BRINGING METHOD TO THE MADNESS : THE ROLE OF PHARMACOGENETICS

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DISCLOSURES:

I AM ONLY RESPONSIBLE FOR WHAT I SAY…….

NOT WHAT YOU UNDERSTAND !!!!

A PERFECT EXAMPLE

- Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine for pain relief following a tonsillectomy and/or adenoidectomy.
- These children = ultra-rapid metabolizers of codeine -genetic variable that causes the liver to convert codeine into life-threatening or fatal amounts of morphine in the body.
- A new Boxed Warning, FDA's strongest warning, will be added to the drug label of codeine-containing products about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy.

CONTENT OUTLINE

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- Pharmacogenetics and Pain Management
- Case Study
- Medication Metabolism
  - Phase I & Phase II Metabolism
  - CYP450 Enzymes
- Metabolism Phenotypes
- Medication Interactions & Pharmacogenetics
- More case studies
- Potential Benefits
- Pharmacogenetic Test reports

OBJECTIVES

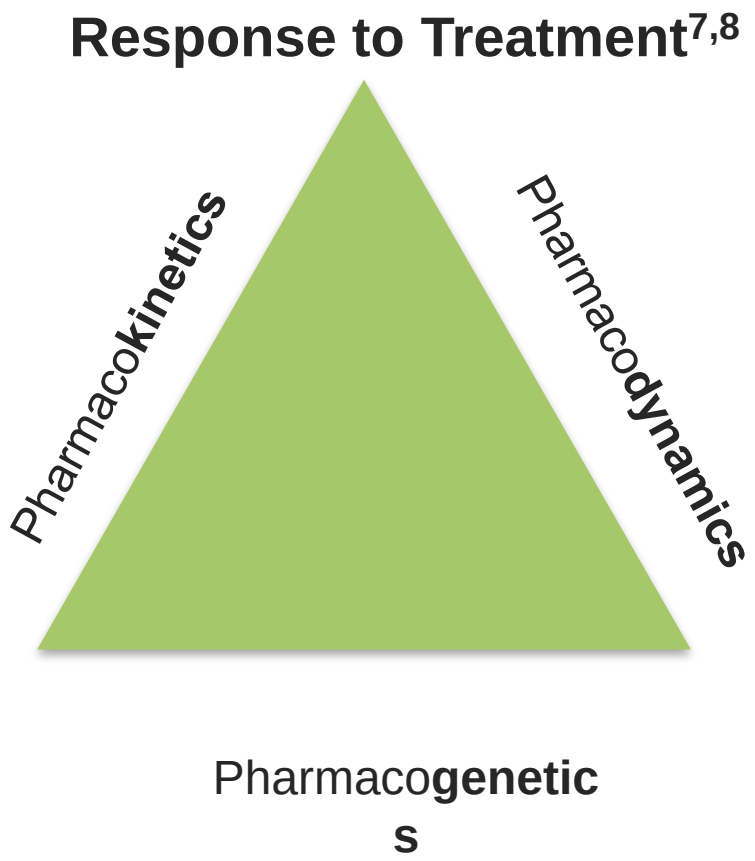
Upon completion of this program, you will be able to:

- Interpret how genetic variations can result in clinically significant differences in medication efficacy and toxicity
- Comprehend how identifying genetic variations may allow clinicians to more effectively personalize each patient's treatment
- Grasp how PGT may allow clinicians to better predict and understand patient's responses to medications
- Understand how incorporating UDT and PGT may improve efficacy and reduce adverse effects of medication treatment

THE MADNESS OF PAIN MX

PAIN MANAGEMENT

- Challenging clinical situations
- Suffering[1]
- Psychological issues[2]
- Financial issues[1]
- Managed care limitations[3,4]
- Substance misuse/abuse[5]
- Polypharmacy[6]
- Comorbid medical conditions[7]



SOOOO……..

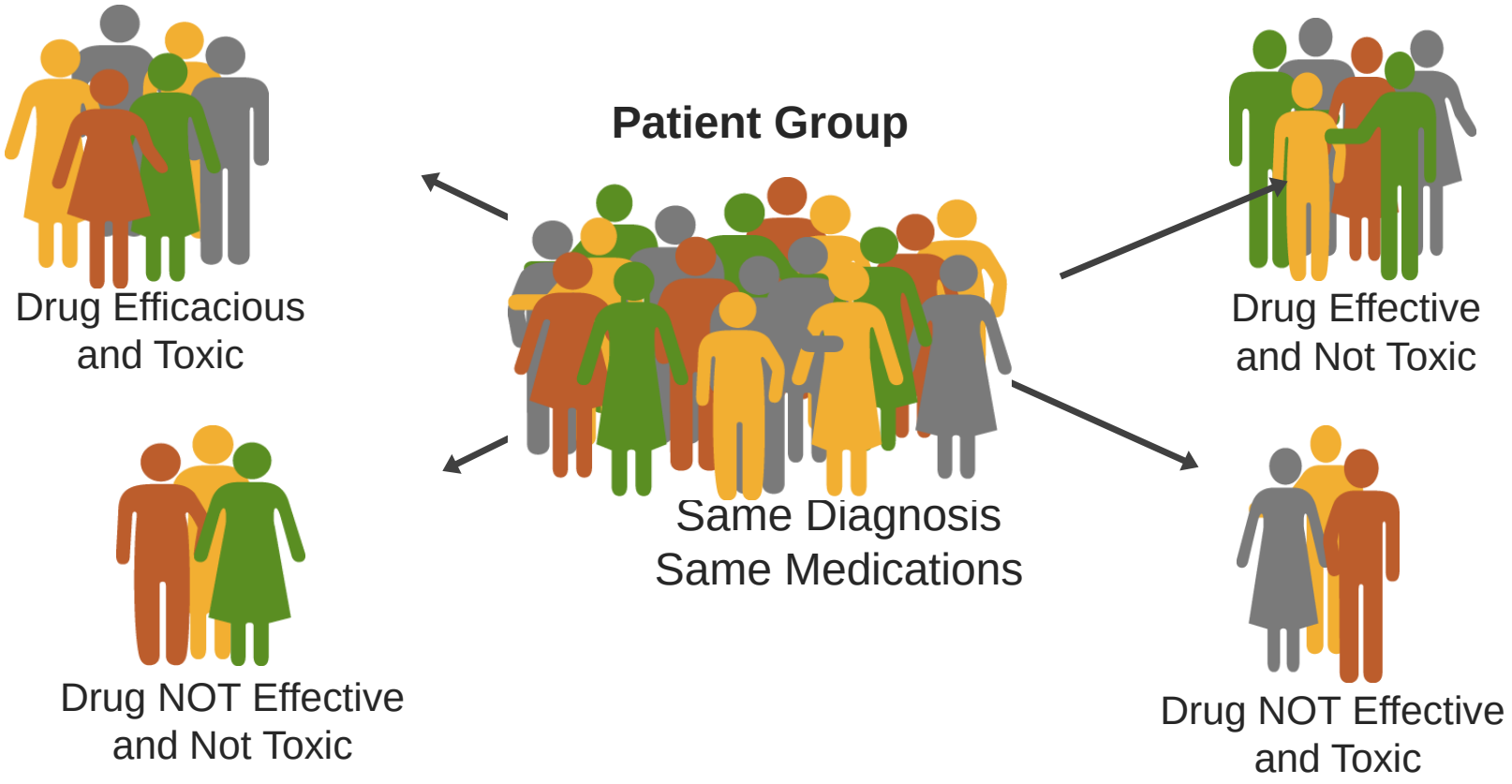
For every complex problem, there is an answer that is clear, simple and wrong"

