Pharmacogenomics and Chronic Pain: Putting science back into the treatment of pain

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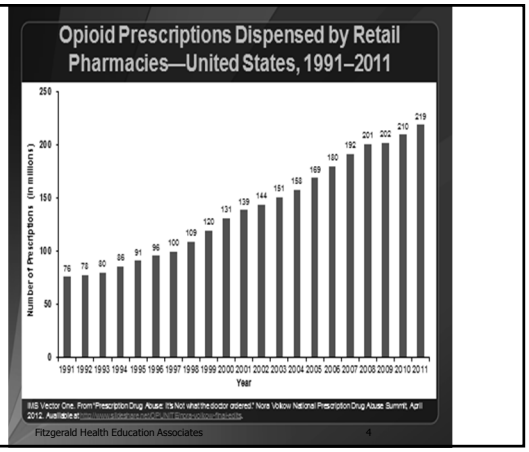
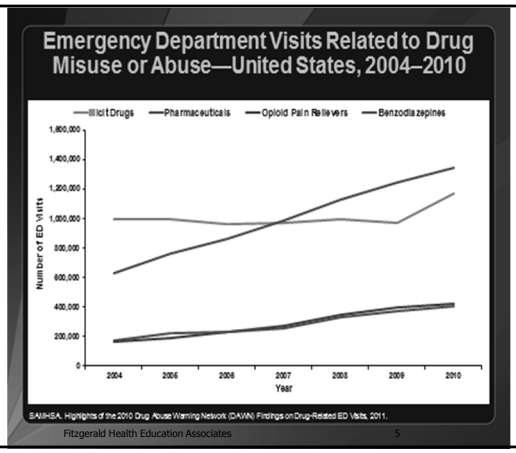
Disclosures

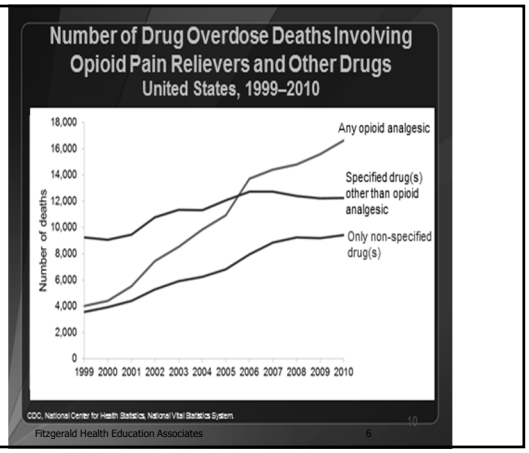
- Consultant
  - McNeil Pharmaceuticals
- Speaker bureau
  - Iroko Pharmaceuticals
  - AstraZeneca
  - Depomed Pharmaceuticals
  - Purdue Pharmaceuticals

Objectives

- Upon completion of this program, the participant will be able to:
  - Identify reasons to perform pharmacogenomics testing on a patient with chronic pain.
  - Describe how pharmacogenomics can help a provider treat patients with chronic pain.
  - Define the terms: Ultra-rapid metabolizer and poor metabolizer.





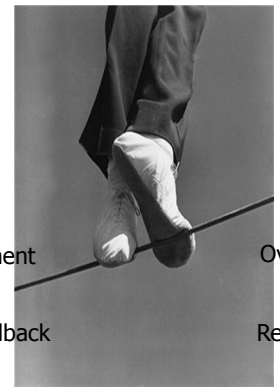


Symptoms

Demands

Under treatment

Negative feedback



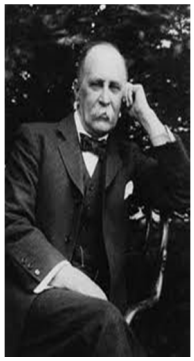
Safety

Adverse events

Overprescribing

Regulatory action

- "If it were not for the great variability among individuals, medicine might as well be a science and not an art."
  - Sir William Osler, 1892



Definitions in Clinical Genetics

- Pharmacodynamics
  - Drug activity at the target site/receptor
- Pharmacokinetics
  - Drug absorption, metabolism, distribution and elimination
- **Pharmacogenomics**
  - **How variations in the human genome affect drug response**
    - **Source:** Janetto P and Bratanow N. *Expert Opin Drug Metab* 2011, 7(6); 745-52

Benefits of Genomics

- Earlier detection of genetic predispositions
- Gene therapies
- **Improved diagnostic/prescribing accuracy and speed**
  - *Decrease in healthcare costs*
  - *Personalized treatment plans*
  - *Rational drug design*

How do we know how a patient will respond to a certain medication?

Or if they will have an adverse affect to that medication?

We don't…Until now!

Cytochrome P450

- Super-family of enzymes located in the liver and mucosal surface of the intestinal tract
- Important roles in the biosynthesis and metabolism of endogenous and exogenous compounds

Cytochrome P450 (continued)

- More than 50 CYP450 enzymes substrates identified in humans
  - 7 metabolize >90% of the clinically most important drugs
  - CYP2D6 is involved in the metabolism of 25% to 30% of all prescribed drugs.
  - CYP2C19 is involved in metabolizing 15%.

