Platinum Diagnostics LLC

DO NOT DISTRIBUTE

PATIENT INFORMATION		SPECIMEN DETAILS		PROVIDER INFORMATION
NAME:	**Emily Issick**	**SPECIMEN TYPE:**	Saliva	**ORDERING PHYSICIAN:** TEST, CRNP, NP-C
ACC #:	120NPYM	**COLLECTION DATE:**	4/17/2021	**PROVIDER:** provider x
DOB:	1/15/1997	**RECEIVED DATE:**	4/20/2021	
SEX:	F	**REPORT DATE:**	6/17/2022	

Pain Report PGx120

Current Patient Medications

All provided patient medications: sertraline, omeprazole, phentermine, loestrin Fe, Pepcid, cetirizine

Patient medications with NO clinical content: Phentermine, Loestrin Fe, Pepcid, Cetirizine

Omeprazole

Prilosec®

Decreased Exposure to Omeprazole (CYP2C19: Ultra-Rapid Metabolizer) — **INFORMATIVE**

Test results indicate an increased risk of therapeutic failure. Monitor for insufficient response and consider a dose increase.

- Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, Johnson JA, Cavallari LH, Shakhnovich V, Thacker DL, Scott SA, Schwab M, Uppugunduri CRS, Formea CM, Franciosi JP, Sangkuhl K, Gaedigk A, Klein TE, Gammal RS, Furuta T. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. Clin Pharmacol Ther. 2020 Aug 8.

Sertraline

Zoloft®

Possible Reduced Response to Sertraline (CYP2C19: Ultra-Rapid Metabolizer) — **INFORMATIVE**

Test results indicate an increased risk of adverse effects or therapeutic failure. Consider standard prescribing and closer monitoring. If therapy failure consider an alternative medication.

- Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.	**ACTIONABLE**	Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA, EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.
Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.		
The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.	**INFORMATIVE**	There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

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Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Pain	Fibromyalgia Agents	Milnacipran (Savella®)		
	Muscle Relaxants	Cyclobenzaprine (Flexeril®, Amrix®) Metaxalone (Skelaxin®) Methocarbamol (Robaxin®)	Carisoprodol (Soma®) Tizanidine (Zanaflex®)	
	NSAIDs	Celecoxib (Celebrex®) Diclofenac (Voltaren®) Flurbiprofen (Ansaid®) Ibuprofen (Advil®, Motrin®) Indomethacin (Indocin®) Ketoprofen (Orudis®) Ketorolac (Toradol®) Meloxicam (Mobic®) Nabumetone (Relafen®) Naproxen (Aleve®) Piroxicam (Feldene®) Sulindac (Clinoril®)		
	Opioids	Alfentanil (Alfenta®) Buprenorphine (Butrans®, Buprenex®) Dihydrocodeine (Synalgos-DC®) Fentanyl (Actiq®) Hydromorphone (Dilaudid®, Exalgo®) Levorphanol (Levo Dromoran®) Meperidine (Demerol®) Methadone (Dolophine®) Morphine (MS Contin®) Oxycodone (Percocet®, Oxycontin®) Oxymorphone (Opana®, Numorphan®) Sufentanil (Sufenta®) Tapentadol (Nucynta®)	Benzhydrocodone (Apadaz®) Hydrocodone (Vicodin®) Oliceridine (Olinvyk)	Codeine (Codeine; Fioricet® with Codeine) Tramadol (Ultram®)

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Dosing Guidance

Codeine

Codeine; Fioricet® with Codeine

Greatly Decreased Exposure to Codeine Active Metabolite (CYP2D6: Poor Metabolizer) — ACTIONABLE

The patient genotype is associated with greatly decreased conversion of codeine to its active metabolite (morphine), which may result in decreased effectiveness.

Consider avoiding prescribing codeine and instead use alternative opioids other than tramadol, or a non-opioid analgesic such as an NSAID or a COX-2 inhibitor. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

Tramadol

Ultram®

Greatly Decreased Exposure to Tramadol Active Metabolite (CYP2D6: Poor Metabolizer) — ACTIONABLE

The patient genotype is associated with greatly decreased conversion of tramadol to its active metabolite (O-desmethyltramadol), which may result in decreased effectiveness.