Safe and clinically appropriate opioid prescribing requires a fundamental understanding of both pain management and laboratory testing

GENETICS

PHARMACOGENETICS

- The study of how genes affect the response to medications
- Intended to maximize efficacy and minimize side effects



1. American Medical Association, Arizona Center for Education and Research on Therapeutics, Critical Path Institute. Pharmacogenomics: increasing the safety and effectiveness of drug therapy. Chicago, IL: American Medical Association; 2011. Report 10-0290:5/11:jt. http://www.ama-assn.org/resources/doc/genetics/pgx-brochure-2011.pdf. Accessed August 16, 2012.

MORE ABOUT PHARMACOGENETICS

- Just as gene variation controls eye color, it also controls how the body reacts to certain drugs
- Basically this testing give you an idea of how quickly your body filters a given drug out of your bloodstream
- Rapid metabolizers filter quickly, may receive no benefit from a “normal” dose
- Poor metabolizers, will build rapidly with a “normal” to potentially dangerous levels
- This testing helps calculate the safest most effective dose for an individual patient

POLYMORPHISMS IN GENES IMPACT MEDICATION RESPONSES

- Polymorphisms, also referred to as genetic variance
- **Single-nucleotide polymorphisms** (SNPs) in the gene encoding for the **Mu-Opioid Receptor (MOR)** may contribute to variability in the analgesic response to morphine[1]
- Polymorphisms in the genes encoding for **opioid transport** have been linked to variability in opioid response[1-2]
- Polymorphisms within **metabolizing enzymes** have an important effect on an individuals response to opioids[3]

FACTORS AFFECTING METABOLISM & OUTCOMES

	Intrinsic (internal)	Extrinsic (external)
Increases Metabolism	• Younger age[1] • Female sex[1] • Liver impairment[2] • Race[3] • Genetic variability[3]	• Sunlight[4] • Excessive alcohol intake[5] • Medication interactions[2] • Diet[6] • Active lifestyle[7]
Decreases Metabolism	• Advanced age[1] • Male sex[1] • Liver impairment[2] • Race[3] • Genetic variability[3]	• Lack of adequate sunlight[4] • Excessive alcohol intake[5] • Medication interactions[2] • Diet[6] • Sedentary lifestyle[7]

STILL AWAKE??

THE ELDERLY PATIENT

Joyce: Clinical Presentation

- 75-year-old female
- Failed back syndrome
- Recent event resulted in presentation to physician's office nearly obtunded

Not a real patient

JOYCE CLINICAL PRESENTATION

- **Medication history**
  - Stable for years on current opioid
  - Current pain regimen:
    - Oxycodone ER 60mg Q12h
    - Oxycodone IR 15mg QID prn
    - Duloxetine 30mg BID
    - Lidocaine topical patch 5%
- **Patient history**
  - No alcohol use
  - No history of drug abuse/misuse
  - PMH: PVD, HTN, dyslipidemia
  - Medications: ASA qd, Propranolol 40mg qd, pravachol 40mg qd