Why does this matter?

Allelic variations in the *CYP2D6* and *CYP2C19* genes result in markedly **increased** or **decreased** drug metabolism, leading to wide variations in clinical effect

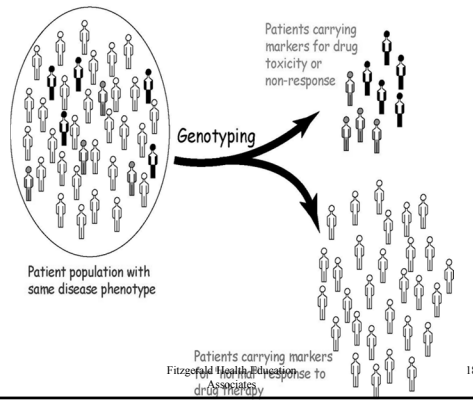
Common Pain Medications with Pharmacogenomic Tests

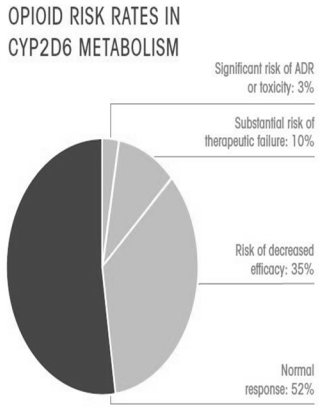
Generic	**Brand**	**Metabolic route**
Alfentanil	Alfenta®	CYP3A4/CYP3A5
Carisoprodol**	Soma®	CYP2C19
Celecoxib	Celebrex®	CYP2C9
Codeine**	Various brands	CYP2D6
Cyclobenzaprine	Flexeril®	CYP1A2, CYP3A4/CYP3A5
Fentanyl	Actiq®, Duragesic®	CYP3A4/CYP3A5
Hydrocodone**	Lortab®, Vicodin®	CYP2D6
Hydromorphone	Dilaudid®	UGT2B7+ (OPRM1)
Ibuprofen	Advil®, Motrin®	CYP2C9
****prodrug; + test not yet available**		

Common Pain Medications with Pharmacogenomic Tests (continued)

Generic	**Brand**	**Metabolic route**
Lidocaine	Various brands	CYP1A2
Methadone	Various brands	CYP2C19, CYP2B6+
Morphine	Various brands	UGT2B7+ (OPRM1)
Naproxen	Aleve®	CYP2C9
Oxycodone**	Oxycontin®, Percocet®	CYP2D6, CYP3A4/5
Oxymorphone	Opana®	UGT2B7+ (OPRM1)
Ropivicaine	Various brands	CYP1A2
Tizanidine	Zanaflex®	CYP1A2
Tramadol**	Ultram®, various	CYP2D6
Zolmipitran	Zomig®	CYP1A2
****prodrug; + test not yet available**		

Manipulating Therapeutic Outcomes



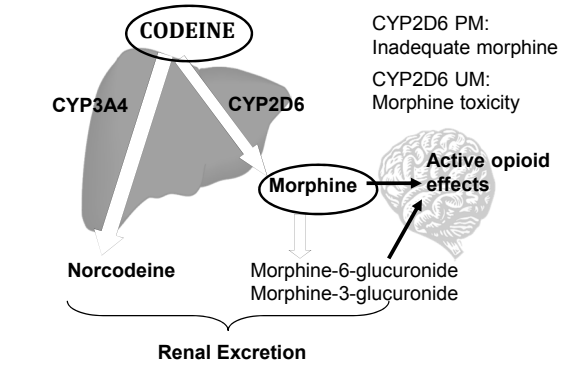


Explanation of Metabolizers

- Example: Codeine is metabolized into morphine.
  - Poor metabolizers: Would not achieve a full therapeutic response
  - Ultra-rapid metabolizer: Metabolize codeine quickly into morphine, potentially leading to a toxic effect
    - Very sedating to these individuals
      - "I can't take anything."

Explanation of Metabolizers (continued)

- In 2007, the FDA issued a warning on "Codeine Use by Nursing Mothers" and noted that nursing infants may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of the drug.



Source: Reynolds KR et al. Clin Lab Med 2008;28:581–598.

Morphine Overdose from Codeine

8-15-12 and 2-20-13
FDA Drug Safety Advisories

Codeine use in certain children after tonsillectomy and/or adenoidectomy can lead to rare, but life-threatening adverse events or death.

- 3 deaths in children ages (2–5 yo) taking codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea.
- 3 deaths in children who were CYP2D6 UMs.
- All children received typical codeine doses, developed toxic levels.