Consider avoiding prescribing tramadol and instead use alternative opioids other than codeine, or a non-opioid analgesic such as an NSAID or a COX-2 inhibitor. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

Benzhydrocodone

Apadaz®

Possible Altered Response to Benzhydrocodone (CYP2D6: Poor Metabolizer) — INFORMATIVE

Benzhydrocodone is a prodrug of hydrocodone and is converted to active hydrocodone by intestinal enzymes. Decreased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence whether these patients have decreased analgesia when taking benzhydrocodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).

- Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC, . Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014 Apr;95(4):376-82.
- Apadaz [package insert]. Coralville, IA: KemPharm Inc.; 2018.

Carisoprodol

Soma®

Altered Sensitivity to Carisoprodol (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

There is insufficient data to allow calculation of dose adjustment. If carisoprodol is prescribed, it is recommended to use a lower dose, and to carefully monitor the patient for side effects.

- Bramness JG, Skurtveit S, Fauske L, Grung M, Molven A, Mørland J, Steen VM. Association between blood carisoprodol:meprobamate concentration ratios and CYP2C19 genotype in carisoprodol-drugged drivers: decreased metabolic capacity in heterozygous CYP2C19*1/CYP2C19*2 subjects? Pharmacogenetics 2003 Jul;13(7):383-8.

Hydrocodone

Vicodin®

Decreased Exposure to Hydrocodone Active Metabolite (CYP2D6: Poor Metabolizer) — INFORMATIVE

The patient genotype is associated with a reduced conversion of hydrocodone to an active metabolite (hydromorphone), which may result in decreased effectiveness.

Hydrocodone can be prescribed at standard label-recommended age- or weight-based dosing. If no response and opioid use is warranted, consider a non-codeine or non-tramadol opioid. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

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Oliceridine

Olinvyk

Increased Exposure to Oliceridine (CYP2D6: Poor Metabolizer)

ACTIONABLE

The patient genotype is associated with decreased metabolism of oliceridine. Patients may require less frequent dosing of oliceridine.

Consider standard prescribing practices with increased monitoring and administer subsequent doses based on severity of pain and patient response.

- Olinvyk [package insert]. Chesterbrook, PA; Trevena, Inc.; 2020.

Tizanidine

Zanaflex®

Possible Non-Response to Tizanidine (CYP1A2: Normal Metabolizer - Higher Inducibility)

INFORMATIVE

There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation. Therefore, careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

- Backman JT, Schröder MT, Neuvonen PJ. Effects of gender and moderate smoking on the pharmacokinetics and effects of the CYP1A2 substrate tizanidine. Eur J Clin Pharmacol 2008 Jan;64(1):17-24.
- Granfors MT, Backman JT, Neuvonen M, Ahonen J, Neuvonen PJ. Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. Clin Pharmacol Ther 2004 Apr;75(4):331-41.
- Al-Ghazawi M, Alzoubi M, Faidi B. Pharmacokinetic comparison of two 4 mg tablet formulations of tizanidine. Int J Clin Pharmacol Ther 2013 Mar;51(3):255-62.
- Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J 2018 12;18(6):760-768.

Alfentanil

Alfenta®

Normal Response to Alfentanil

INFORMATIVE

Pharmacogenetic guidance: alfentanil is primarily metabolized by CYP3A4 and CYP3A5. Studies in healthy subjects showed that CYP3A5 genotype had no effect on the systemic or apparent oral clearances, or pharmacodynamics of alfentanil. **Polypharmacy guidance:** Alfentanil should be used with caution when prescribed to patients taking CYP3A4 inhibitors or inducers.

- Alfenta [package insert]. Lake Forest, IL: Akorn, Inc.; 2016.