Case Study

JOYCE: URINE DRUG TEST (UDT) RESULTS

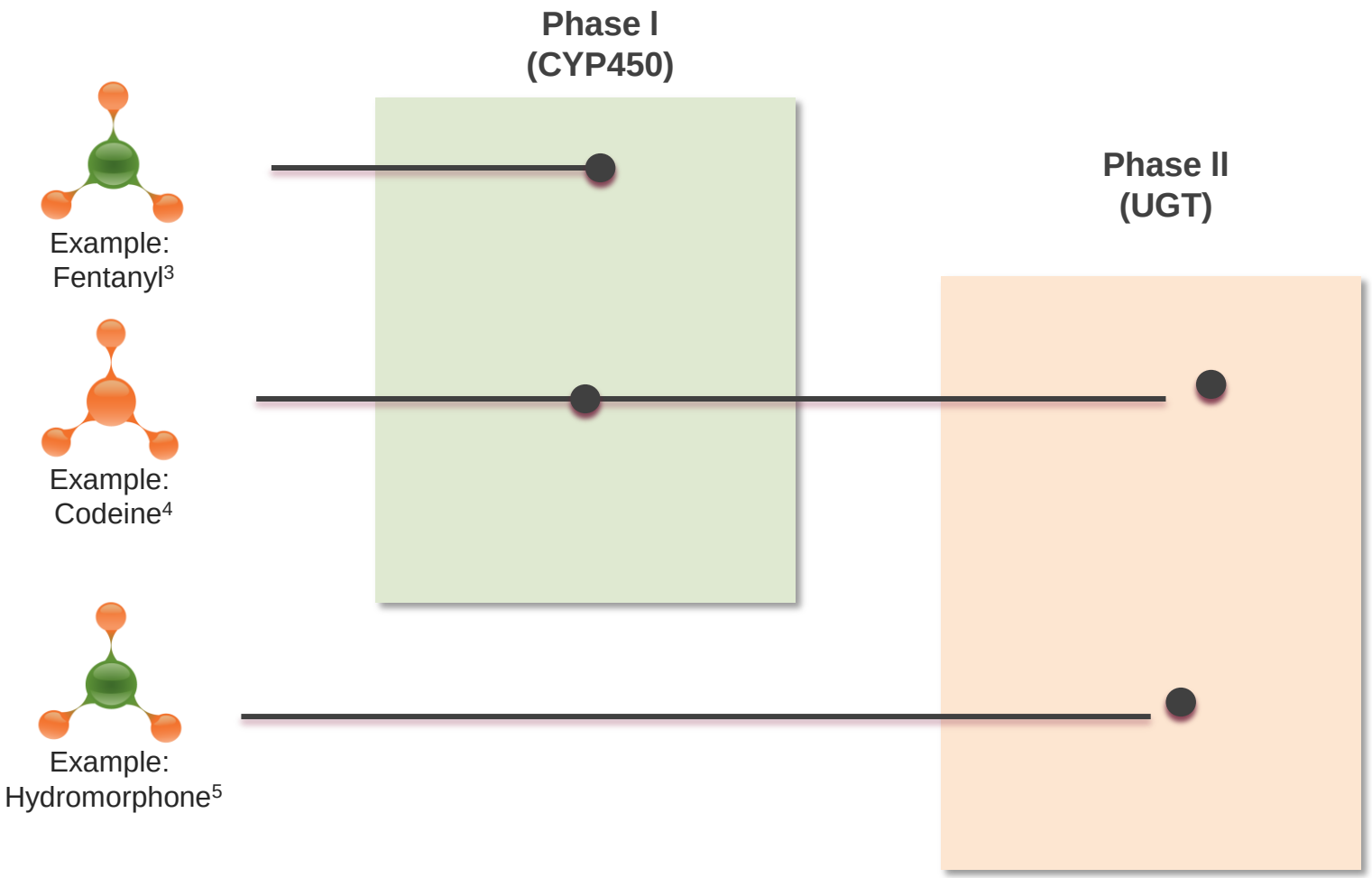
UDT Laboratory LC-MS/MS Test

Medication	Form	Outcome	Result
Oxycodone	Parent	Positive	28854
Oxymorphone	Metabolite	Positive	608
Noroxycodone	Metabolite	Positive	2284
Duloxetine	Parent	Positive	277

THE MINDS^{SM} ASSESSMENT TO GUIDE PERSONALIZED CARE

M	Metabolism
I	Interaction of Medications
N	Not Taking & Timing
D	Disease State
S	Substance Abuse

MEDICATION METABOLISM: TYPICALLY OCCURS IN PHASE I AND PHASE II REACTIONS[1,2]

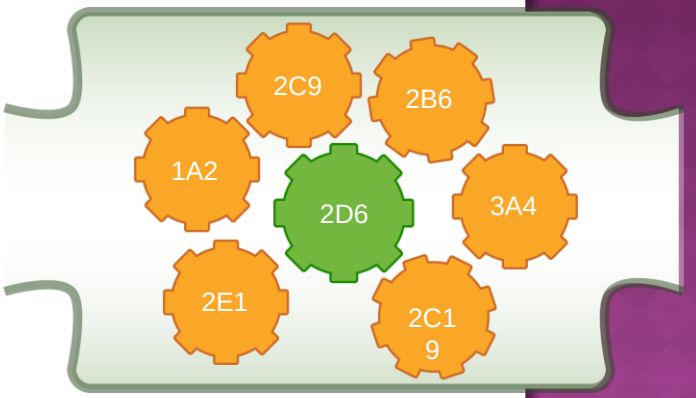


CYP450 = cytochrome P450;

UGT = UDP-glucuronosyltransferase.

PHASE I METABOLISM

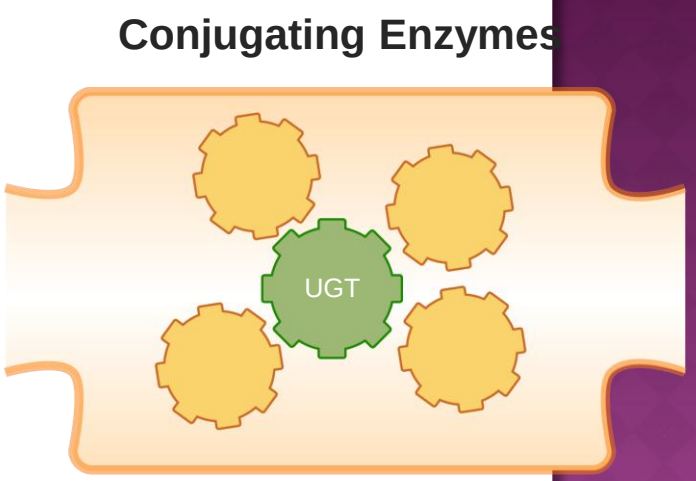
- Common CYP450 enzymes: CYP2C19, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4[1,2]
- Those most relevant to medication metabolism include CYP2D6 and CYP3A4[3]
- Codeine, oxycodone, hydrocodone, fentanyl, methadone, and tramadol are metabolized by Phase 1 enzymes[4]