Explanation of Metabolizers (continued)

- Example: Hydrocodone
  - Metabolizes into hydromorphone
  - Ultra-rapid metabolizer: Patient can get some relief, but UDT can show high levels of hydromorphone – and they can have significant adverse effects.
  - Poor metabolizer: Poor pain relief

Explanation of Metabolizers (continued)

- If a patient is complaining about a drug not being effective, or about adverse effects
  - Genomics testing can guide your therapy

When to Use Genomic Testing in Pain Management

- When a patient is not getting appropriate pain relief, on an appropriate dose of medication
- When a patient is complaining of significant adverse effects of a medication, and pain is not controlled

When to Use Genomic Testing in Pain Management (continued)

- At the onset of prescribing, if patients report…
  - "Nothing works for me."
  - "Everything makes me feel horrible."
- **Where ever you see a need in your prescribing**

Pain Management Genetic Analysis

Analgesic	Polymorphic Genes
Codeine	CYP2D6
Fentanyl	ABCB1, CYP3A4, CYP3A5, OPRM1
Oxycodone	CYP2D6
Methadone	ABCB1, CYP2B6, CYP3A4, CYP2D6
Morphine	ABCB1, COMT, UGT2B7, OPRM1
Tramadol	CYP2D6

ABCB1=ATP-binding cassette, subfamily B, member 1
OPRM1=mu-opioid receptor gene
COMT=catechol-O-methyltransferase
UGT=uridine 5'-diphosphate-glucuronosyltransferase

Jannetto P and Bratanow N. *Expert Opin Drug Metab Toxicol.* 2011; 7(6): 745-52.

CYP2D6: Tramadol Experience

Study population	Adult post-operative analgesia patients (N= 271)
Design	Prospective study of CYP2D6 PM and EM phenotypes
Treatment regimen	24-hour post-op tramadol dosing relative to phenotype
Results: PM vs. EM	Non-responders: 47% vs. 22% Needing rescue meds: 43% vs. 22%

PM=Poor metabolizer
EM=Extensive metabolizer

Stamer UM, et al. *Pain.* 2003; 105: 231-8.

Opioid Receptor: OPRM1 variations

- Encodes μ-opioid receptor
- 118A > G variation = substitution of asparagine for aspartate
- ↓ morphine, alfentanil, fentanyl, and methadone response
- 20-30% population prevalence
  - 1-2% African Americans
  - 50% Japanese

Argoff C. *Clin J Pain.* 2010;26(1):S16-20.

Jannetto P and Bratanow N. *Expert Opin Drug Metab Toxicol.* 2011; 7(6): 745-52.

Catechol-*O*-methyltransferase (COMT)

- Catecholamines are metabolized by COMT and involved in pain modulation
- COMT activity may contribute to variable analgesic response
- 1947G > A = 3-4 fold ↓ in COMT activity
- Homozygous GG patients require higher morphine doses to achieve pain control

Jannetto P and Bratanow N. *Expert Opin Drug Metab Toxicol.* 2011; 7(6): 745-52.

PGx Targets Summary

Gene	Variant	Opioids Affected	Outcome(s)
CYP2D6	Poor; ultra rapid metabolizers	Codeine, Tramadol, Oxycodone	↓ analgesia; excessive side effects
ABCB1	3435C > T	Morphine	TT carriers experience greater pain relief
OPRM1	118A > G	Morphine, Alfentanil, Fentanyl, Methadone	↑ dose requirements due to ↓ efficacy
COMT	1947G > A	Morphine	GG carriers experience less pain relief

Jannetto P and Bratanow N. *Expert Opin Drug Metab Toxicol.* 2011; 7(6): 745-52.

CYP Polymorphism and NSAIDs

- Many NSAIDs are metabolized by CYP2C9.
  - Diclofenac
  - Meloxicam
  - Indomethacin
  - Celecoxib
  - Ibuprofen
  - Naproxen

CYP Polymorphism and NSAIDs (continued)

- Potential encoding variation by the *2 and *3 alleles
- Resulting in poor metabolism, and thus **prolonged action of NSAIDs with either allele**

Warfarin and NSAID Bleeding Risk

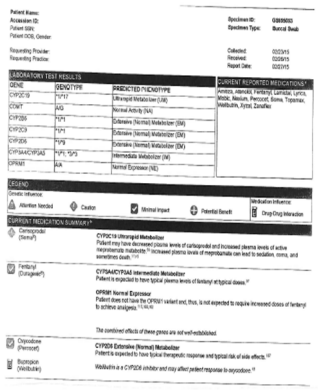
- CYP2C9 is also important for warfarin metabolism.
- Patients with the *CYP2C9 *2* or *3* genotypes taking both an NSAID and warfarin have been shown to have a significantly higher risk for an elevated prothrombin time, compared to patients with the wild-type *2C9* genotype

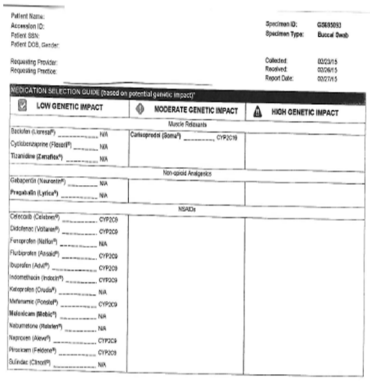
Case Study

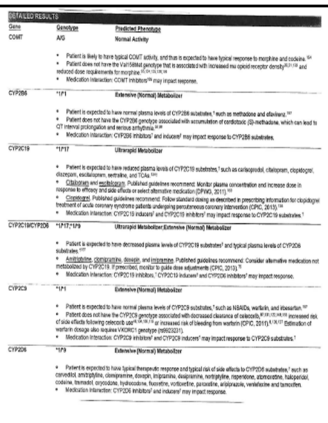
- Middle-aged male, chronic pain patient
- 2 pain clinics released him due to negative UDT when prescribed hydrocodone.
- 3rd pain clinic ordered PGXL testing.