Buprenorphine

Butrans®, Buprenex®

Normal Response to Buprenorphine

INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. Buprenorphine is primarily metabolized by CYP3A4 to norbuprenorphine and by UGT enzymes (mainly UGT1A1 and 2B7). The effects of genetic variants in these enzymes on its response have not been studied. **Polypharmacy guidance:** The concomitant use of buprenorphine with all CYP3A4 inhibitors may result in an increase in the drug levels, which could increase or prolong adverse drug effects. Monitor patients receiving buprenorphine with a CYP3A4 inhibitor. CYP and UGT inducers may decrease buprenorphine levels.

- Butrans [package insert]. Stamford, CT: Purdue Pharma L.P.; 2014.

Celecoxib

Celebrex®

Normal Celecoxib Exposure (CYP2C9: Normal Metabolizer)

ACTIONABLE

Celecoxib therapy can be initiated at standard label-recommended dosage and administration.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers.

Osteoarthritis, Rheumatoid Arthritis, Ankylosing Spondylitis, Acute Pain, Primary Dysmenorrhea: Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Acute Migraine: Consider using for the fewest number of days per month, as needed.

Osteoarthritis and Hypertension (co-formulation with amlodipine): Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.
- Celebrex [package insert]. New York City, NY: Pfizer; 2019.
- Consensi [package insert]. Hot Springs, AR: Burke Therapeutics, LLC.; 2020.
- Elyxyb [package insert]. Bridgewater, NJ: Promius Pharma, LLC.; 2020.

Cyclobenzaprine
Flexeril®, Amrix®

Normal Response to Cyclobenzaprine — INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available. Cyclobenzaprine is excreted primarily as a glucuronide via the kidneys, and as an N-demethylated metabolite by CYP3A4, CYP1A2, and to a lesser extent CYP2D6. Due to the minor involvement of CYP2D6 in the metabolism of cyclobenzaprine, the polymorphism of this enzyme is not of concern in its the clinical use.

- Flexeril [package insert]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceutical, Inc.; 2013.

Diclofenac
Voltaren®

Normal Diclofenac Exposure — INFORMATIVE

Pharmacogenetic guidance: Diclofenac is extensively metabolized by hydroxylation and direct glucuronidation. About 50% of diclofenac is eliminated as a 4-hydroxymetabolite, a reaction mediated by CYP2C9. Other CYP enzymes including CYP2C8, CYP2C19 and CYP3A4 are also involved in the formation of a 5-hydroxymetabolite. A substantial portion of the drug is also directly glucuronidated by UGT2B7 and UGT2B4. Genetic polymorphisms of CYP2C9 have not been found to affect the response to diclofenac. No dosing recommendations or genetically guided drug selection are recommended.
Polypharmacy guidance: Co-administration of diclofenac with CYP2C9 inhibitors may enhance the drug exposure and toxicity of whereas co-administration with CYP2C9 inducers may lead to compromised efficacy of diclofenac. A dosage adjustment may be warranted when diclofenac is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.
- Voltaren [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.

Dihydrocodeine
Synalgos-DC®

Normal Response to Dihydrocodeine (CYP2D6: Poor Metabolizer) — INFORMATIVE

Decreased conversion of dihydrocodeine to the more active metabolite dihydromorphine is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence whether these patients have decreased analgesia when taking dihydrocodeine. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms.

- Fromm MF, Hofmann U, Griese EU, Mikus G. Dihydrocodeine: a new opioid substrate for the polymorphic CYP2D6 in humans. Clin Pharmacol Ther 1995 Oct;58(4):374-82.
- Kirkwood LC, Nation RL, Somogyi AA. Characterization of the human cytochrome P450 enzymes involved in the metabolism of dihydrocodeine. Br J Clin Pharmacol 1997 Dec;44(6):549-55.

Fentanyl
Actiq®

Good Response to Fentanyl (OPRM1: Normal OPRM1 Function) — INFORMATIVE

The patient does not carry the OPRM1 118A>G variant. Acute postoperative and cancer pain: the patient is expected to experience good analgesia at standard fentanyl doses. Because fentanyl has a narrow therapeutic window, it is advised to carefully titrate this drug to a tolerable dose that provides adequate analgesia with minimal side effects.