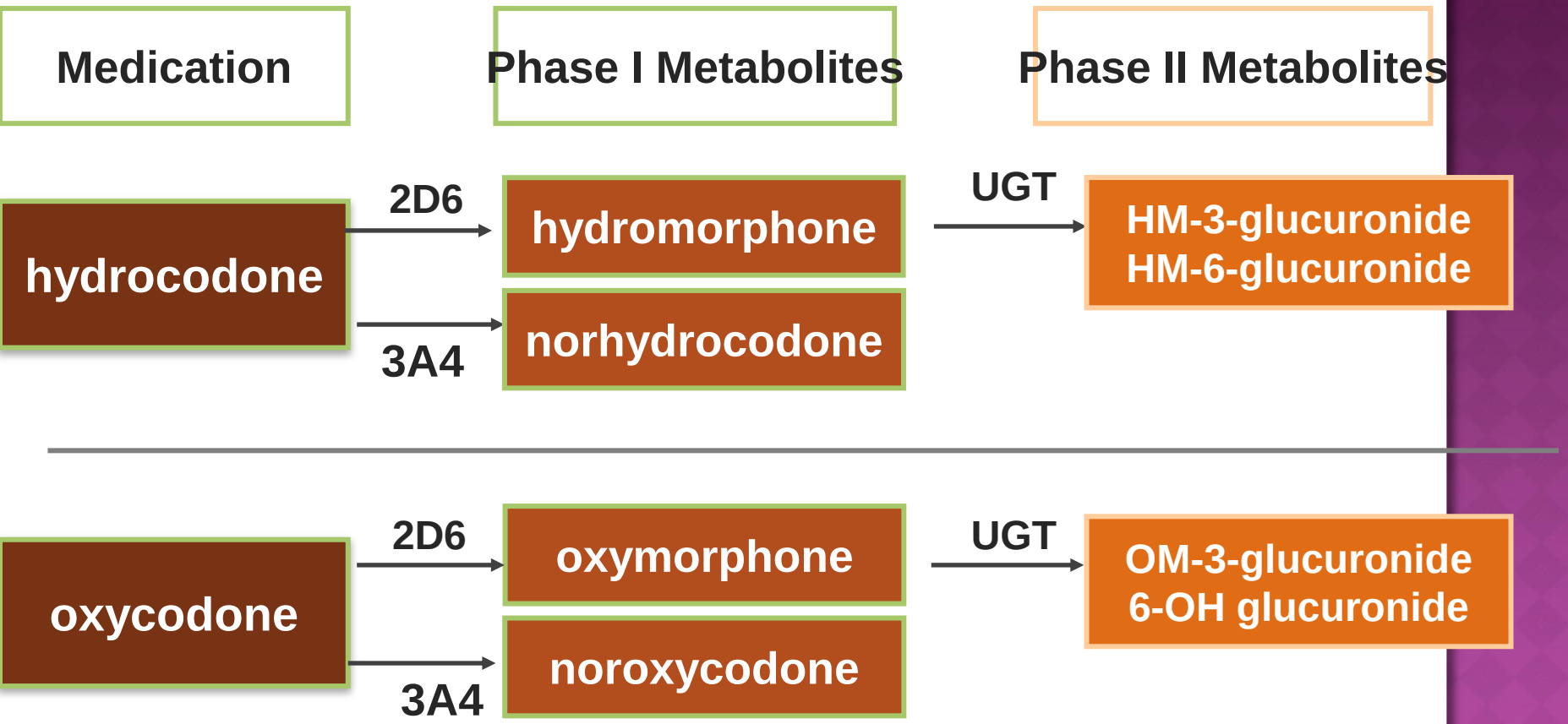
CYP450 = cytochrome P450

PHASE II METABOLISM

- There are several important superfamilies of enzymes active in phase II metabolism[1]
- Enzymes of the UDP-glucuronosyltransferase (UGT) superfamily are important for opioid metabolism[2]
- Morphine, oxymorphone, and hydromorphone are metabolized by phase 2 glucuronidation[2]



METABOLIC PATHWAY OF COMMONLY PRESCRIBED OPIOIDS[1,2]



UGT = UDP-glucuronosyltransferase.

CYP450 ENZYMES

2C9

- Metabolizes 10%-20% of medications[1-3]
  - NSAIDs[3]
  - Antidepressants
    - SSRIs[2] (eg, paroxetine)
  - Anticoagulants[1,3]
    - Warfarin

3A4

- Metabolizes 40%-50% of medications[1,2,4]
  - Opioids (eg, fentanyl)[5]
  - HIV medications[5]
  - HMG-CoA reductase inhibitors (ie, statins)[5]

CYP = cytochrome P450; HIV = human immunodeficiency virus;
HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; NSAID = nonsteroidal anti-inflammatory drug;
SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

CYP450 ENZYMES (CONT.)

- Metabolizes 20%-30% of medications[1-3]
  - Antidepressants[3]
    - SSRIs
    - TCAs
  - Opioids[4]

- Metabolizes 2%-8% of medications[2,5]
  - Methadone[5]
  - Steroids[5]
  - Anesthetics[5]

- Metabolizes 2%-5% of medications[2,3]
  - SSRIs[2]
  - Anticonvulsants[6]
  - Proton pump inhibitors[2,6]

CYP450 = cytochrome P450
HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A

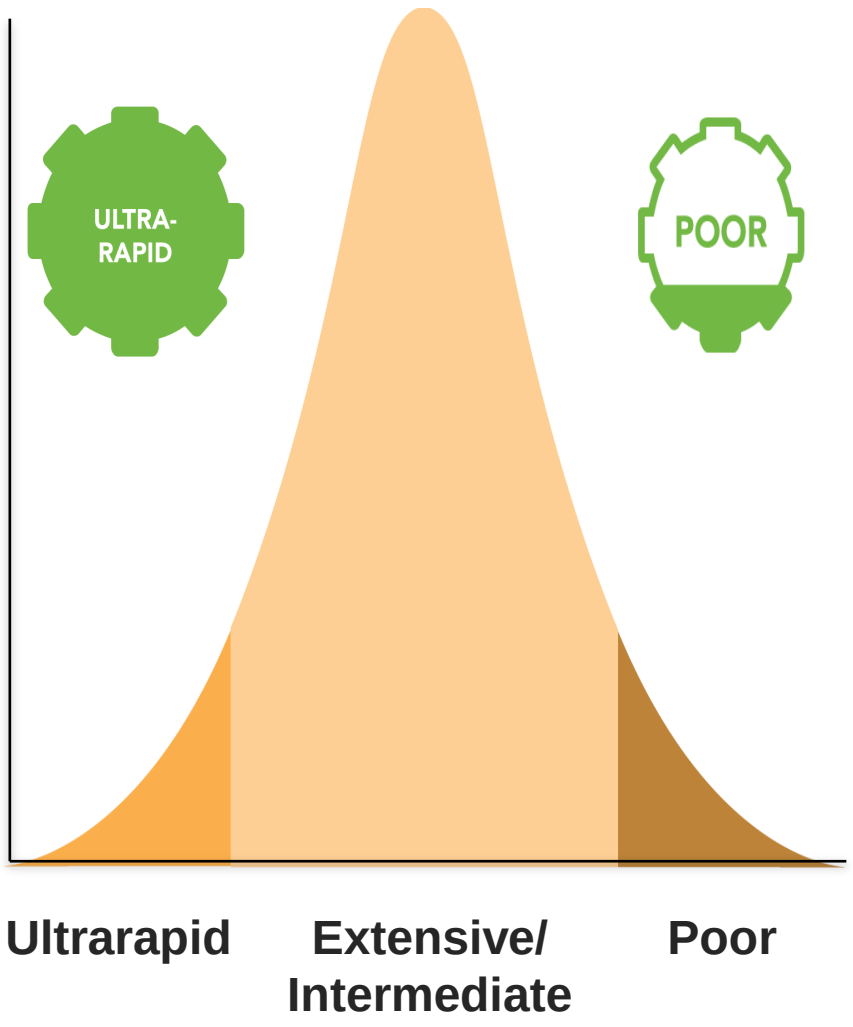
SSRI = selective serotonin reuptake inhibitor
TCA = tricyclic antidepressant.

