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Pharmacogenetics in Clinical Practice: Focus on Opioids

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Disclosures

- Jeanine
  - Ethicon
  - Published author in included paper
- Melissa Murfin
  - Volunteer member of CPIC

Objectives

Explain	Explain how genetics plays a role in drug metabolism/response
Interpret	Interpret clinical differences between metabolic phenotypes and activity scores
Utilize	Utilize prescribing recommendations to optimize choice of medications with clinical correlations to genomic variants

PGX Potential

- Minimize drug toxicity
- Maximize drug efficacy
- Predict patients with alternate response to drug intervention
- Help practitioners understand the variability of drug responses
- Assist in drug discovery and development

Pharmacogenetic Prescribing

Decrease potential for adverse drug reactions

Improve likelihood of medication response

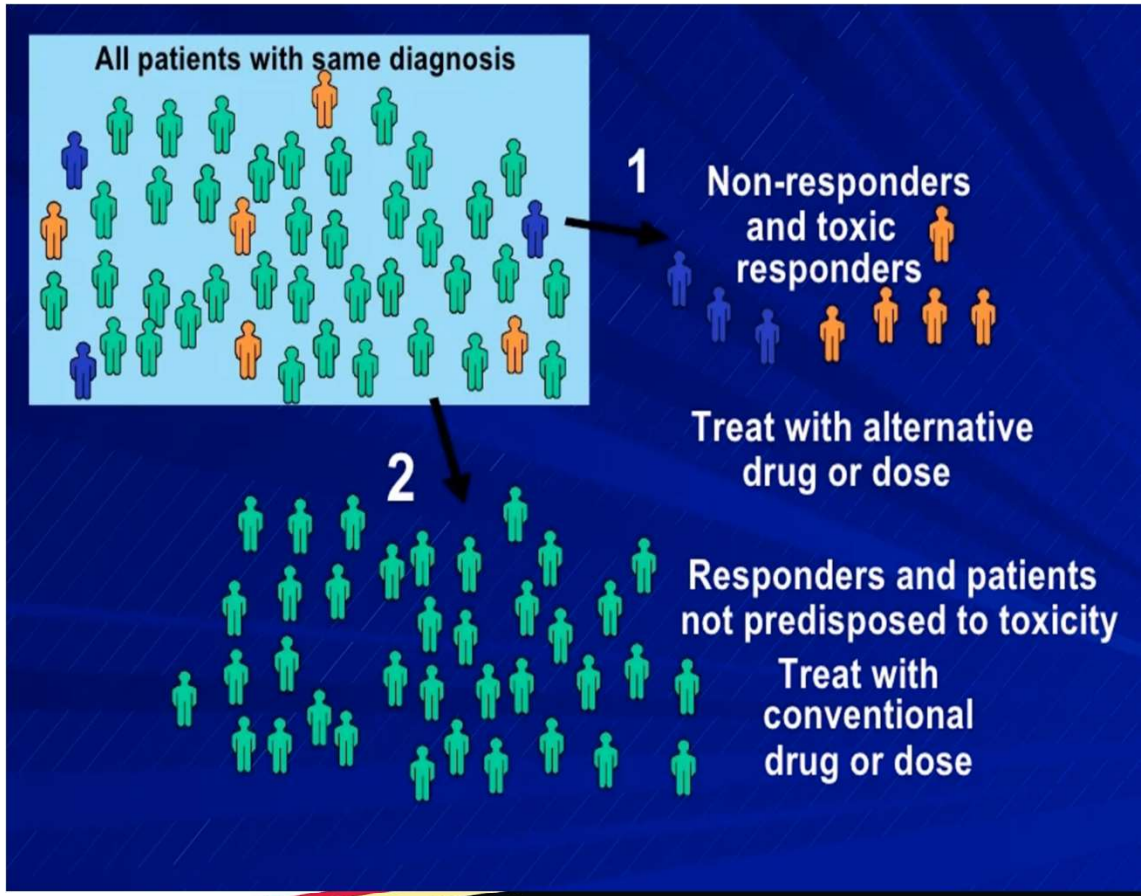
Pharmacogenetic Prescribing

CURRENTLY

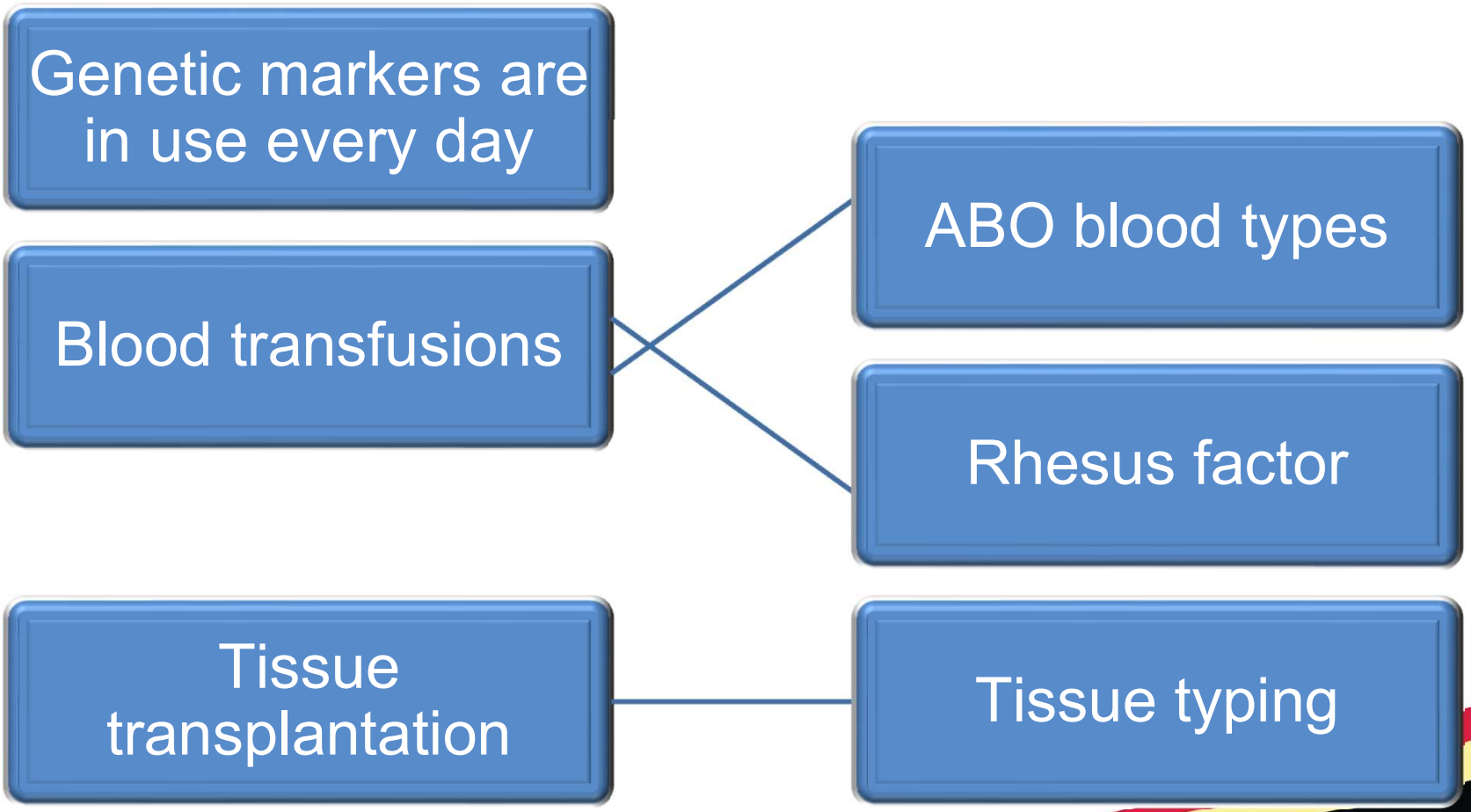
- One size fits all
- Works for up to 40% of patients