- Zhang F, Liao Q, Li L, Wang SY, Hu R, Tang YZ, Ouyang W. The correlation between post-operative fentanyl requirements and μ-opioid receptor gene A118G polymorphism in patients undergoing radical gastrectomy. Exp Ther Med 2013 Apr;5(4):1147-1152.
- Landau R, Liu SK, Blouin JL, Carvalho B. The effect of OPRM1 and COMT genotypes on the analgesic response to intravenous fentanyl labor analgesia. Anesth Analg 2013 Feb;116(2):386-91.
- Khalil H, Sereika SM, Dai F, Alexander S, Conley Y, Gruen G, Meng L, Siska P, Tarkin I, Henker R. OPRM1 and COMT Gene-Gene Interaction Is Associated With Postoperative Pain and Opioid Consumption After Orthopedic Trauma. Biol Res Nurs 2017 03;19(2):170-179.
- Hwang IC, Park JY, Myung SK, Ahn HY, Fukuda K, Liao Q. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. Anesthesiology 2014 Oct;121(4):825-34.

Flurbiprofen
Ansaid®

Normal Flurbiprofen Exposure (CYP2C9: Normal Metabolizer) — ACTIONABLE

Rheumatoid Arthritis and Osteoarthritis: Flurbiprofen therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when flurbiprofen is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.
- Ansaid [package insert]. New York City, NY: Pfizer; 2016.

Hydromorphone
Dilaudid®, Exalgo®

Normal Response to Hydromorphone — INFORMATIVE

No genetically guided drug selection or dosing recommendations are available. Hydromorphone is not metabolized by CYPs, and genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Hydromorphone can be prescribed at standard label-recommended dosage and administration.

- Dilaudid [package insert]. Stamford, CT: Purdue Pharma L.P.; 2011.
- Exalgo [package insert]. Hazelwood, MO: Mallinckrodt Inc.; 2015.

Ibuprofen
Advil®, Motrin®

Normal Ibuprofen Exposure (CYP2C9: Normal Metabolizer) — ACTIONABLE

Pain, Dysmenorrhea, Rheumatoid Arthritis, Osteoarthritis, Fever and Other Anti-Inflammatory Uses: Ibuprofen therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when ibuprofen is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.
- IBUPROFEN- ibuprofen tablet [package insert]. Indiana, PA: RemedyRepack Inc.. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=495558. Rev Jun 2020.

Indomethacin
Indocin®

Normal Indomethacin Exposure — INFORMATIVE

Pharmacogenetic guidance: Indomethacin is metabolized mainly by O-demethylation to its inactive metabolite O-desmethyl indomethacin, a reaction catalyzed by CYP2C9. Genetic polymorphisms of CYP2C9 have not been found to affect the response to indomethacin. No genetically guided drug selection or dosing recommendations are available.

- Tivorbrex [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; 2019.
- Indocin [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; 2019.

Ketoprofen
Orudis®

Normal Response to Ketoprofen — INFORMATIVE

Pharmacogenetic guidance: Ketoprofen is primarily eliminated by glucuronidation (by UGT1A3, UGT1A9 and UGT2B7) and no major implication of CYP2C9 in the metabolism of this drug has been demonstrated. No genetically guided drug selection or dosing recommendations are available.

- Oruvail [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; 2007.

Ketorolac
Toradol®

Normal Response to Ketorolac — INFORMATIVE

Pharmacogenetic guidance: Ketorolac is metabolized by glucuronidation (UGT enzymes) and oxidation but the enzymes catalyzing the oxidation are not well characterized. No genetically guided drug selection or dosing recommendations are available.

- Sprix [package insert]. Wayne, PA: Egalet US Inc; 2018.

Levorphanol
Levo Dromoran®

Normal Response to Levorphanol — INFORMATIVE

Pharmacogenetic guidance: Levorphanol is metabolized by glucuronidation which is mediated by UGT2B7. There are no studies documenting the impact of genetic polymorphisms of this metabolizing enzyme on levorphanol response. And no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Enzyme inducing drugs are expected to increase levorphanol clearance significantly.