NSAID = nonsteroidal anti-inflammatory drug

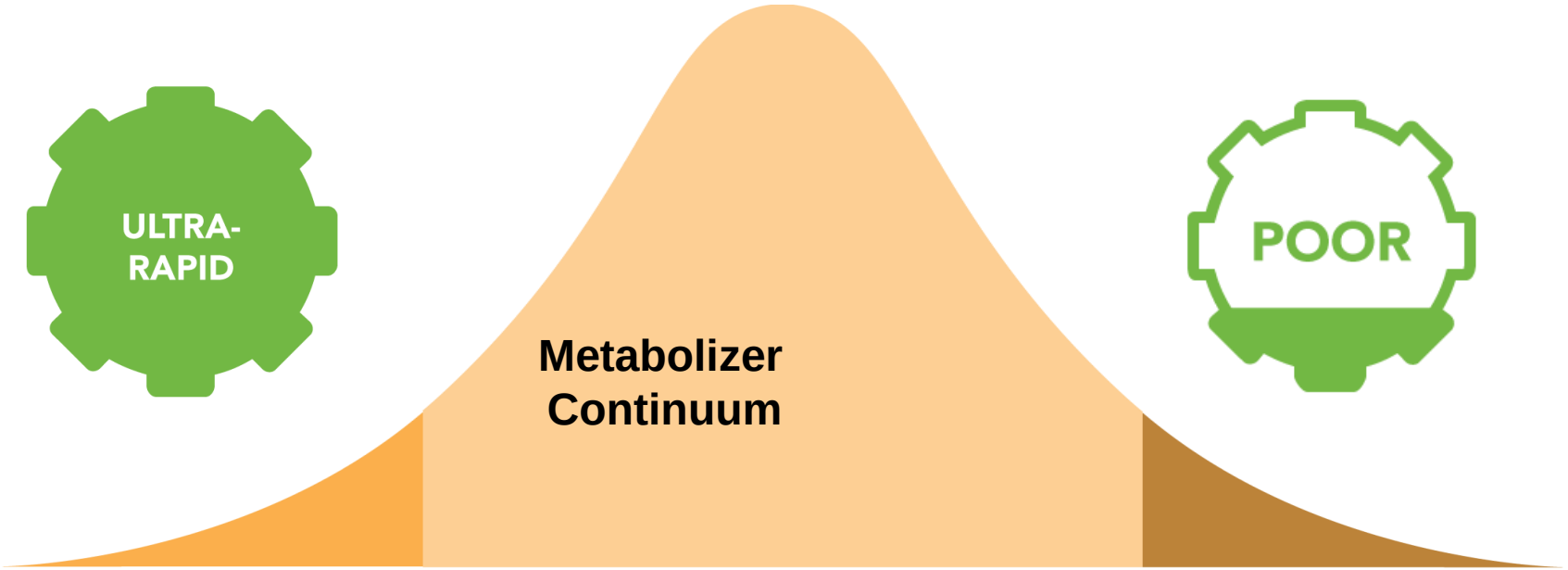
LET'S LOOK AT VARIABLES IN PRACTICE

METABOLISM PHENOTYPES

- **Ultrarapid metabolizer**
  - Metabolizes medications at a significantly higher rate than normal
- **Extensive metabolizer (normal)**
  - Metabolizes medications at a normal rate
- **Intermediate metabolizer**
  - Metabolizes medications at a somewhat lower rate than normal
- **Poor metabolizer**
  - Metabolizes medications at a significantly lower rate than normal



CLINICAL CONSEQUENCES OF GENETIC POLYMORPHISM: ACTIVE PARENT COMPOUND



Decreased pain relief[1,2]

Drug excreted rapidly[1,2]

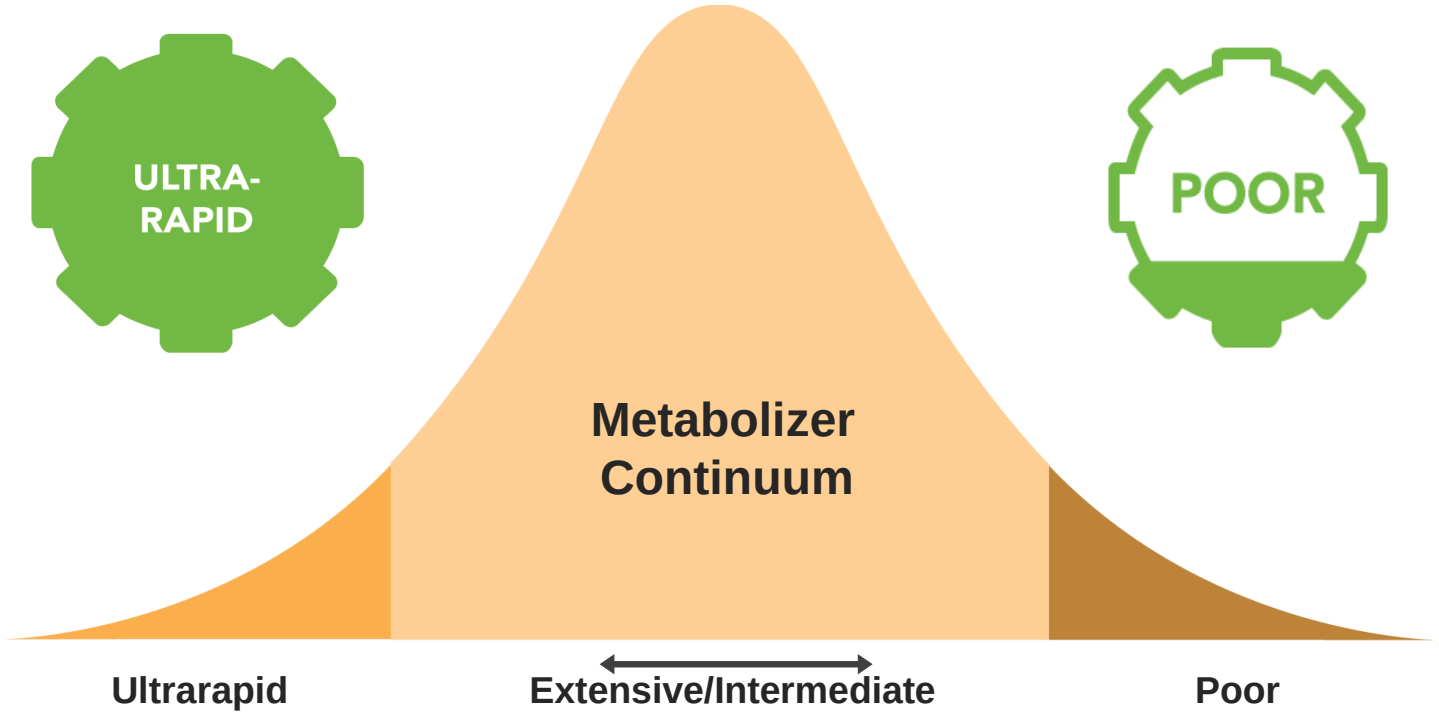
High doses required for effect[2]

Increased pain relief[1,2]

Risk of adverse events due to accumulation[1,2]

Low doses required for effect[2]

CLINICAL CONSEQUENCES OF GENETIC POLYMORPHISM: PRODRUG (INACTIVE PARENT COMPOUND)



Increased pain relief[1,2]

High active metabolite[1,2]

Low doses required for effect[2]

Decreased pain relief[1,2]

Low active metabolite[1,2]

High doses required for effect[2]

MEDICATION INTERACTIONS

MEDICATION INTERACTIONS & PHARMACOGONETICS

- Polypharmacy is extremely common in the US[1]
- Adverse effects increase exponentially with ≥ 4 prescription medications[2]
- Medication interactions often occur due to changes in metabolism[3]
  - Due to other medications metabolized through the same pathways
  - Due to inducers/inhibitors of the same pathways
- Metabolic differences may increase risk for medication interactions

Case Study

JOYCE REVISITED

- **Current pain regimen:**
  - Oxycodone ER 60mg Q12h
  - Oxycodone IR 15mg QID prn
  - Duloxetine 30mg BID
  - Lidocaine topical patch 5%