CUSTOMIZED

- Drug or dose specifically chosen for the patient
- Ideal for 60% of the of the population
- Decreased risk of ADR



Biomarkers in Practice



Adverse drug reactions (ADRs)

US Emergency Dept (ED) visits from 2017 – 2019

National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project

38.6% led to hospitalization

6.1 per 1000 due to ADRs

https://pubmed.ncbi.nlm.nih.gov/34609453/

Drug Response

Prodrugs

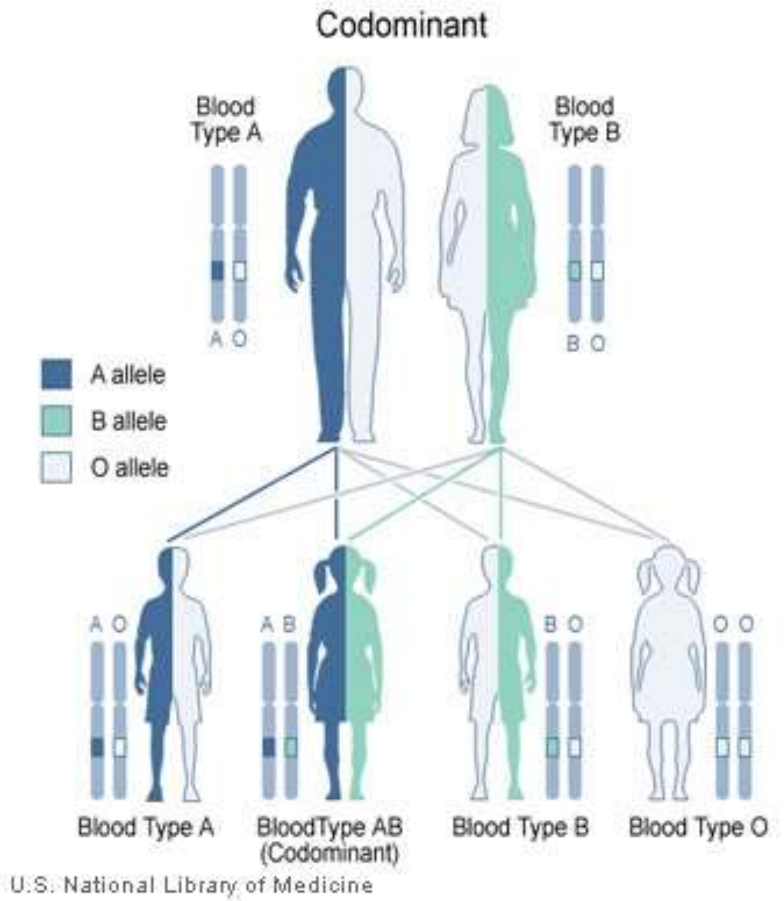
- Clopidogrel (Plavix)
- Codeine

Antidepressants

- 20 - 50 out of 100 patients with symptomatic improvement

https://www.ncbi.nlm.nih.gov/books/NBK361016/#:~:text=Studies%20involving%20adults%20have%20shown,within%20one%20to%20two%20years.

Pharmacogenetics

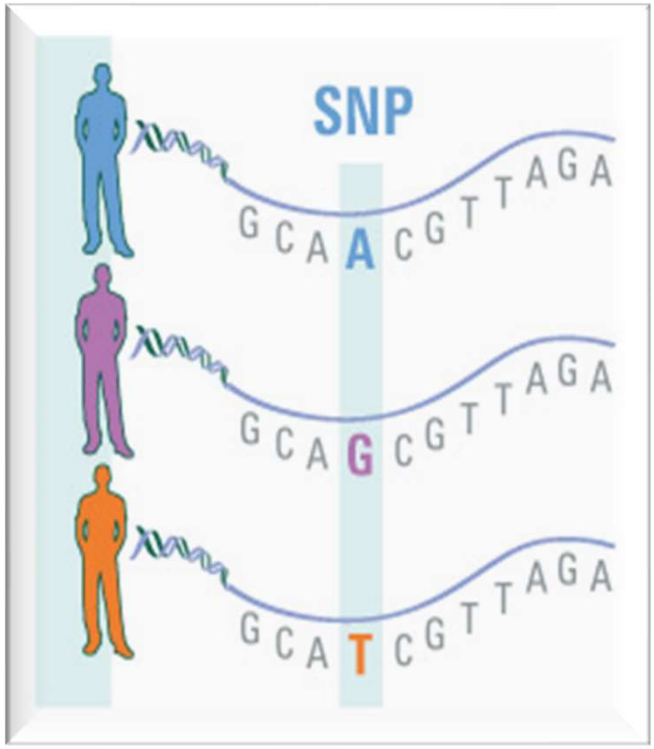


- Polymorphisms
  - Genetic variation among individuals within a specific species or population
  - Promotes genetic diversity
  - Ex: blood types

http://wikidoc.org/index.php/ABO_blood_group_system

Single Nucleotide Polymorphisms (SNPs)