- LEVORPHANOL TARTRATE- levorphanol tartrate tablet [package insert]. Solana Beach, CA: Sentynl Therapeutics, Inc. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=242855. Rev Dec 2016.

Meloxicam
Mobic®

Normal Meloxicam Exposure (CYP2C9: Normal Metabolizer) — ACTIONABLE

Pain, Rheumatoid Arthritis and Osteoarthritis: Meloxicam therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when meloxicam is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.
- Anjeso [package insert]. Malvern, PA: Baudax Bio; 2020.
- Mobic [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2016.
- Qmiiz ODT [package insert]. Lake Forest, IL: TerSera Therapeutics LLC.; 2018.
- Vivlodex [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; 2015.

Meperidine
Demerol®

Normal Response to Meperidine — INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. Meperidine is metabolized to normeperidine by multiple CYPs, including CYP2B6, CYP3A4, and CYP2C19. The effects of genetic variants in these enzymes have not been studied. **Polypharmacy guidance:** In patients taking **strong CYP inducers**, meperidine metabolism is increased resulting in higher levels of its neurotoxic metabolite normeperidine. In presence of ritonavir, meperidine's exposure is significantly reduced while normeperidine concentrations are increased. Based on these findings, the risk of narcotic-related adverse effects from this combination appears to be minimal. However, increased concentrations of normeperidine suggest a potential for toxicity with increased dosages or long-term therapy. This combination should be avoided is possible.

- Ramírez J, Innocenti F, Schuetz EG, Flockhart DA, Relling MV, Santucci R, Ratain MJ. CYP2B6, CYP3A4, and CYP2C19 are responsible for the in vitro N-demethylation of meperidine in human liver microsomes. Drug Metab Dispos 2004 Sep;32(9):930-6.

Metaxalone
Skelaxin®

Normal Response to Metaxalone — INFORMATIVE

Pharmacogenetic guidance: Metaxalone is extensively metabolized by multiple CYP enzymes, including CYP1A2, CYP2D6, CYP2E1, and CYP3A4. Genetic polymorphisms of these enzymes are unlikely to affect its exposure to a significant extent. no genetically guided drug selection or dosing recommendations are available.

- Skelaxin [package insert]. Brisol, TN: King Pharmaceuticals, Inc.; 2008.

Methadone
Dolophine®

Normal Methadone Exposure (CYP2B6: Rapid Metabolizer) — INFORMATIVE

There are limited studies documenting the effect of CYP2B6 genetic variations on methadone exposure.

For Addiction Treatment: Consider standard prescribing and monitoring practices.

For Pain Management: Consider standard prescribing and monitoring practices.

- Dennis BB, Bawor M, Thabane L, Sohani Z, Samaan Z. Impact of ABCB1 and CYP2B6 genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction: a systematic review and meta-analysis. PLoS One 2014 ;9(1):e86114.
- Kharasch ED. Current Concepts in Methadone Metabolism and Transport. Clin Pharmacol Drug Dev 2017 Mar;6(2):125-134.
- Ahmad T, Valentovic MA, Rankin GO. Effects of cytochrome P450 single nucleotide polymorphisms on methadone metabolism and pharmacodynamics. Biochem Pharmacol 2018 07;153():196-204.

Methocarbamol
Robaxin®

Normal Response to Methocarbamol — INFORMATIVE

Pharmacogenetic guidance: Methocarbamol is metabolized via dealkylation and hydroxylation. The enzymes responsible for the metabolism of this drug have not been characterized. No genetically guided drug selection or dosing recommendations are available.

- Robaxin [package insert]. Milwaukee, WI: Schwarz Pharma, Inc.; 2003.

Milnacipran
Savella®

Normal Response to Milnacipran — INFORMATIVE

Pharmacogenetic guidance: milnacipran is minimally metabolized by UGT enzymes and primarily excreted unchanged in urine. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** coadministration of drugs that inhibit or induce CYP or UGT enzymes are unlikely to affect the exposure of milnacipran.

- Savella [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2013.

