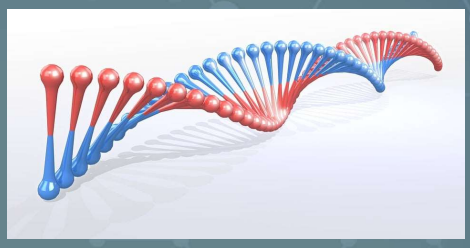
Synchrony PHARMACY
The Art of Healing...A History of Caring

Medications, DNA and Improving Care

Rob Leffler, RPh, BCGP, FASCP
Vice President of Clinical Services
Synchrony Pharmacy



1

Objectives

- Identify what pharmacogenomic testing is and how it can be utilized
- Describe how pharmacogenetic tests can inform prescribing decisions
- Discuss pros and cons of pharmacogenetic testing
- Identify patients that could benefit from pharmacogenomic testing
- Explain why pharmacogenomic testing is valuable to another healthcare professional

Synchrony PHARMACY

2

Personalized Medicine

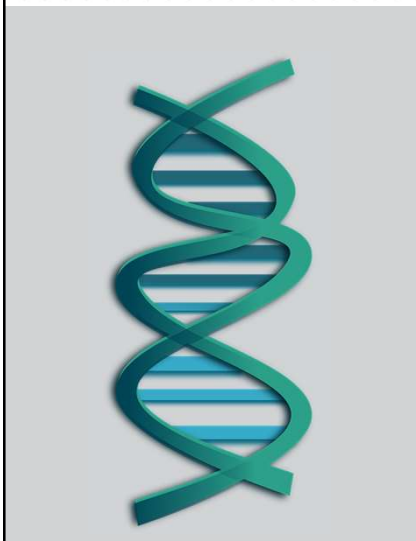
- Provide the "right patient with the right drug at the right dose at the right time"
- Genetic or protein biomarkers that may predict medication response or adverse effects
- Pharmacogenomics
  - Subset of personalized medicine currently implemented in certain practice settings[1]

https://www.genome.gov/27530645/faq-about-pharmacogenomics/
[1]Relling and Evans (2015) *Nature* 526(7573):343-50.

Synchrony PHARMACY

3

PGx/PGX and PGt



- Genomics
  - Genome – Study of the entire DNA sequence
- Pharmacogenomics (PGx or PGX)
  - Study of how a person's genes affect a person's response to particular drugs
  - More general term for the interface of genomics and therapeutics
- Pharmacogenetics (PGt)
  - Study of how one gene affects a person's response to a particular drug

https://ghr.nlm.nih.gov/handbook/precisionmedicine/precisionvspersonalized

4

Focusing in on Geriatrics

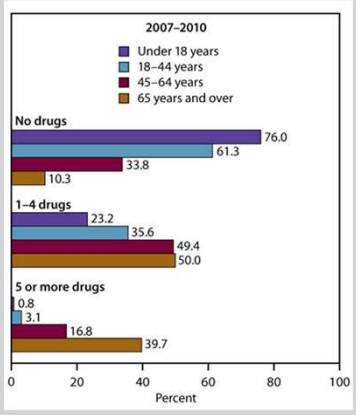
- Treating geriatric patients can be difficult due to polypharmacy
  - About 40% of geriatric patients are on ≥5 Rx medications[1]
  - Long-term care residents take an average of 8.5 prescriptions on a regular basis[2]
- The prevalence and severity of adverse drug reactions (ADRs) is increased in older people
  - 5-10% of hospital admissions amongst older people are related to ADRs[3]
  - Older people are 4x more likely to be admitted to hospital because of ADR (16.6% vs. 4.1%) and are more likely to have preventable ADRs (88% vs. 24%)[4]

[1]Qato (2008) *JAMA* 300(24):2867-78.
[2]Stevenson (2014) *Med Care* 52(10):884-90.
[3]Davies (2015) *Br J Clin Pharmacol* 80(4): 796-807.
[4]Beijer (2002) *Pharm World Sci* 24(2):46-54.

Synchrony PHARMACY

5

Why Are Adverse Drug Reactions Increased?