Medication	Form	Outcome	Result
Oxycodone	Parent	Positive	28854
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Noroxycodone	Metabolite	Positive	2284
Duloxetine	Parent	Positive	277

Case Study

PHARMACOGENETIC TEST (PGT) RESULTS

Pharmacogenetic Test (PGT) results: CYP2D6 poor metabolizer

Metabolism Profile	Parent Drug	Metabolite(s)	Potential Clinical Impact
POOR CYP2D6	HIGH	LOW	

- Unexpected therapeutic response
- Increased risk for adverse effects
- Increased risk for medication interactions
- Possible need for dose adjustment or medication change

JOYCE ADDITIONAL CONSIDERATIONS

Pharmacogenetic test (PGT) results: CYP2D6 PM

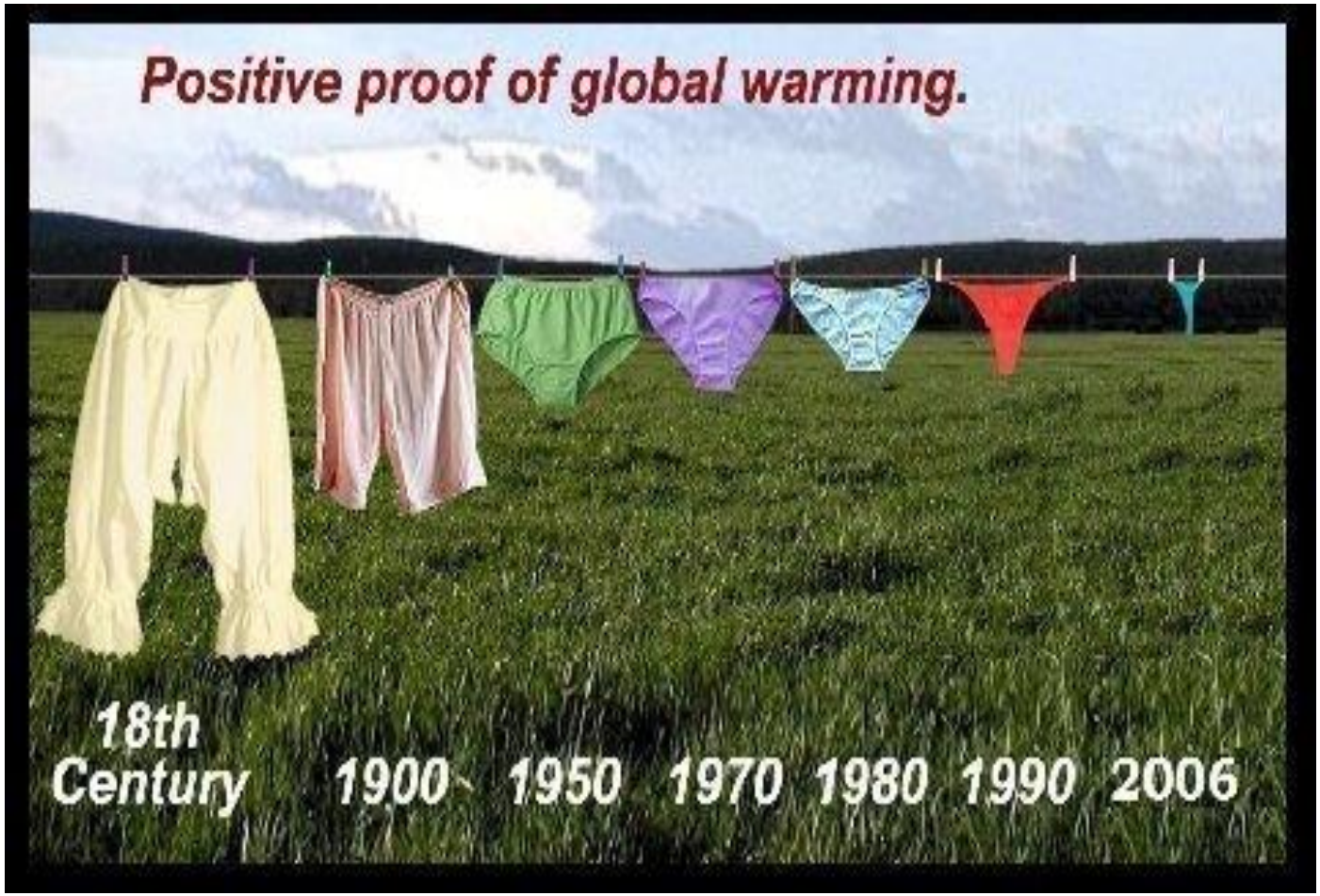
- **She had been stable on her opioid for many years;**
- **But had been started on fluconazole by her PCP for a fungal infection**

Fluconazole is a potent CYP3A4 inhibitor

Administration of CYP3A4 inhibitors can increase opioid concentrations, thereby prolonging and intensifying both analgesic and adverse effects

Her CYP2D6 PM status put her at an increased risk for medication interactions, and the addition of fluconazole meant both metabolic clearance pathways were inhibited (CYP2D6 & CYP3A4)

RED FLAGS TO LOOK FOR



POTENTIAL INDICATORS OF A GENETIC METABOLIC DEFECT

- Patients reporting little or no pain relief with hydrocodone, codeine and/or tramadol (may indicate a CYP2D6 Poor Metabolizer)
- Patients who report a severe adverse event within 30 minutes of taking an opioid such as codeine, oxycodone or hydrocodone (may indicate a CYP2D6 Rapid Metabolizer)
- Patients reporting numerous opioid allergies or a family history of intolerance to numerous opioids

POTENTIAL INDICATORS OF A GENETIC METABOLIC DEFECT (CONT.)

- Patients reporting a past experience that required a higher than typical dose of anesthesia
- Patients with a genetic or inheritable disease that is the cause of their pain E.G ankylosing spondylitis, Marfan's syndrome
- Patients reporting adverse events to alcohol or the need to use higher amounts of alcohol for any effect

POTENTIAL BENEFITS OF PHARMACOGENETIC TESTING

Potential Benefit	Examples/Comments
• Explain or predict patient response to medication[1]	• Higher-than-expected adverse effects[1] • Lower-than-expected efficacy[1] • Treatment failure[1]
• Avoid medication interactions	• Some medications inhibit or induce CYP450 enzymes
• Reduce the need for opioid rotation	• More predictive opioid trials • Reduce the likelihood of repeat negative outcomes if rotating between products that are metabolized in the same way
• Document decision to continue current medication regimen	• Explanation for higher doses to achieve optimal analgesia
• Individualize treatment	• Help prescribers find the most effective and safest medication for a patient[1,2]

James: Clinical Presentation

- 42-year-old male
- Chronic low back pain resulting from car accident
- Referred for inadequate pain relief and pain-related difficulty performing daily activities despite multiple opioid dose increases