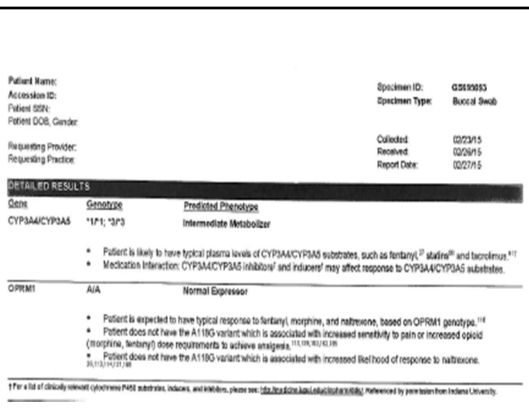
Case Study (continued)

- 3rd pain clinic ordered pharmacogenomics testing (mouth swab)
  - **2D6 poor metabolizer**
    - Pt does not produce hydromorphone= Negative UDT and lack of pain relief
  - **2C19 extensive metabolizer**
    - Pt now taking low dose methadone and pain is controlled









Patient Name:
Accession ID:
Patient SSN:
Patient DOB, Gender:

Specimen ID: G5859093
Specimen Type: Buccal Swab

Requesting Provider:
Requesting Practice:

Collected: 02/23/15
Received: 02/26/15
Report Date: 02/27/15

DETAILED RESULTS

Gene	Genotype	Predicted Phenotype
CYP3A4/CYP3A5	*1/*3	Intermediate Metabolizer

- Patient is likely to have typical plasma levels of CYP3A4/CYP3A5 substrates, such as fentanyl,[2] alfaine[3] and tacrolimus.[4,7]
- Medication Interaction: CYP3A4/CYP3A5 inhibitors[1] and inducers[1] may affect response to CYP3A4/CYP3A5 substrates.

OPRM1	A/A	Normal Expressor

- Patient is expected to have typical response to fentanyl, morphine, and naltrexone, based on OPRM1 genotype.[7,8]
- Patient does not have the A118G variant which is associated with increased sensitivity to pain or increased opioid (morphine, fentanyl) dose requirements to achieve analgesia.[7,8,9,10,11,12,13,14]
- Patient does not have the A118G variant which is associated with increased likelihood of response to naltrexone.[8,9,10,11,12,13,14]

† For a list of clinically relevant cytochrome P450 substrates, inducers, and inhibitors, please see: http://medicine.iupui.edu/clinpharm/ddis/ Referenced by permission from Indiana University.

In Conclusion…

- Benefit: Improved diagnostic/ prescribing accuracy and speed
  - Decrease in healthcare costs
  - Personalized treatment plans
  - Rational drug design
- Who
  - *"Nothing works"*
  - *"Everything sedates me."*
- **Where ever you see a need**

References

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- Sidhasivam S. and Chidambaran, V. (2012) Pharmacogenomics of Opioids and Perioperative Pain Management. *Pharmacogenomics. 13(15)1719-40.*

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Questions?

End of Presentation
Thank you for your time and attention.

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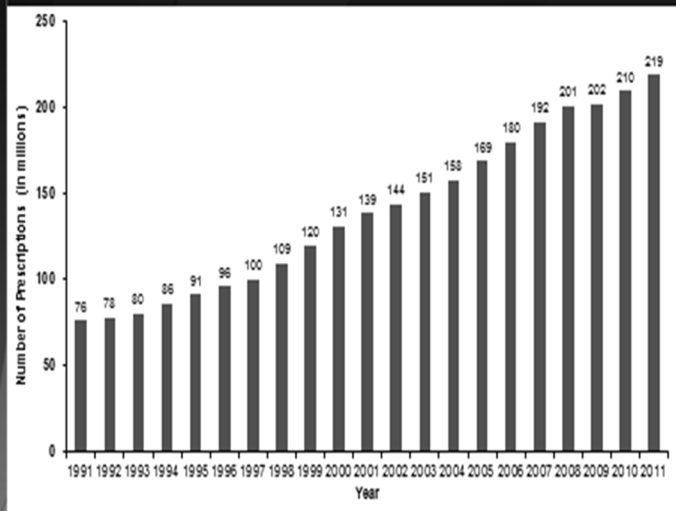
Opioid Prescriptions Dispensed by Retail Pharmacies—United States, 1991–2011