- Single nucleotide exchanged for another at a point on the individual's genome
- Normal genetic variation
- Some cause change in amino acid or protein code
- Some have NO effect
- Genotype

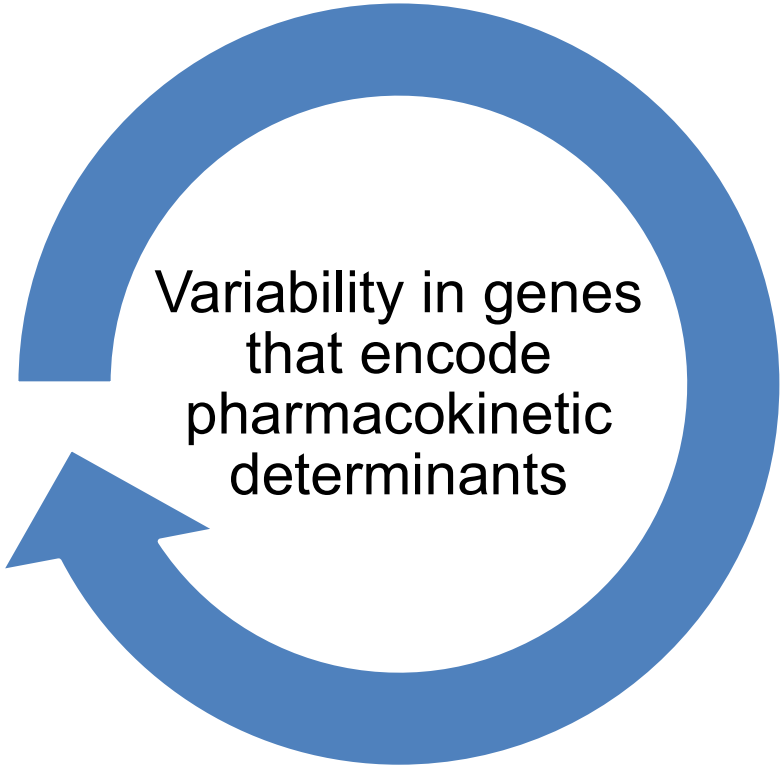


http://www.broadinstitute.org/education/glossary/snp

Pharmacogenetics

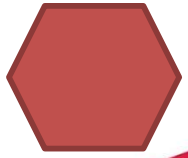
Drug response determined by	• Genetic factors • Environmental factors
Twin studies	• 75 – 85% of variation in $t_{1/2}$ due to genetics
Question	• Which genetic variants are clinically relevant?

Pharmacogenetic Phenotypes

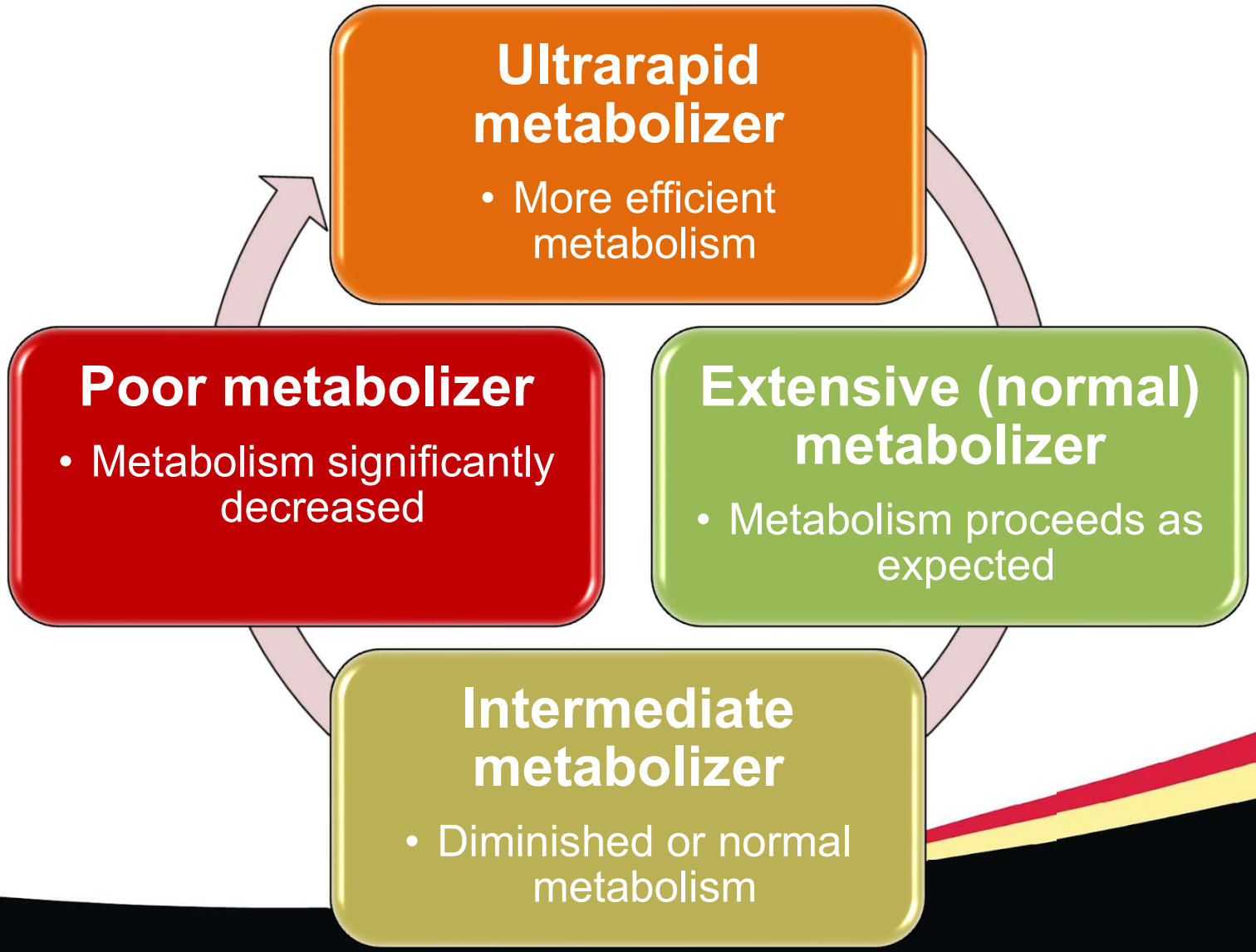


- Metabolizing enzymes
- Determine therapeutic response and ADRs
- Some are monogenic
  - Ex: fast vs slow acetylation
- Some are multigenic
  - Ex: CYP 450 Extensive vs poor metabolizers