Not a real patient

JAMES INITIAL EVALUATION

- **Pain characteristics**
  - Moderate to severe chronic pain
- **Medication history**
  - Ibuprofen: Inadequate relief
  - Tramadol: Inadequate relieF
  - Hydrocodone/APAP
    - Minimal pain relief despite multiple dose increases
- **Comprehensive assessment**
  - Ruled out other disease states or medical conditions that may impact response to opioid treatment by history, physical & exam
  - Benefit-risk appropriate for opioids

Case Study

JAMES: URINE DRUG TESTING (UDT) RESULT

- UDT Laboratory LC-MS/MS Test

Medication	Form	Outcome	Result
Hydrocodone	Parent	Positive	5764
Norhydrocodone	Metabolite	Positive	4918
Hydromorphone	Metabolite	Negative	--

- UDT indicates that James is taking the prescribed medication
- No other medications detected that could affect response
- Consider pharmacogenetic testing to guide treatment plan

THE MINDS^{SM} ASSESSMENT TO GUIDE PERSONALIZED CARE

M	Metabolism
I	Interaction of Medications
N	Not Taking & Timing
D	Disease State
S	Substance Abuse

PHARMACOGENETIC TEST PANELS

- **Opioids (CYP2D6)**
  - Codeine (eg, Tylenol® No. 3); Hydrocodone (eg, Vicodin®, Lortab®); Oxycodone (eg, OxyContin®); Tramadol (eg, Ultram®)
- **Benzodiazepines (CYP2C19, UGT2B15)**
  - Diazepam (eg, Valium®); Lorazepam (eg, Ativan®); Oxazepam (eg, Serax®)
- **SSRIs/SNRIs (CYP2D6, CYP2C19)**
  - Citalopram (eg, Celexa®); Paroxetine (eg, Paxil®); Venlafaxine (Effexor®)
- **Tricyclic Antidepressants (CYP2D6)**
  - Amitriptyline (eg, Elavil®); Desipramine (eg, Norpramin®); Imipramine (eg, Tofranil®); Nortriptyline (eg, Aventyl®)
- **Methadone (CYP2B6)**
  - Methadone

Case Study

PHARMACOGENETIC TEST (PGT) RESULTS

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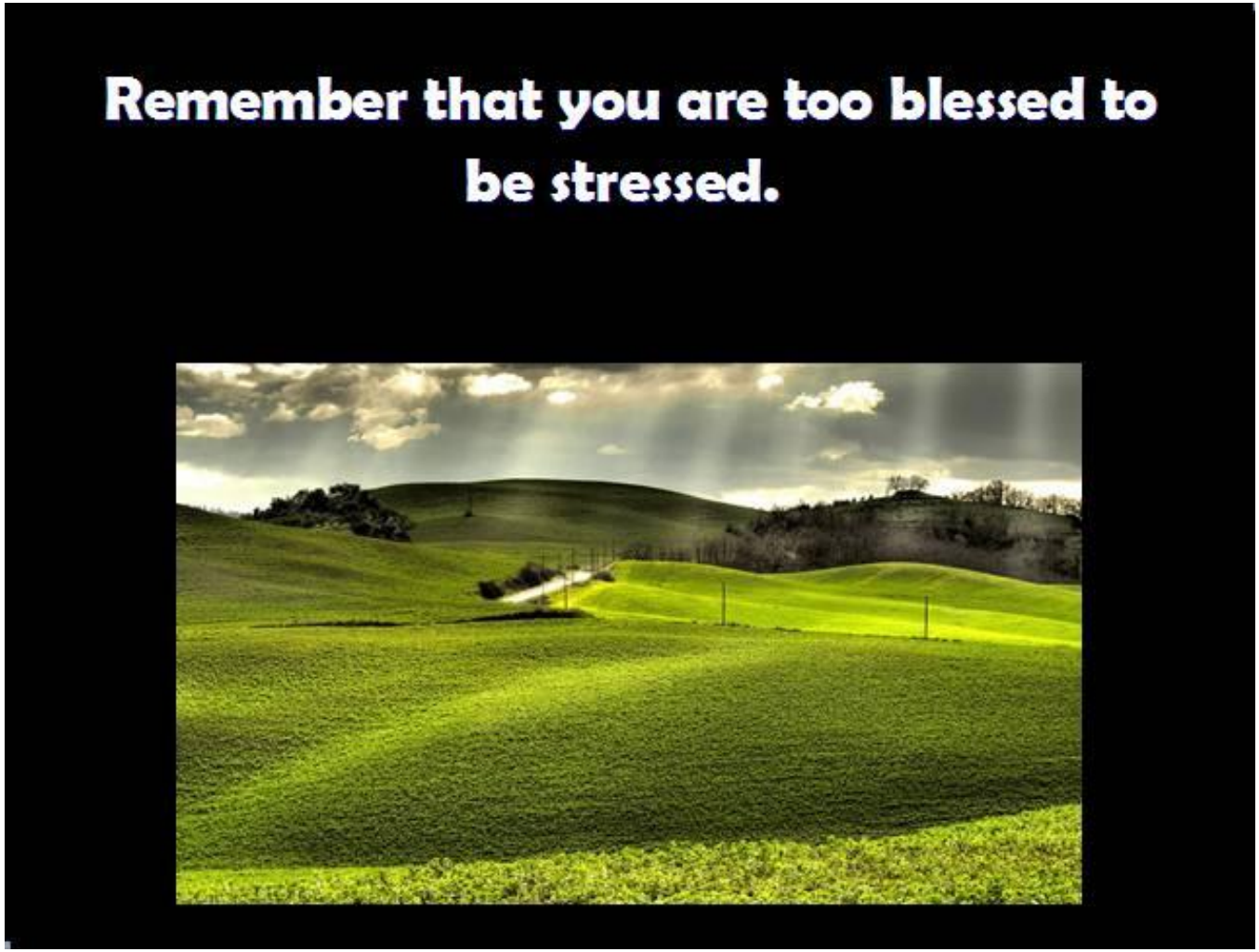
Metabolism Profile	Parent Drug	Metabolite(s)	Potential Clinical Impact
POOR CYP2D6	HIGH	LOW	• Unexpected therapeutic response • Increased risk for adverse effects • Increased risk for medication interactions • Possible need for dose adjustment or medication change

MORE CASE STUDIES



MORE CASE STUDIES

- Elderly lady similar to Joyce (high dose oxycodone originally) – opioid rotation to MORPHINE :

- **calculated equivalent dose - 30% → good analgesia for patient but …….**

  severe somnolence + cognitive dysfunction

  CD6 poor metabolizer.