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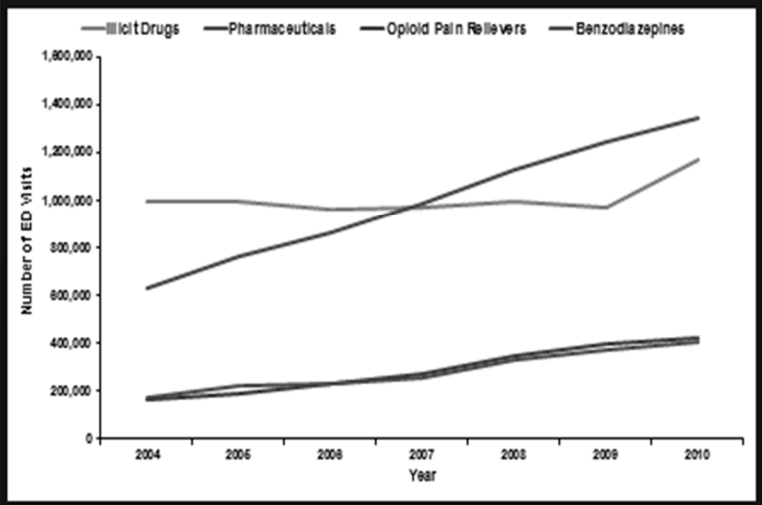
Emergency Department Visits Related to Drug Misuse or Abuse—United States, 2004–2010



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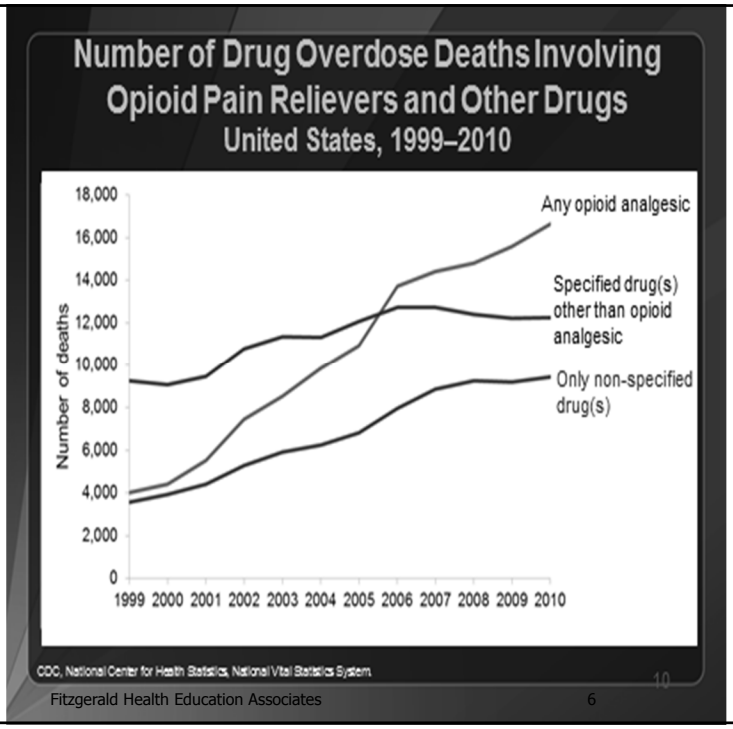

Common Pain Medications with Pharmacogenomic Tests

Generic	**Brand**	**Metabolic route**
Alfentanil	Alfenta®	CYP3A4/CYP3A5
Carisoprodol**	Soma®	CYP2C19
Celecoxib	Celebrex®	CYP2C9
Codeine**	Various brands	CYP2D6
Cyclobenzaprine	Flexeril®	CYP1A2, CYP3A4/CYP3A5
Fentanyl	Actiq®, Duragesic®	CYP3A4/CYP3A5
Hydrocodone**	Lortab®, Vicodin®	CYP2D6
Hydromorphone	Dilaudid®	UGT2B7+ (OPRM1)
Ibuprofen	Advil®, Motrin®	CYP2C9
****prodrug; + test not yet available**		

Common Pain Medications with Pharmacogenomic Tests (continued)

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Methadone	Various brands	CYP2C19, CYP2B6+
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Naproxen	Aleve®	CYP2C9
Oxycodone**	Oxycontin®, Percocet®	CYP2D6, CYP3A4/5
Oxymorphone	Opana®	UGT2B7+ (OPRM1)
Ropivicaine	Various brands	CYP1A2
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Zolmipitran	Zomig®	CYP1A2
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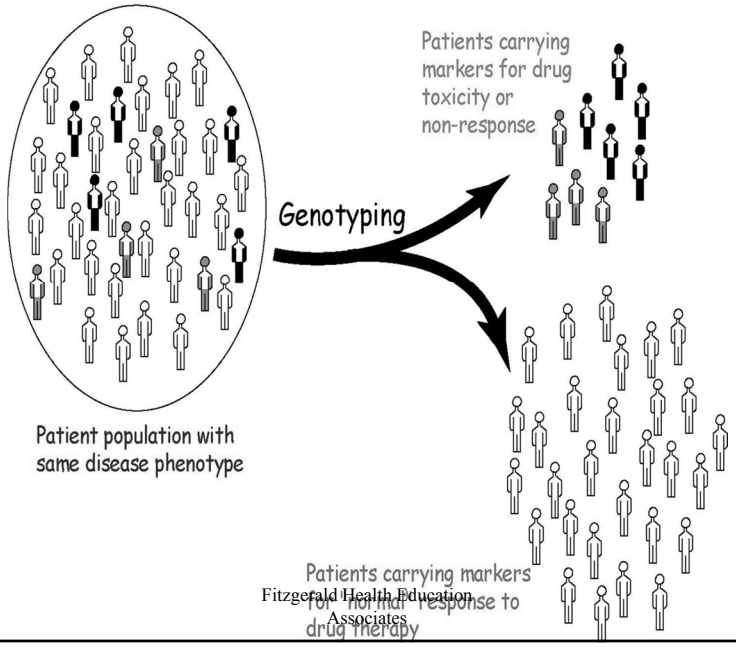
Manipulating Therapeutic Outcomes