PHENOTYPE	GENOTYPE	EFFECTS
A. extensive or normal drug metabolizers (EM) (75 – 85%)	homozygous or heterozygous for wild type allele.	Normal metabolism.No dose modification needed.
B.intermediate metabolizer phenotype (IM) (10 - 15%)	heterozygous for the wild type allele	may require lower than average drug dose for optimal therapeutic response.
C. poor metabolizers (PM) (5 – 10%)	mutation or deletion of both alleles	accumulation of drug substrates in their systems with attendant effects.
D. ultrarapid metabolizers (UM) (2 – 7%)	gene amplification .	drug failure



Metabolic Phenotypes



Clinical Phenotypes

Ultrarapid metabolizer

- Drug may be rendered ineffective
- Prodrug may have greater efficacy
- Activity score > 2

Extensive (normal) metabolizer

- Metabolism proceeds as expected
- Activity score 1 - 2

Intermediate metabolizer

- Diminished or normal metabolism
- Activity score 0.5

Poor metabolizer

- Drug may become toxic
- Prodrug may be ineffective
- Activity score 0

FDA Table of Pharmacogenetic Associations

- Initially published 2020
- Now includes 300+ drugs
- Pharmacogenetic associations that support therapeutic recommendations
- Evidence-based information on safety or response
- Evidence of only pharmacokinetic impact
- Statins, SSRIs SNRI, beta blockers, PPIs, anticoagulants

CPIC Guidelines

https://cpicpgx.org/

Pharmacogenetic Guidelines

- Warfarin
- Clopidogrel
- Allopurinol
- Statins
- SSRIs
- NSAIDs

Opioids in PGx

CYP2D6

Codeine, tramadol, hydrocodone, oxycodone, methadone

Ultrarapid and poor metabolizers

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Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update

KR Crews[1], A Gaedigk[2,3], HM Dunnenberger[1], JS Leeder[2,3], TE Klein[4], KE Caudle[1], CE Haidar[1], DD Shen[5,6], JT Callaghan[7,8], S Sadhasivam[9,10], CA Prows[11,12], ED Kharasch[13] and TC Skaar[7]

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[b,c]

Clin Pharmacol Ther. 2014 Apr;95(4):376-82

AORI PGx Study

ELSEVIER

The Journal of Arthroplasty
Volume 37, Issue 6, Supplement, June 2022, Pages S76-S81

Proceedings of The Knee Society 2021

Prospective Randomized Study Using Pharmacogenetics to Customize Postoperative Pain Medication Following Hip and Knee Arthroplasty

William G. Hamilton MD [a], Jeanine M. Gargiulo PA-C [a], Thomas R. Reynolds BS [b], Nancy L. Parks MS

Purpose

- Eval if PGx testing can effectively customize pts pain medication following total joint replacement

Methods

- 107 primary TJR pts
- Buccal swabs for pre-op PGx testing
- Randomized to control or custom (pts blinded)
- Pain scores x 10 days postop
- Medication log
- Mediation converted to MEQ

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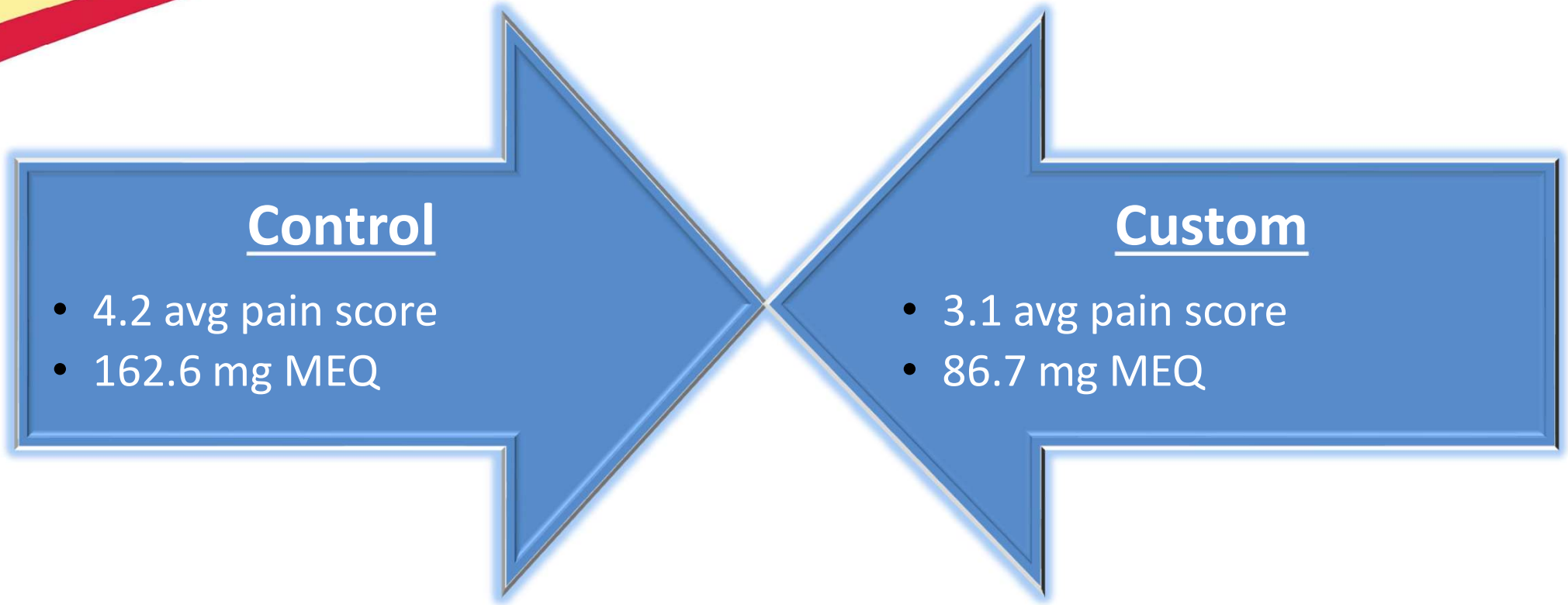
AORI PGx Study