- **morphine through different pathway (UGT)**
- **usual dosing equivalent calculations NOT applicable**
- **Consider starting much lower dose as if first opioid prescription/opioid naive**

MORE CASE STUDIES

- Another patient

  intermediate for 2CP + 2D6, ultrarapid metabolizer 2C19

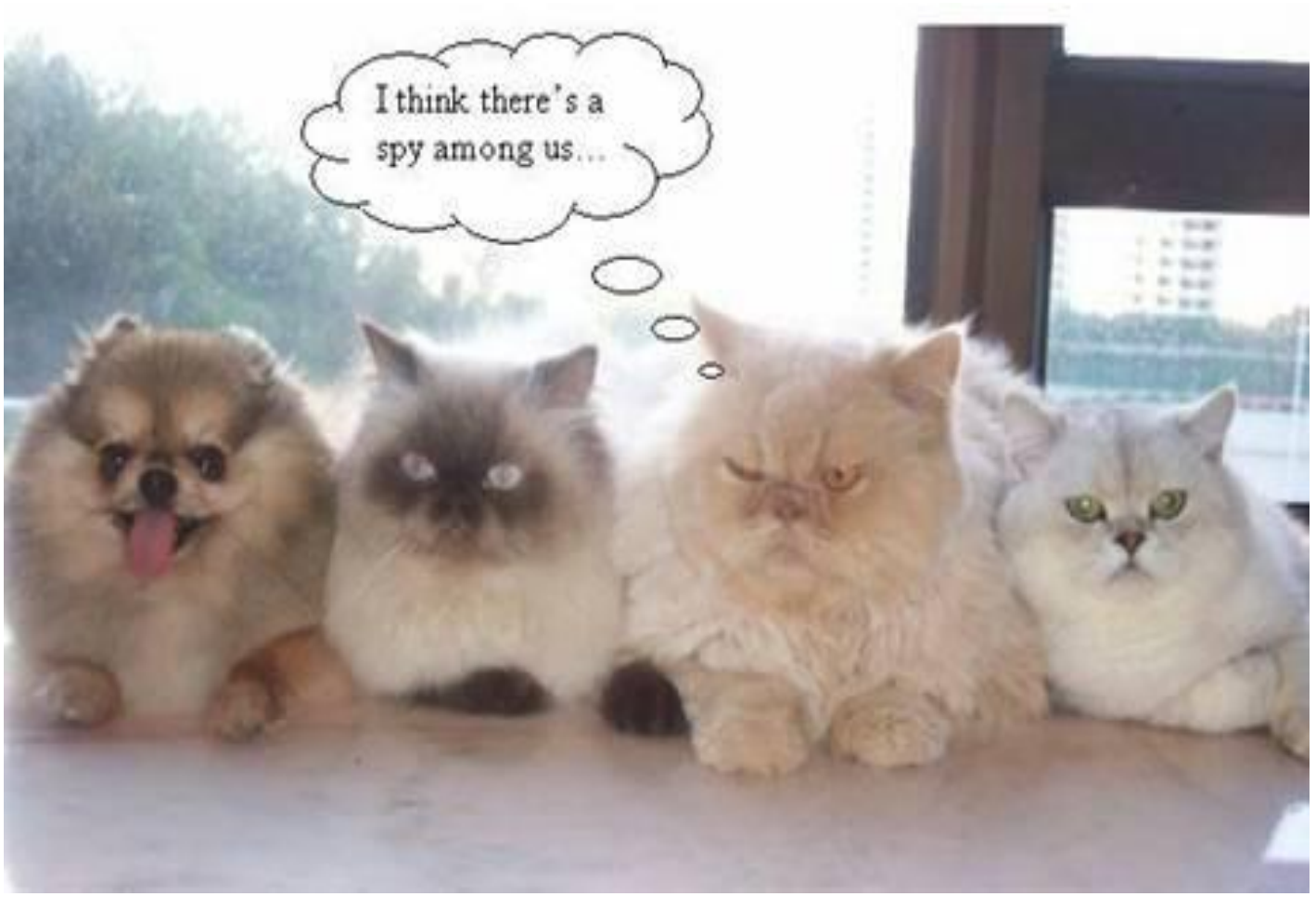
- Patient on 60mg QID oxycodone but only 40% relief for 3-4 hrs with each dose

  2D6 poor metabolizer

  (Changed to oxymorphone IR – 60% relief for 5-6 hours)

Best choices for both patients would be Exalgo, oxymorphone ER, Butrans

PHARMACOGENTICS IN URINE DRUG SCREENING – SOME PITFALLS



MORE EXAMPLES

- In cases where patients are being given codeine and concomitant antidepressants like Wellbutrin or Paxil, which are 2D6 inhibitors, the urine drug screen may be negative for morphine
- 10% lack 2D6 activity to convert codeine to morphine
- So unexpected UDS results may be caused by pharmacogenetic variability, false positives, false negatives, and/or aberrant behaviours
- Point of care UDS testing is contraindicated

YET MORE EXAMPLES

- Rapid metabolizers have shorter duration of action for prodrugs like hydrocodone and oxycodone
- If focus of UDT only on PARENT medications - may yield false negative results
- For some medications like carisoprodol, buprenorphine, methadone, a negative result for the parent drug may be common and should not be interpreted as an unexpected or non adherent UDT
- Be more suspicious of high parent drug but no metabolite, as patient may have “shaved” some of parent drug into urine to fool screen

TEST REQUIREMENTS

- Simple DNA test – either cheek swab or saliva sample (1ml)
- Painless, simple, takes less than 5 minutes
- Results easy to understand and utilize clinically
- Covered by Medicare

SUMMARY OF DRUGS

SUMMARY OF DRUGS

- Codeine: CYP2D6; CYP3A4
- Hydrocodone: CYP2D6; CYP3A4
- Oxycodone: CYP2D6; CYP3A4
- Fentanyl: CYP3A4; CYP3A5
- Methadone: CYP3A4; CYP2C19; CYP2D6
- Meperidine: CYP3A4; CYP2C19
- Buprenorphine: CYP3A4; CYP3A5; CYP2C19; 2D6
- Sufentanil : CYP3A4
- Tapentadol:CYP2C9; CYP2C19; CYP2D6; UGT
- Oxymorphone (Opana) : liver, none CYP450
- Hydromorphone: primarily UGT, liver

TAKE HOME MESSAGE!

SUMMARY

- **Pharmacogenetic testing (PGT) may help to…**
  - Explain and predict patient response to medication[1,2]& abnormal UDT results
  - Avoid medication interactions[1,3]
  - Reduce the number of opioid rotations by avoiding the use of medications that may repeat negative outcomes because of a genetic variant[1]
  - Support the decision to continue or change medication regimen[3]
  - Find a safe & effective medication for the individual patient[1,2]

SUMMARY

- **Pharmacogenetic testing (PGT) may help to…**
- Prevent likelihood of an adverse drug reaction
- Increase drug efficacy
- Improve patient medication compliance, especially with knowledge of their genetic test results
- Reduce healthcare costs by preventing adverse events or poor efficacy or unhelpful opioid rotations or trials

QUESTIONS ??