight Gain	✓ + trazodone (Oleptro)	
- tramadol(Ultram) CYP 2C19 Poor Metabolizer	✓ + trazodone (Oleptro)	
✓- codeine CYP 2C19 Poor Metabolizer		

Drug Guide

Normal

A drug in green font indicates that no genetic issues of clinical relevance were found for this drug among the genes tested.

Pain Management Neuropsychiatric

- methadone
+ Suboxone (buprenorphine and naloxone)
+ Buprenorphine

Pain Management

x lidocaine (xylocaine, various brands)
+ meperidine (Demerol)
x naproxen (Aleve)
- oxycodone++ (Oxycontin)
x ropivacaine (Naropin)
x tapentadol (Nucynta)
x tizanidine (Zanaflex)
+ alfentanil (Alfenta)

Increased Risk

A drug in yellow font indicates that genetic issues of clinical relevance were found for this drug. Extra caution should be observed when considering this drug for this patient.

Neuropsychiatric - Precognitive Drug

x tacrine (Cognex)

Neuropsychiatric - Anxiolytic

- diazepam (Valium)
+ alprazolam (Xanax)
+ midazolam (Versed)
x phenobarbital
+ triazolam (Halcion)
+ buspirone (BuSpar)
+ zolpidem (Ambien)

Antipsychotic

- haloperidol (Haldol)
+ lurasidone (Latuda)
x olanzapine (Zyprexa)

Extreme Risk

A drug in red font Indicates that serious genetic issues of clinical relevance were found for this drug and extreme caution or avoidance of this drug should be observed when considering this drug for this patient.

Neuropsychiatric - Antidepressant

+ desvenlafaxine (Pristiq)
x doxepin (Sinequan, Silenor, Prudoxin, Zonalon)
x escitalopram (Lexapro)
- fluoxetine (Prozac)
x amitriptyline (Elavil)
x imipramine (Tofranil)
+ mirtazapine (Remeron)
+ nefazodone (Serzone)
- nortriptyline (Aventyl,Pamelor)
- paroxetine (Paxil)
- sertraline (Zoloft)
+ trazodone (Oleptro)

Summary of Genes Tested

Genes affecting drug metabolism

Gene (Genotype)	Phenotype (Gene expression)	What it means
CYP1A2 *1F/*1F	Ultra Rapid Metabolizer	Extremely rapid metabolism expected for the enzyme controlled by this gene, especially in smokers. It may be difficult to achieve effective drug concentrations.
CYP2B6 *1/*1	Extensive Metabolizer	The patient is an extensive (normal) metabolizer, and changes in metabolism are not generally expected.
CYP2C19 *1/*17	Ultra Rapid Metabolizer	Extremely rapid metabolic enzyme activity expected for the enzyme controlled by this gene. It may be difficult to achieve effective drug concentrations. ++ Caution should be observed with pro-drugs, e.g., clopidogrel. Excessive active metabolite formation may occur and a high risk for adverse drug reactions exists (e.g., for clopidogrel this can lead to increased risk for serious bleeding).
CYP2C9 *1/*2	Intermediate Metabolizer	This genotype predicts less than normal metabolic enzyme activity for the enzyme controlled by this gene. Increased potential for drug accumulation and adverse drug reactions.
CYP2D6 2N *1/*41	Intermediate Metabolizer	This genotype predicts less than normal metabolic enzyme activity for the enzyme controlled by this gene. Increased potential for drug accumulation and adverse drug reactions. ++ Caution should be observed with pro-drugs, e.g., codeine. Less than normal active metabolite formation is expected and a full effect of the drug may not be achieved.

Summary of Genes Tested

Genes affecting response or function

Gene (Genotype)	Phenotype (Gene expression)	What it means
APOE E3/E3		This diplotype is associated with normal cardiovascular disease risk.
COMT G/G	Normal Activity	This genotype is associated with normal COMT activity.
Factor II G/G	Normal Risk	The patient is wildtype for Factor II Prothrombin. Patients with this genotype (G/G) are associated with a normal risk of developing an abnormal blood clot.
Factor V Leiden G/G	Normal Risk	The patient is wildtype for Factor V Prothrombin. Patients with this genotype (G/G) are associated with a normal risk of developing an abnormal blood clot.
MTHFR CC-677/AC-1298	Impaired Function	This genotype predicts impaired function of the enzyme methylenetetrahydrofolate reductase (MTHFR). This enzyme plays a crucial role in converting dietary folate into methylfolate, the active form of this critical B vitamin. Impaired MTHFR function is associated with methylfolate deficiency which can lead to impaired neurotransmitter synthesis and other biochemical abnormalities. Patients with these MTHFR variants are associated with improved depression treatment outcomes with L-methylfolate treatment adjunctive to SSRI/SNRI therapy. This genotype is also associated with increased plasma homocysteine levels which may be associated with an increased risk of premature cardiovascular disease. Dietary supplementation with L-methylfolate supplements may be beneficial to your health.
OPRM1 A/A	Normal Responder	Normal opiate receptor function expected. Morphine and other active opiates (e.g., oxymorphone, fentanyl) should produce a usual analgesic response.

Detailed Explanation of Findings

Gene	Phenotype (Gene expression)	What it means
CYP1A2	Ultra Rapid Metabolizer	Extremely rapid metabolism expected for the enzyme controlled by this gene, especially in smokers. It may be difficult to achieve effective drug concentrations.