- 24/107 (22.4%) had genetic variations
- Custom postop pain prescribing based on PGx testing can achieve lower pain levels while reducing consumption of pain medication

Patient Potential

- Simple, painless test
- Typically, 1 in a lifetime
- Easy to interpret information
- Insight into medication sensitivity
  - Dosage changes
  - Medication avoidance
- Confidence in medical decision-making process
- Ability to become one's own advocate

Methodology

Practitioner orders a pharmacogenetic test

Collect specimen, buccal cells

Send to the lab/prep for pickup

Specimen test run by the lab

Data analyzed and report generated

Practitioner receives and reviews results with patient

Barriers

- Who will pay?
- Proactive vs reactive testing
- Validity of testing
  - Direct to consumer options
- Funding and resource allocation

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PGx lab testing options

- Single Gene
- LabCorp
- Quest
- Point of care
- Spartan Rx
- Luminex
- Multigene
- OneOme
- Invitae
- GeneSight

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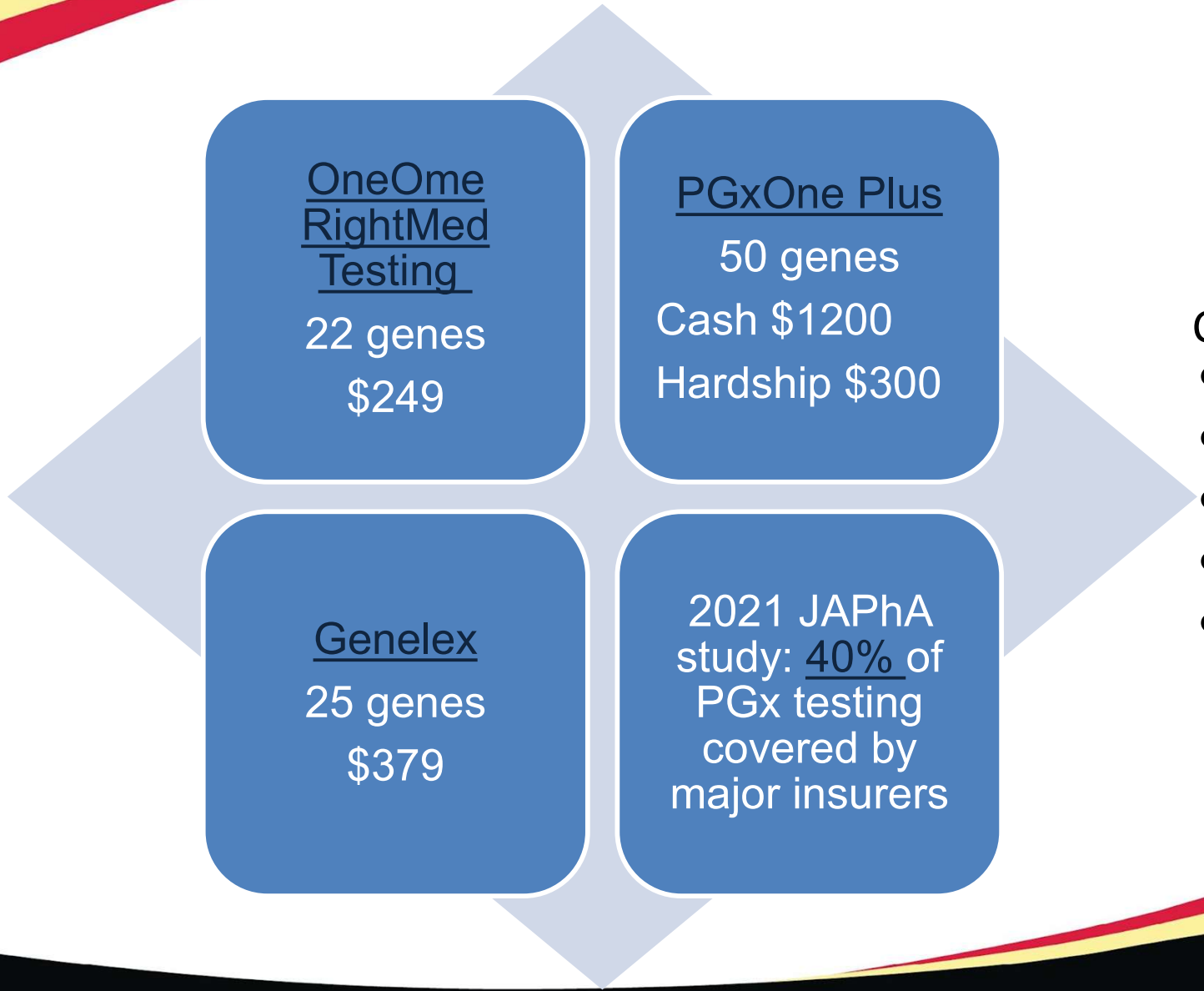
PGx testing