Prescription drug use in the past 30 days, by number of drugs taken and age: United States 2007-2010.[4]

- Comorbidities[1,2]
- Polypharmacy[2]
- Physiologic Changes[2,3]
  - Pharmacokinetic changes
  - Pharmacodynamic changes

[1]Nobili (2011) *J Comorb* 1:28-44.
[2]Davies (2015) *Br J Clin Pharmacol* 80(4): 796-807.
[3]Brunton (2018) *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 13th ed
[4]Katzung (2012) *Basic and Clinical Pharmacology*, 12th ed

6

The Role of PGx in Geriatric ADRs

- Frequently hospitalized older adults (≥65 year old) showed **significantly higher frequency of PGx polymorphisms** compared to matched older adults with polypharmacy rarely admitted to hospital[1]
  - ≥3 hospital admissions in last 2 years and taking ≥5 medications
  - Limitation: 6 cases and 6 controls (nested case-control)
- CYP450 substrates associated with **greater readmission rates and greater healthcare costs**[2]
  - At discharge, at least one CYP450 substrate was associated with 10% increase in odds of 90-day readmission (OR of 1.104 in claims and 1.128 in EMR; P<0.001)
  - Substrates of CYP450 2D6 and 1A2 reported out individual risk in both cohorts
  - Any CYP450 substrate associated with increased monthly medical costs (+$397, p<0.003)

[1]Finkelstein (2016) *Pharmacogenomics Pers Med* 9:107-116.
[2]McCoy (2017) *Pharmacogenomics J* 17(4):382-385.

Synchrony PHARMACY

7

Cardiology Example

- Heart Attack (Myocardial Infarction)
  - For a major heart attack, two primary treatment approaches:
    - Open-heart bypass surgery
    - Stent placement
  - After stent placement
    - Control blood pressure
    - Control cholesterol
    - Prevent additional clots
- Clopidogrel, prasugrel, or ticagrelor used to prevent additional clots
  - Too much drug: bleeding
  - Too little drug: clotting

8

Cardiology - continued

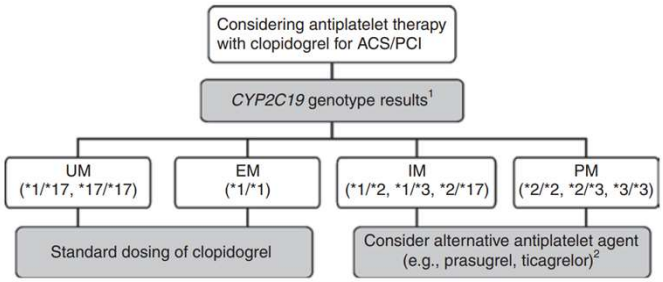
CPIC dosing guidelines for clopidogrel and CYP2C19[1]

- FDA label updated (9/2016) to consider alternatives in CYP2C19 PMs
- Not all studies show genotype influences clinical response[2]

Decreased CYP2C19 *in vivo* activity with older age[3]

- No age dosage adjustment on FDA label

CPIC dosing guidelines

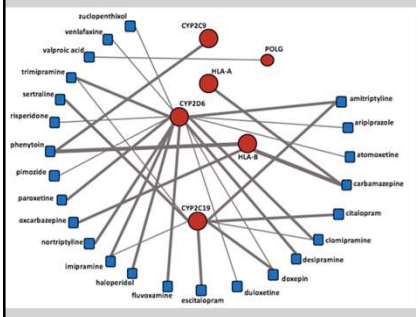


[1]Scott (2013) *Clin Pharmacol Ther* 94(3): 317–323.
[2]Rodriguez-Gonzalez (2018) *J Clin Pharmacol* 58(10):1274-1283.
[3]Bebia (2004) *Clin Pharmacol Ther* 76(6):618-27.

Synchrony PHARMACY

9

Depression Example



- STAR*D found % patients achieving remission decreases with added medication trials[1]
- HCPs underestimate patient emotional burden from multiple medication failures[2]
- Example of geriatric consideration:
  - Citalopram maximum dose 20mg/daily due to QTc risk
  - CYP2C19 variation, not dose or serum level, shown to be associated with QTc prolongation[3]

[1]Rush (2006) *Am J Psychiatry* 163(11):1905-17. [2]Mago (2018) *Ann Gen Psychiatry* 17:20. [3]Kumar (2014) *J Psychopharmacol* 28(12):1143-8. [4]Bousman (2018) *Curr Opin Psychiatry* [Epub ahead of print]

10

How Much Do We Know?