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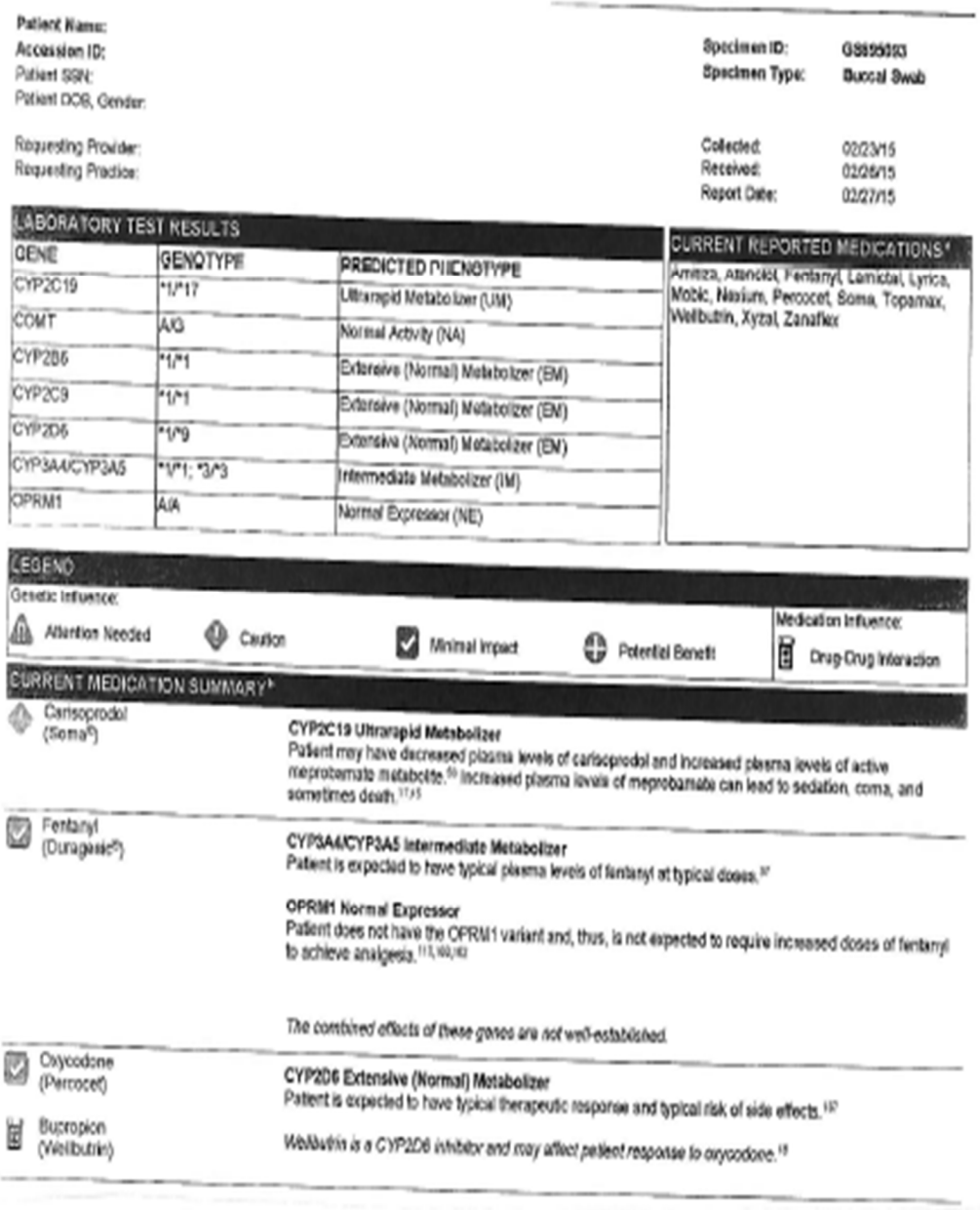

Patient Name:
Accession ID:
Patient SSN:
Patient DOB, Gender:

Requesting Provider:
Requesting Practice:

Specimen ID: GS895933
Specimen Type: Buccal Swab

Collected: 02/23/15
Received: 02/26/15
Report Date: 02/27/15

LABORATORY TEST RESULTS

GENE	GENOTYPE	PREDICTED PHENOTYPE
CYP2C19	*1/*17	Ultrarapid Metabolizer (UM)
COMT	A/G	Normal Activity (NA)
CYP2B6	*1/*1	Extensive (Normal) Metabolizer (EM)
CYP2C9	*1/*1	Extensive (Normal) Metabolizer (EM)
CYP2D6	*1/*9	Extensive (Normal) Metabolizer (EM)
CYP3A4/CYP3A5	*1/*1; *3/*3	Intermediate Metabolizer (IM)
OPRM1	A/A	Normal Expressor (NE)