CPT codes

• 2C19	81225
• 2D6	81226
• 2C9	81227
• 3A4/5	81401
• SLCO1B1	81479

https://www.sciencedirect.com/science/article/abs/pii/S1544319119304522

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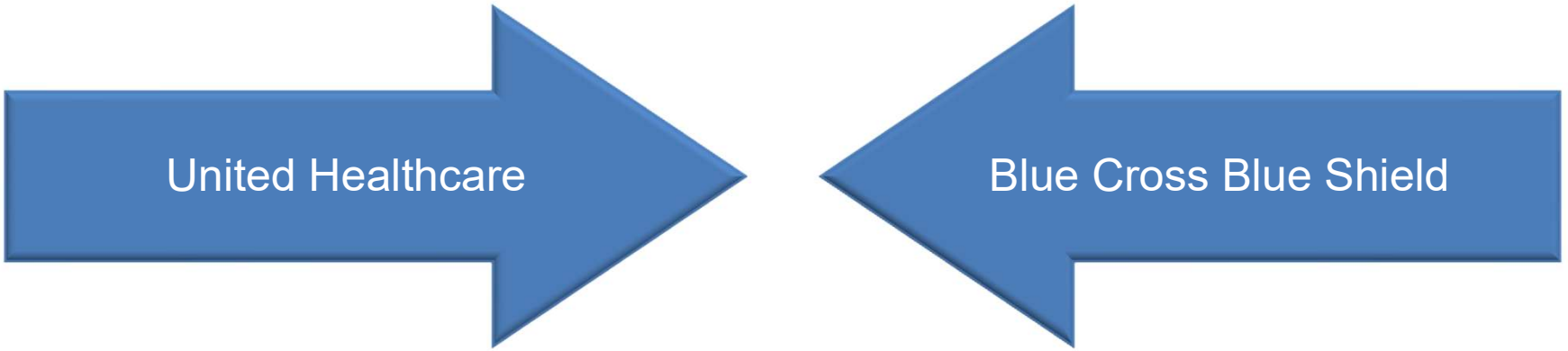
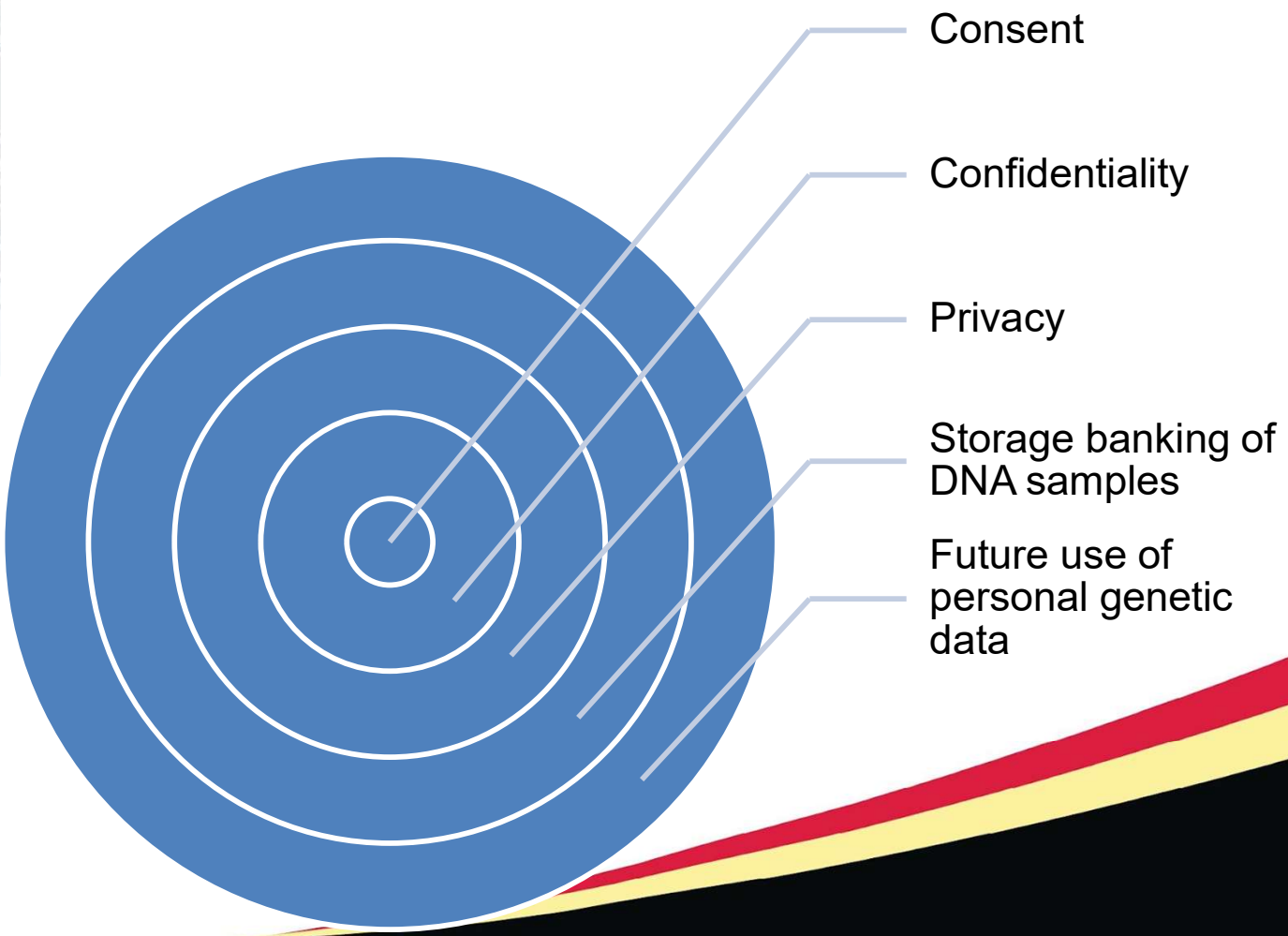
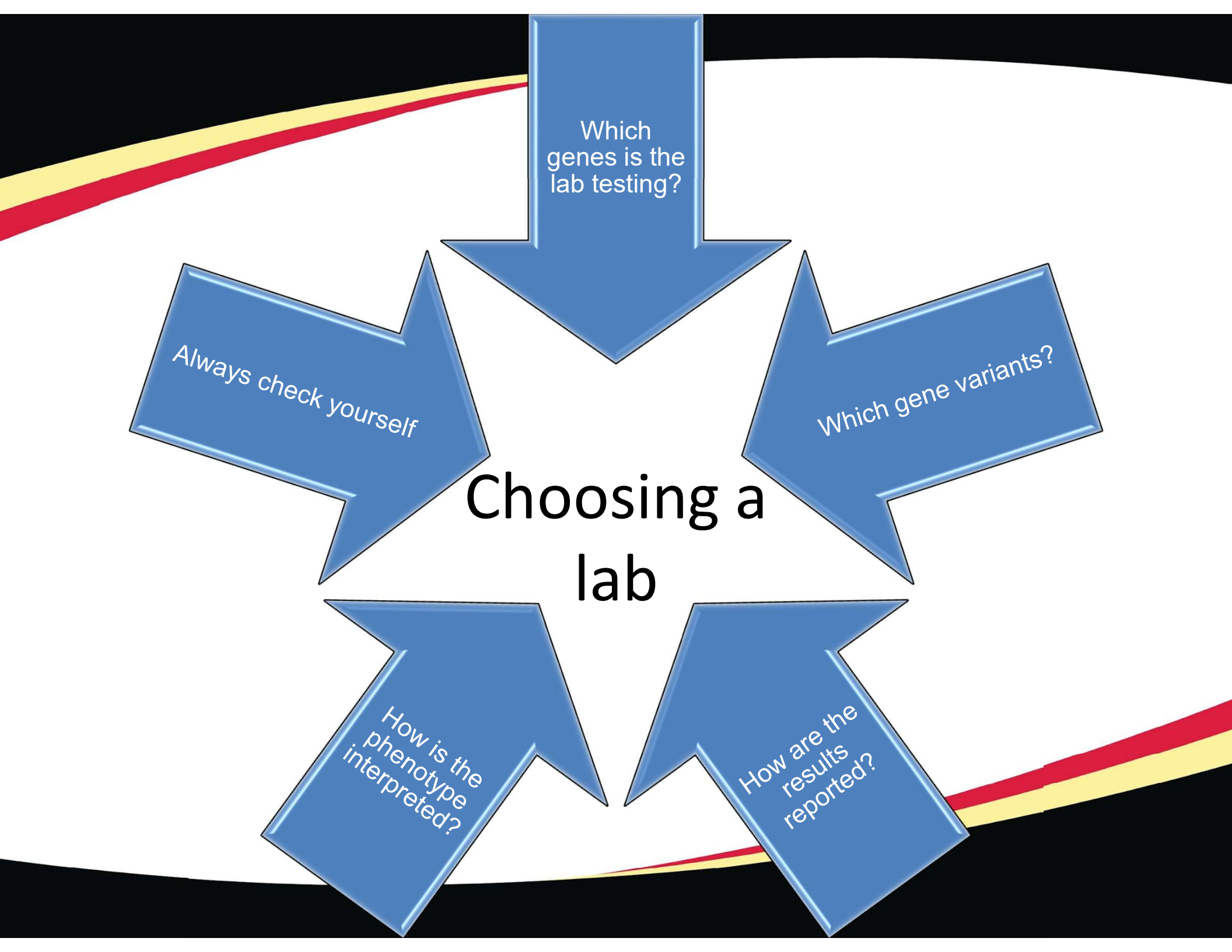
Insurance Coverage