- Medications impacted by pharmacogenetics are used commonly
  - From the Top 200 most frequently prescribed drugs
    - 13 medications list relevant pharmacogenetic information
  - Up to 25% of patients take a medication where pharmacogenetics information has been shown to be relevant
  - More than 90% of medications are metabolized by just 6 liver enzymes that are assayed with PGX testing

Vaughan KTL, et al. J Med Lib Assoc 2014;102(1):47-51.
Tom Lynch, PharmD, Amy Price, MD, Eastern Virginia Medical School, Norfolk, Virginia *Am Fam Physician.* 2007 Aug 1;76(3):391-396.

11

Drugs w/PGX Guidelines

- Clinical Pharmacogenetics Implementation Consortium (CPIC)
  - 23 guideline publications
    - Antidepressants (e.g., TCAs, SSRIs)
    - Anticoagulants (warfarin)
    - Pain medications (e.g., codeine)
- Royal Dutch Association for the Advancement of Pharmacy Pharmacogenetics Working Group
  - 52 drugs are mentioned in their guidelines
- Food and Drug Administration (FDA)
  - 130 commonly prescribed drugs have dosing guidelines based on PGX
- 80% of the population carry at least one gene mutation affecting drug metabolism

Synchrony PHARMACY

12

FDA Dosing Guidelines

- July 2015 – a new medication for schizophrenia and depression was approved
  - Brexpiprazole (Rexulti)
  - 7-10% of the population have decreased clearance of CYP2D6
    - Adverse drug reactions due to increased drug exposure at standard doses
  - Dose adjustment by 50% for
    - CYP2D6 poor metabolizers
    - CYP2D6 inhibitor
    - CYP2D6 inducers (Ultra metabolizers may metabolize too quickly to have a therapeutic response)

Synchrony PHARMACY

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205422s000lbl.pdf. Accessed 10/4/16

13

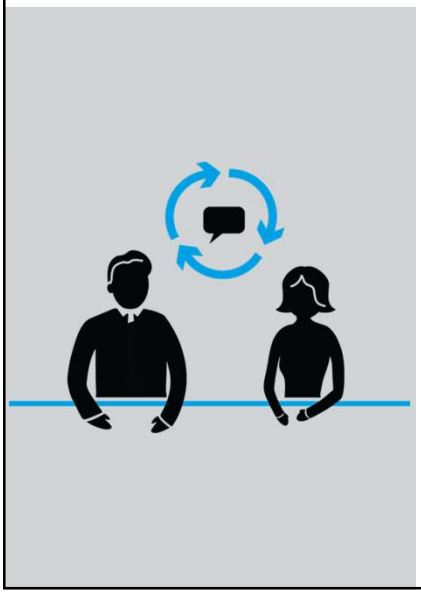
How Much is there Still to Learn?

- Knowledge about pharmacogenetics is lacking
  - Only 29% of physicians report any education related to pharmacogenetics (14.7% in medical school, 23.0% in postgraduate training)
  - Only 10.3% of physicians felt adequately informed about pharmacogenetic testing
  - Only 12.9% of physicians have ordered a pharmacogenetic test in last 6 months
- This is changing . . .

Stanek EJ, et al. Clin Pharmacol Ther 2012;91(3):450-8.

14

What Are We Trying to Do?



- Improve the patient care
- Improve population health
- Reduce per capita cost of health care

http://www.aha.org/content/15/brief-3aim.pdf

15

Cost

- Cost of pharmacogenetic testing
- Cost of drug therapy
  - Plavix/clopidogrel 75mg ($9-90 for 30ct Rx) *taken once daily*
  - Effient/prasugrel 10mg ($363-406 for 30ct Rx, brand-only) *taken once daily*
  - Brilinta/ticagrelor 90mg ($315-352 for 60ct Rx, brand-only) *taken twice daily*
- Savings
  - Potential $225-300 savings per month by using clopidogrel
  - How much does a blood clot cost?
  - How much does excessive bleeding cost?

Goodrx.com
Mauri L, et al. NEJM 2014;371(23):2155-66.