CURRENT REPORTED MEDICATIONS*

Ambien, Atenolol, Fentanyl, Lamictal, Lyrica, Mobic, Nexium, Percocet, Soma, Topamax, Wellbutrin, Xyzal, Zanaflex

LEGEND

Genetic Influence:
Attention Needed | Caution | Minimal Impact | Potential Benefit

Medication Influence:
Drug-Drug Interaction

CURRENT MEDICATION SUMMARY*

Carisoprodol (Soma®)

CYP2C19 Ultrarapid Metabolizer
Patient may have decreased plasma levels of carisoprodol and increased plasma levels of active meprobamate metabolite.[59] Increased plasma levels of meprobamate can lead to sedation, coma, and sometimes death.[17,18]

Fentanyl (Duragesic®)

CYP3A4/CYP3A5 Intermediate Metabolizer
Patient is expected to have typical plasma levels of fentanyl at typical doses.[97]

OPRM1 Normal Expressor
Patient does not have the OPRM1 variant and, thus, is not expected to require increased doses of fentanyl to achieve analgesia.[113,160,163]

The combined effects of these genes are not well-established.

Oxycodone (Percocet)

CYP2D6 Extensive (Normal) Metabolizer
Patient is expected to have typical therapeutic response and typical risk of side effects.[157]

Bupropion (Wellbutrin)

Wellbutrin is a CYP2D6 inhibitor and may affect patient response to oxycodone.[19]

Patient Name:
Accession ID:
Patient SSN:
Patient DOB, Gender:

Requesting Provider:
Requesting Practice:

Specimen ID: GS635083
Specimen Type: Buccal Swab

Collected: 02/23/15
Received: 02/26/15
Report Date: 02/27/15

MEDICATION SELECTION GUIDE (based on potential genetic impact)*

LOW GENETIC IMPACT	MODERATE GENETIC IMPACT	HIGH GENETIC IMPACT
Muscle Relaxants		
Baclofen (Lioresal®) N/A Cyclobenzaprine (Flexeril®) N/A Tizanidine (Zanaflex®) N/A	Carisoprodol (Soma®) CYP2C19	
Non-opioid Analgesics		
Gabapentin (Neurontin®) N/A Pregabalin (Lyrica®) N/A		
NSAIDs		
Celecoxib (Celebrex®) CYP2C9 Diclofenac (Voltaren®) CYP2C9 Fenoprofen (Nalfon®) N/A Flurbiprofen (Ansaid®) CYP2C9 Ibuprofen (Advil®) CYP2C9 Indomethacin (Indocin®) CYP2C9 Ketoprofen (Orudis®) N/A Meferamic (Ponstel®) CYP2C9 Meloxicam (Mobic®) N/A Nabumetone (Relafen®) N/A Naproxen (Aleve®) CYP2C9 Piroxicam (Feldene®) CYP2C9 Sulindac (Clinoril®) N/A		

Patient Name:
Accession ID:
Patient SSN:
Patient DOB, Gender

Requesting Provider
Requesting Practice

Specimen ID: GS835033
Specimen Type: Buccal Swab

Collected: 02/23/15
Received: 02/26/15
Report Date: 02/27/15

MEDICATION SELECTION GUIDE (based on potential genetic impact)

LOW GENETIC IMPACT	MODERATE GENETIC IMPACT	HIGH GENETIC IMPACT
Opioids		
Alfentanil (Alfenta®) — CYP3A4/5		
Buprenorphine (Butrans®) — CYP3A4/5		
Butorphanol (Stadol®) — N/A		
Codeine [DDI 1] — COMT, CYP2D6, OPRM1		
Fentanyl (Duragesic®) — CYP3A4/5, OPRM1		
Hydrocodone (Vicodin®) [DDI 1] — CYP2D6		
Hydromorphone (Dilaudid®) — N/A		
Meperidine (Demerol®) — N/A		
Methadone (Dolophine®) — CYP2B6		
Morphine (Avinza®) — COMT, OPRM1		
Oxycodone (Oxycontin®) [DDI 1] — CYP2D6		
Oxymorphone (Opana ER®) — N/A		
Sufentanil (Sufenta®) — CYP3A4/5		
Tapentadol (Nucynta®) — N/A		
Tramadol (Ultram® ER) [DDI 1] — CYP2D6		

[1] Prescribed Medications are in bold face. Medications are rated as low, moderate, or high genetic impact based on patient's Laboratory Test Results in this report. For genes that are not included in the Laboratory Test Results, normal activity is assumed, i.e., extensive metabolizer (EM) for CYP2D6, CYP2C9, CYP2C19, CYP2C19, and intermediate metabolizer (IM) for CYP3A5/CYP3A4. The medication listed as N/A is not evaluated for the medication shown. Low genetic impact also includes medications not metabolized or with minor effects on metabolism by CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and/or UGT2B15, depending on results of clinical tests. Each medication is annotated with the genetic association with its clinical interpretation. Abbreviations used: NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

[DDI 1] Medication is a CYP2D6 inhibitor and may affect response to this medication. [2]

DETAILED RESULTS

Gene	Genotype	Predicted Phenotype
COMT	A/G	Normal Activity

- Patient is likely to have typical COMT activity, and thus is expected to have typical response to morphine and codeine.[154]
- Patient does not have the Val158Met genotype that is associated with increased mu opioid receptor density[30,31,118] and reduced dose requirements for morphine.[55,124,125,126,154]
- Medication interaction: COMT inhibitors[126] may impact response.