- Psychiatric medication pharmacogenetic testing:
  - Pt with MDD or GAD diagnosis
  - Pt has failed at least one antidepressant
  - Specific multigene panels
- CYP2D6, CYP2C9, and CYP2C19 for specific medications
- PGx testing for warfarin
- Once per lifetime

Ethical Barriers




Which genes is the lab testing?
Which gene variants?
How are the results reported?
How is the phenotype interpreted?
Always check yourself
Choosing a lab

Ethics & Barriers

People are treated unfairly due to differences in their DNA that increase their chance of getting a certain disease

Insurance
- Refusing coverage to pt with genetic predisposition to cancer diagnosis

Employers
- Using DNA information to hire or fire workers

Genetic Information Non-discrimination Act, 2008

Federal law protecting Americans from being treated unfairly because of differences in DNA that may affect their health

Clinician Barriers

Familiarity

- Little or no exposure to principles of PGx
- Ordering logistics
- Confidence in clinical correlation
- Not widely used in clinical practice
- EMR charting limitations

Patient education

- Time and workload burden
  - Extra diagnostic step

Champions of PGx

Collaborative practice

MD

PA and other APPs

RN

Pharmacist

Patient and advocates

PGx testing will improve prescribing for all drugs!

Fact

Fiction

While it can help with many drugs, not all variability in drug response is from genetics

Many drugs have wide therapeutic ranges

Incorporating PGx knowledge in treatment will always ensure better patient outcomes

Fact

Fiction

The Truth

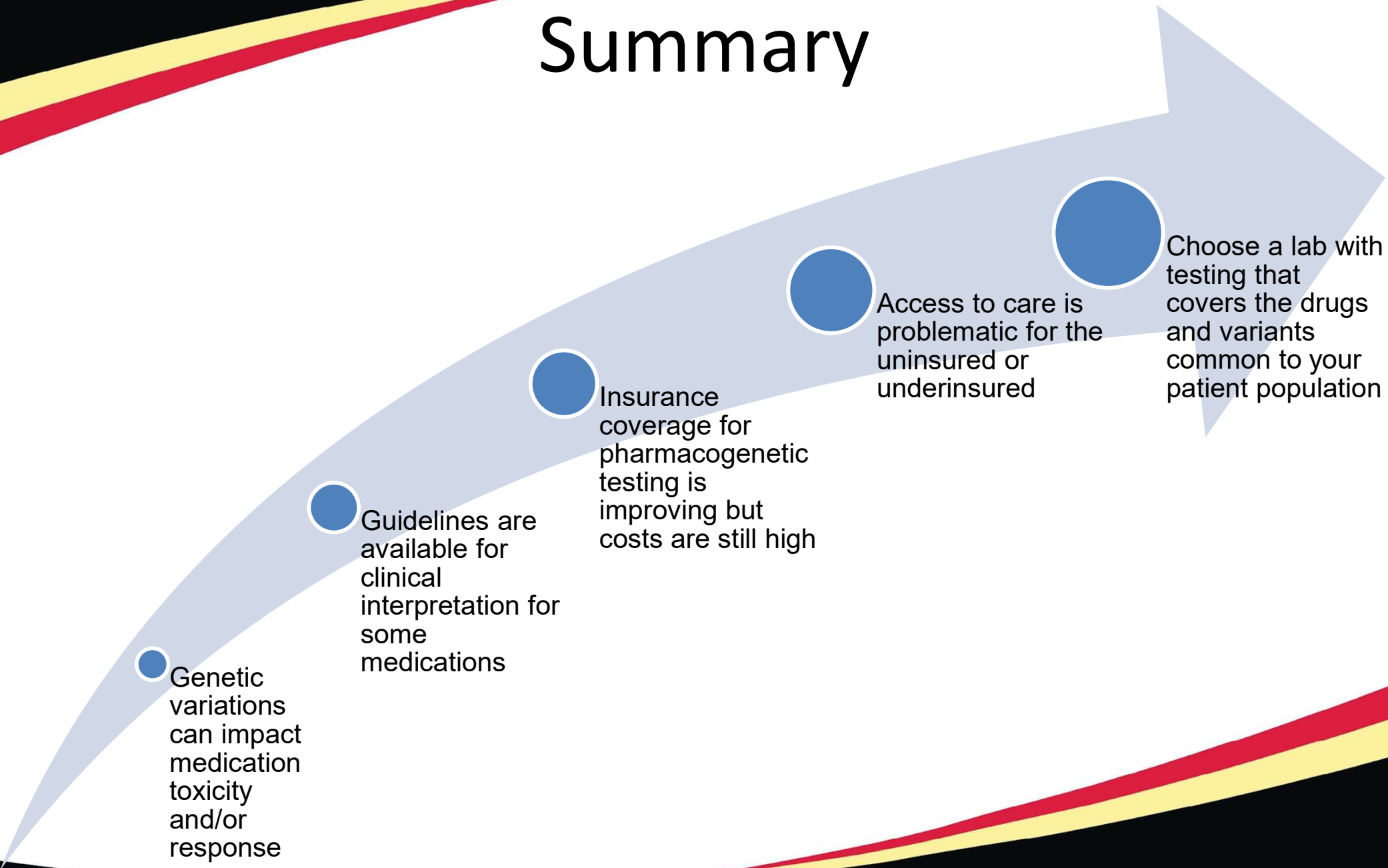
PGx does not mitigate for **extrinsic** factors