Synchrony PHARMACY

16

Cost: Long-Term Care

- Long-term care residents, over age 45, with 5 or more Rx medications
- 132 patients received testing for 17 genes, data reviewed by a pharmacist for clinical recommendations
- Approximately half of tested were found to have actionable findings; of those with actionable findings, pharmacist recommendation was for adjustment of 1-3 drugs
- Drug cost savings alone: $621 per patient saved annually (2-3 year average length of stay?)
- Limitation: variability of the pharmacist vs. guidelines

Saldivar JS, Taylor D, Sugarman EA, et al. Pharmgenomics Pers Med 2016;9(1-6).

17

Cost Example:

- 76 year old male: famotidine, gabapentin, levothyroxine, metoclopramide, mirtazapine, morphine, omeprazole, promethazine, sertraline, tamsulosin
- CYP2C19 *1/*17 (UM) – ultra rapid metabolizer
- HTR2A (rs6311 G/G) – increased susceptibility to SSRI-induced side effects
- Discontinue sertraline (SSRI) likely little contribution to combination antidepressant therapy with mirtazapine
- Estimated savings $907 annually

Saldivar JS, Taylor D, Sugarman EA, et al. Pharmgenomics Pers Med 2016;9(1-6).

Synchrony PHARMACY

18

More Information about Costs

- Medicare B patients
  - Many Medicare B patients have no copay for PGX testing
- Aetna patients
  - Clopidogrel (Plavix)
  - Tetrabenazine (Xenazine)
- Medicaid patients
  - Many state Medicaid plans cover PGX testing

Synchrony PHARMACY

19

What Are the Potential Benefits?

- Improve efficacy of therapy
- Reduce/avoid adverse drug reactions
- Select the correct starting dose
- Reduce total health care costs

20

What Are the Potential Challenges?

- Training/Education
  - Usefulness
  - When to order
  - How to obtain the sample
  - What to do with the results
- Individual patient-level cost
- Doesn't help with every medication

Synchrony PHARMACY

21

More Challenges

- Epigenetics – gene expression is modified rather than the genetic code itself
  - Traumatic life events or early chronic stress can affect susceptibility to disease
- Phenoconversion – looking strictly at genotype doesn't tell us everything
  - Genotype in one test showed 4% expected to be poor metabolizers of venlafaxine
  - Blood tests showed that 27% were poor metabolizers

J Clin Psychiatry. 2013 Jun;74(6):614-21. doi: 10.4088/JCP.12m07807. Epub 2013 Mar 13

Synchrony PHARMACY

22

Who Might be Tested?

- Mental health
  - > 2 Psychoactive medications
  - Trigger MDS QI profile for symptoms of depression without treatment
  - Psychiatric hospitalizations
  - Side effects
  - Persistent symptoms or poor response
  - One study indicated 87% of SSRIs have a gene conflict

23

Who Might be Tested?

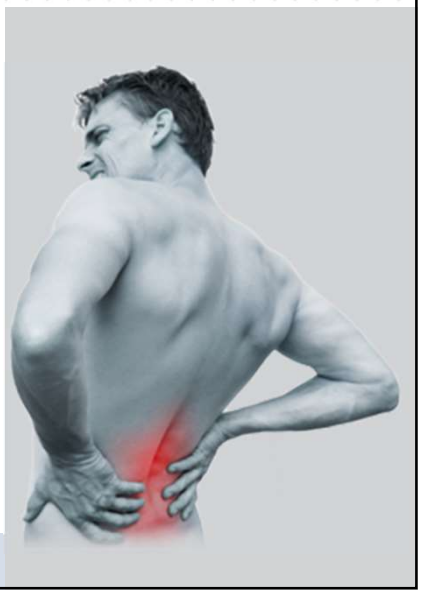
- Mental health – continued
  - Only 30-40% achieve remission with 1st drug
  - About 50% of antidepressant response is due to genetic polymorphisms
  - Matching drugs to symptoms may not increase response
    - Ex: Sedating antidepressant for a depressed patient with insomnia
    - This was no more helpful with depression than a stimulating medication

1. Kemp, et al. 2008 2. Fabbri, et al 2014. e. Simon, et al. 1998

24

Who Might be Tested?

- Pain management
  - New diagnosis
  - New medication
  - Persistent symptoms
  - Multiple changes in drug therapy
  - Side effects
  - Pain medication allergies



Synchrony PHARMACY

25

Who Might be Tested?

- Pain management – continued
  - 80% of patients experiencing an adverse event related to opioids have altered CYP2D6 metabolism

26

Who Might be Tested?