COMMON MEDICINES METABOLIZED BY CYP1A2

Neuropsychiatric

amphetamine (Adderall) *
asenapine (Saphris)
clomipramine (Anafranil) *
clozapine (Clozaril)
duloxetine (Cymbalta)
mirtazapine (Remeron
olanzapine (Zyprexa)
paroxetine (Paxil) *
perphenazine (Trilafon) *
promazine (Sparine) tacrine (Cognex) tiagabine (Gabitril) *
thioridazine (Mellaril)
ziprasidone (Geodon) *

Miscellaneous

caffeine
carvedilol (Coreg) *
clopidogrel (Plavix) *
estradiol
propranolol (Inderal)
ritonavir (Norvir) *
theophylline

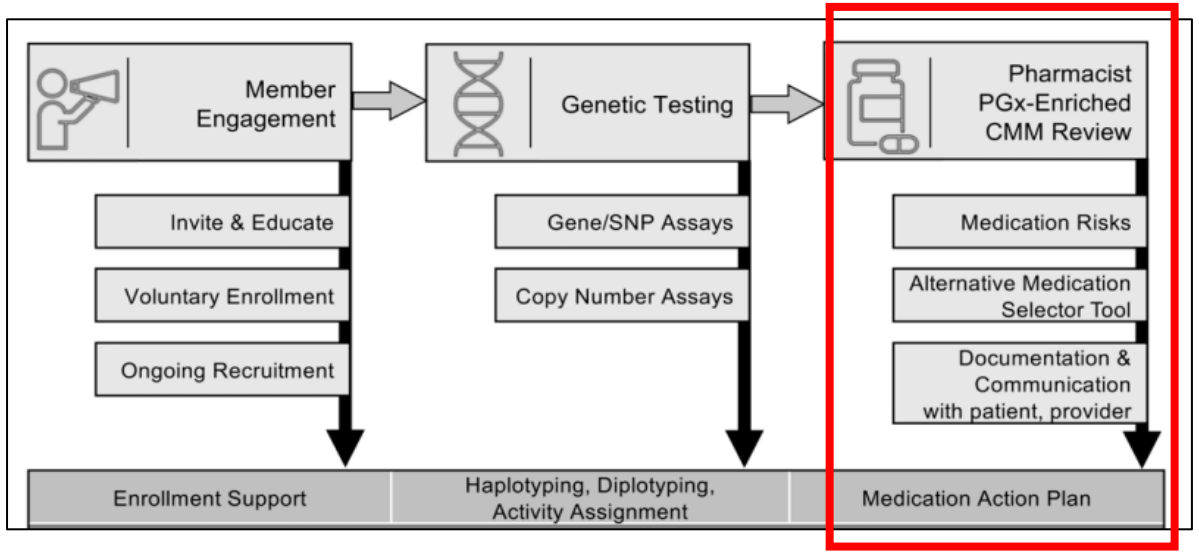
Pain and Local Anesthetics

cyclobenzaprine (Flexeril)
naproxen (Aleve)
tizanidine (Zanaflex)
zolmitriptan (Zomig)
lidocaine (xylocaine, various brands)
ropivacaine (Naropin)

Medication Support Tool

Prescribed or Contemplated Gene Interactions	Major Drug Interaction	Moderate Drug Interaction
+ alprazolam (Xanax)		✓ + trazodone (Oleptro)
x citalopram (Celexa) DRD2 (rs1079598) C/C Increased Risk of Antipsychotic Weight Gain	✓ + trazodone (Oleptro)	
- tramadol(Ultram) CYP 2C19 Poor Metabolizer	✓ + trazodone (Oleptro)	
✓ - codeine CYP 2C19 Poor Metabolizer		
✓ + trazodone (Oleptro)	x citalopram (Celexa) - tramadol (Ultram)	+ alprazolam (Xanax)

Implementation of PGx Requires Team Efforts



- Patient education and engagement
- PGx testing
- Comprehensive medication risk evaluation
- Pharmacist intervention
- Efficient clinical decision support tools
- Dissemination of information to physicians

PGx Resources

- CPIC (cpicpgx.org)
  - Clinical Pharmacogenetics Implementation Consortium
  - International consortium that facilitates the use of pharmacogenetic tests for patient care
- FDA (FDA)
  - Table of gene-drug interactions that appear in FDA-approved drug labeling
- PharmGKB (PharmGKB)
  - NIH-funded pharmacogenomics knowledge resource
  - Collects, curates and disseminates clinical guidelines, drug labels, actionable gene-drug associations and genotype-phenotype relationships

PGx Medicare Reimbursement (L38294)

Medical record:

1. The patient has a diagnosis for which pharmacologic therapy is reasonable and necessary, and the drug or drugs that the clinician is considering using must be reasonable and necessary for the treatment of the patient’s diagnosis.
2. The clinician has made an initial personalized decision for the patient based on the patient’s diagnosis, the patient’s other medical conditions, other medications the patient is taking, professional judgement, clinical science and basic science pertinent to the drug (e.g. mechanism of action, side effects), the patient’s past medical history and when pertinent family history and the patient's preferences and values.
3. The provider performing the service must have a record of what drug(s) is/are being considered and for what indication(s) to ensure the test performed is reasonable and necessary.

PGx Medicare Reimbursement (L38294)

--Support single gene or multi-gene PGx tests

--Currently, does not support combinatorial PGx testing

--Support PGx testing for refining the usage of actionable drugs

--Currently, does not support PGx testing for medication selection

Presenter info

- Educated and trained in Molecular Genetics from BS, PhD, and Postdoctoral Fellowship.
- Studied virus-induced cancer at UW
- Cofounded FidaLab in 2016 and dedicated service to LTC communities in NW for the last 5 years.