- Patient compliance
- Drug interactions
- Social factors

PGx does not mitigate for all **intrinsic** factors

- Organ dysfunction (kidney and liver)
- Physiologic status (pregnancy)
- Disease state (diabetic, heart failure)
- Age

Summary


Genetic variations can impact medication toxicity and/or response
Guidelines are available for clinical interpretation for some medications
Insurance coverage for pharmacogenetic testing is improving but costs are still high
Access to care is problematic for the uninsured or underinsured
Choose a lab with testing that covers the drugs and variants common to your patient population

PGx Take Home

Informed prescribing

Develop patient confidence in treatment

Increase patient compliance

Improve accuracy of drug choice and dosage

Allow improvements in drug development

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Clinical Pearls

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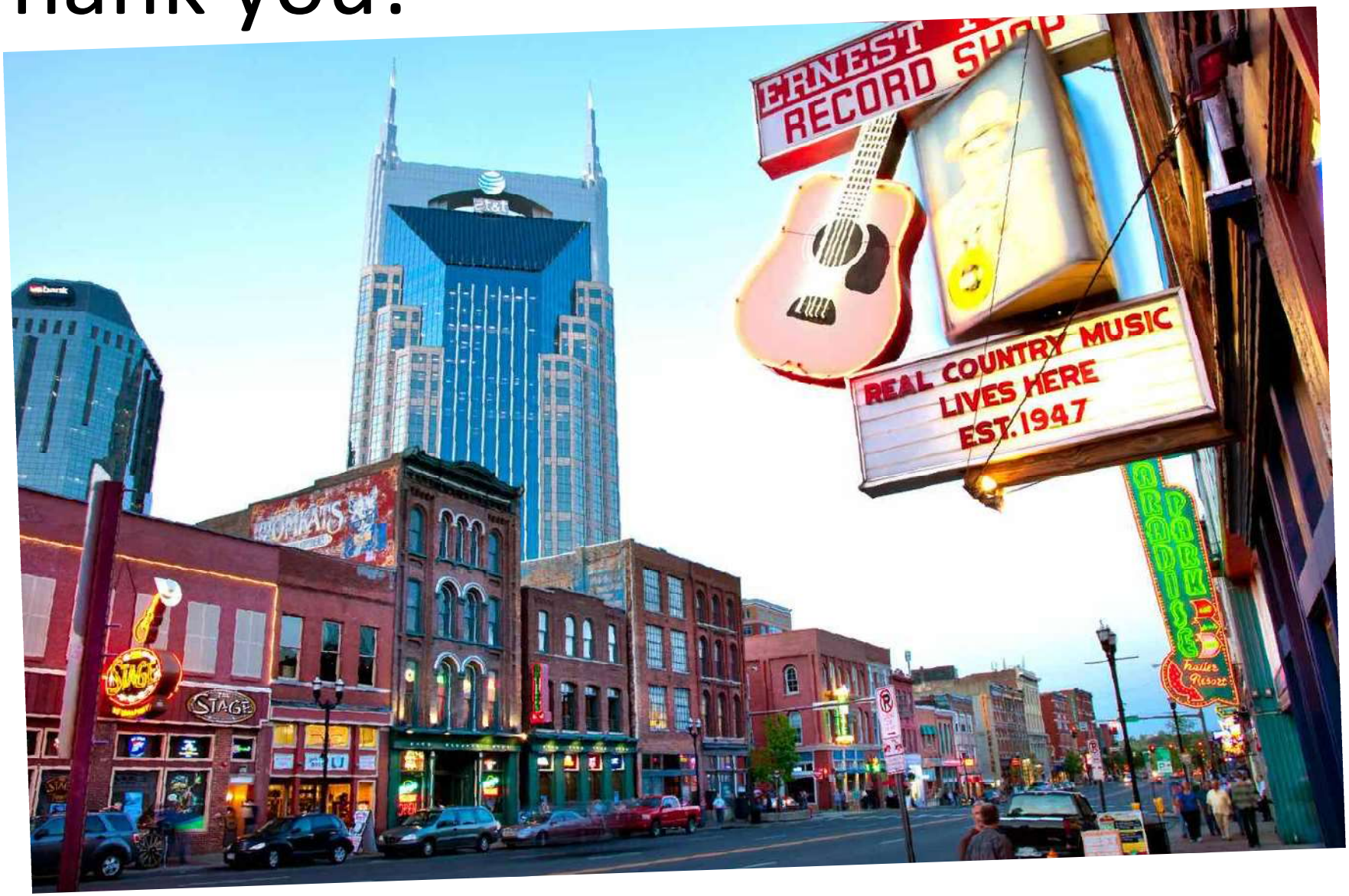
Thank you!


ERNEST
RECORD SHOP
REAL COUNTRY MUSIC
LIVES HERE
EST. 1947
STAGE
STAGE

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