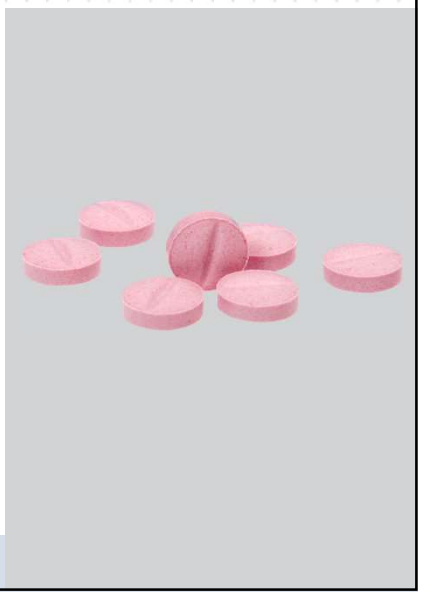
- Cardiovascular disease
  - clopidogrel (Plavix), ticagrelor (Brilinta), prasugrel (Effient)
    - European/African ancestry ~30% have a *2
    - Oceanian ancestry: ~ 60% have a *2
    - 36% of the population has a CYP2C19 variant causing clopidogrel to be ineffective
    - 28% of the population has a CYP2C19 variant that increases risk of bleeding on clopidogrel

Synchrony PHARMACY

27

Who Might be Tested?

- Cardiovascular disease – continued
  - Statins
    - Branded drugs
    - Simvastatin – dosing recommendations based on phenotype
  - Warfarin
    - Dosing



Synchrony PHARMACY

28

Who Might be Tested?

- Others
  - Mental status change
  - Unexplained falls
  - Increased fatigue
  - Unexplained weight loss/gain
  - Non-responders
  - Need for increased ADL help

29

The Art of Persuasion

- Emphasize the benefits
  - Less trial and error prescribing
  - Minimize adverse drug reactions
  - Improve quality of life
  - Manage health care costs

Synchrony PHARMACY

30

Frequent Questions from Prescribers

- I'm not trained to interpret the results
  - Work with a group that helps interpret the results
  - It's a collaborative process
  - Set goals for testing
- I don't want the liability of having the information available
  - Do you want the liability of not testing?
- There isn't enough evidence to support it's use
  - That may have been true at one time – FDA, CPIC, PharmGKB
  - Using a lab that recommends evidence-based recommendations

31

Frequent ?'s from Patients/Families

- How much will it cost?
  - This can't always be predicted. It can vary from nothing to an average lab copay – if covered.
  - Contact the provider and see if coverage can be determined
    - How much is preventing a heart attack worth?
    - How much is effectively treating behaviors or depression worth?
- I don't want my DNA tested/Social concerns about information genetically linked diseases
  - This information is kept completely private/HIPAA
  - The tests look at drug metabolism – pharmacogenetics not genetic tests

Synchrony PHARMACY

32

This is Simple . . . Let's Get Started

- Mechanism-based vs. evidence-based approach to treatment
- Other drugs affected? Inducers/Inhibitors
- Drug-drug-gene interactions?
- Multiple genes at once?
- More complicated interpretation?
- Lacking guidelines?
- Does One plus One equal Two? (No)

Hirsh/Rokach B, et al. Pharmacother 2015;2:140-7.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm327922.htm
Kisor DF, et al. Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. JBL 2013.

Synchrony PHARMACY

33

How Do We Succeed?

- Use a single lab
- Work with a PGX trained pharmacist
- Use it as one piece of information with other available data
- Have reasonable expectations – a normal metabolizer isn't a bad thing; no news can be good news
- Use to guide therapy selection
- Use evidence-based recommendations

Synchrony PHARMACY

34

How Do We Get Involved?

- Get order from a prescriber
- Test kit
  - Billing information
  - Test swabs
- Send to lab
- Receive test results

Synchrony PHARMACY

35

QUESTIONS?

Rob Leffler, R.Ph., BCGP, FASCP
Vice President of Clinical Services
e: rob.leffler@synchronyhs.com

Synchrony PHARMACY

36

2024 Annual Meeting
Session #10: Medications, DNA & Improving Care
November 20, 2024

Scan this code with your phone to access the training's evaluation form!

Synchrony PHARMACY

37

37