CYP2B6	*1/*1	Extensive (Normal) Metabolizer

- Patient is expected to have normal plasma levels of CYP2B6 substrates,[1] such as methadone and efavirenz.[157]
- Patient does not have the CYP2B6 genotype associated with accumulation of cardiotoxic (S)-methadone, which can lead to QT interval prolongation and serious arrhythmia.[30,158]
- Medication interaction: CYP2B6 inhibitors[1] and inducers[1] may impact response to CYP2B6 substrates.

CYP2C19	*1/*17	Ultrarapid Metabolizer

- Patient is expected to have reduced plasma levels of CYP2C19 substrates,[1] such as carisoprodol, citalopram, clopidogrel, diazepam, escitalopram, sertraline, and TCAs.[1,141]
- Citalopram and escitalopram. Published guidelines recommend: Monitor plasma concentration and increase dose in response to efficacy and side effects or select alternative medication (DPWG, 2011).[159]
- Clopidogrel. Published guidelines recommend: Follow standard dosing as described in prescribing information for clopidogrel treatment of acute coronary syndrome patients undergoing percutaneous coronary intervention (CPIC, 2013).[138]
- Medication interaction: CYP2C19 inducers[1] and CYP2C19 inhibitors[1] may impact response to CYP2C19 substrates.[1]

CYP2C19/CYP2D6	*1/*17;*1/*9	Ultrarapid Metabolizer;Extensive (Normal) Metabolizer

- Patient is expected to have decreased plasma levels of CYP2C19 substrates[1] and typical plasma levels of CYP2D6 substrates.[1,57]
- Amitriptyline, clomipramine, doxepin, and imipramine. Published guidelines recommend: Consider alternative medication not metabolized by CYP2C19. If prescribed, monitor to guide dose adjustments (CPIC, 2013).[76]
- Medication interaction: CYP2C19 inhibitors,[1] CYP2C19 inducers[1] and CYP2D6 inhibitors[1] may impact response.

CYP2C9	*1/*1	Extensive (Normal) Metabolizer

- Patient is expected to have normal plasma levels of CYP2C9 substrates,[1] such as NSAIDs, warfarin, and irbesartan.[160]
- Patient does not have the CYP2C9 genotype associated with decreased clearance of celecoxib,[87,131,132,148,155] increased risk of side effects following celecoxib use[48,106,109,119] or increased risk of bleeding from warfarin (CPIC, 2011).[8,126,127] Estimation of warfarin dosage also requires VKORC1 genotype (rs9923231).
- Medication interaction: CYP2C9 inhibitors[1] and CYP2C9 inducers[1] may impact response to CYP2C9 substrates.[1]

CYP2D6	*1/*9	Extensive (Normal) Metabolizer

- Patient is expected to have typical therapeutic response and typical risk of side effects to CYP2D6 substrates,[1] such as carvedilol, amitriptyline, clomipramine, doxepin, imipramine, desipramine, nortriptyline, risperidone, atomoxetine, haloperidol, codeine, tramadol, oxycodone, hydrocodone, fluoxetine, vortioxetine, paroxetine, aripiprazole, venlafaxine and tamoxifen.
- Medication interaction: CYP2D6 inhibitors[1] and inducers[1] may impact response.

Patient Name:
Accession ID:
Patient SSN:
Patient DOB, Gender:

Requesting Provider:
Requesting Practice:

Specimen ID: G5690053
Specimen Type: Buccal Swab

Collected: 02/23/15
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DETAILED RESULTS

Gene	Genotype	Predicted Phenotype
CYP3A4/CYP3A5	*1/*1; *3/*3	Intermediate Metabolizer

- Patient is likely to have typical plasma levels of CYP3A4/CYP3A5 substrates, such as fentanyl,[37] statins[80] and tacrolimus.[81]
- Medication Interaction: CYP3A4/CYP3A5 inhibitors† and inducers† may affect response to CYP3A4/CYP3A5 substrates.

OPRM1	A/A	Normal Expressor

- Patient is expected to have typical response to fentanyl, morphine, and naltrexone, based on OPRM1 genotype.[118]
- Patient does not have the A118G variant which is associated with increased sensitivity to pain or increased opioid (morphine, fentanyl) dose requirements to achieve analgesia.[113,139,163,182,195]
- Patient does not have the A118G variant which is associated with increased likelihood of response to naltrexone.[39,113,114,131,188]

† For a list of clinically relevant cytochrome P450 substrates, inducers, and inhibitors, please see: http://medicine.iupui.edu/clinpharm/ddis/. Referenced by permission from Indiana University.