PATIENT INFORMATION

NAME: Emily Issick
ACC #: 120NPYM
DOB: 1/15/1997
SEX: F

Morphine
MS Contin®

Good Response to Morphine (OPRM1: Normal OPRM1 Function) — INFORMATIVE

The patient does not carry the OPRM1 118A>G variant. Acute postoperative and cancer pain: the patient is expected to experience good analgesia at standard morphine doses. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

- Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, Teo YY, Tan EC. A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. Anesthesiology 2008 Sep;109 (3):520-6.
- Klepstad P, Rakvåg TT, Kaasa S, Holthe M, Dale O, Borchgrevink PC, Baar C, Vikan T, Krokan HE, Skorpen F. The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004 Nov;48(10):1232-9.
- Matic M, Simons SH, van Lingen RA, van Rosmalen J, Elens L, de Wildt SN, Tibboel D, van Schaik RH. Rescue morphine in mechanically ventilated newborns associated with combined OPRM1 and COMT genotype. Pharmacogenomics 2014 Jul;15(10):1287-95.

Morphine
MS Contin®

Average Response to Morphine (COMT: Intermediate COMT Activity) — INFORMATIVE

The patient carries one COMT Val158Met variant, which translates to a reduced COMT function. The patient may require average to low doses of morphine for adequate pain control. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

- Rakvåg TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain 2008 Dec;4():64.
- Rakvåg TT, Klepstad P, Baar C, Kvam TM, Dale O, Kaasa S, Krokan HE, Skorpen F. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 2005 Jul;116(1-2):73-8.
- Matic M, Simons SH, van Lingen RA, van Rosmalen J, Elens L, de Wildt SN, Tibboel D, van Schaik RH. Rescue morphine in mechanically ventilated newborns associated with combined OPRM1 and COMT genotype. Pharmacogenomics 2014 Jul;15(10):1287-95.

Nabumetone
Relafen®

Normal Response to Nabumetone — INFORMATIVE

Pharmacogenetic guidance: Nabumetone is a prodrug, which is converted by CYP1A2 to an active metabolite (6-MNA) that is further metabolized by CYP2C9 to an inactive metabolite. Theoretically, individuals with reduced CYP2C9 activity (i.e CYP2C9 poor metabolizers) may have higher levels of the active metabolite, but it is unknown whether this results in altered drug response. No genetically guided drug selection or dosing recommendations are available.
Polypharmacy Guidance: CYP1A2 inhibitors may inhibit the activation of nabumetone to its active metabolite resulting in a reduction in the therapeutic effects of this drug. On the other hand, CYP1A2 inducers (i.e smoking) may result in higher levels of nabumetone active metabolite, which may affect the response to this drug.

- Ralafen [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2011.

Naproxen
Aleve®

Normal Sensitivity to Naproxen — INFORMATIVE

Pharmacogenetic guidance: UGT2B7 is responsible for hepatic naproxen acyl glucuronidation, which is the primary elimination pathway for this drug (60% of total clearance). CYP2C9 and CYP1A2 are responsible for the formation of O-desmethylnaproxen but this pathway is not the primary pathway for the elimination for naproxen. Genetic polymorphism of CYP2C9 has not been found to affect the response to naproxen. No genetically guided drug selection or dosing recommendations are available.

- Naprosyn [package insert]. Alpharetta, GA: Canton Laboratories, LLC; 2017.

Oxycodone
Percocet®, Oxycontin®

Decreased Exposure to Oxycodone Active Metabolite (CYP2D6: Poor Metabolizer) — INFORMATIVE

The patient genotype may be associated with the reduced conversion of oxycodone to an active metabolite (oxymorphone), but this does not appear to translate into decreased analgesia or side effects.

Oxycodone can be prescribed at standard label-recommended age- or weight-based dosing and monitoring.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

Oxymorphone
Opana®, Numorphan®

Normal Response to Oxymorphone — INFORMATIVE

No genetically guided drug selection or dosing recommendations are available. Oxymorphone is not metabolized by CYPs, and genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Oxymorphone can be prescribed at standard label-recommended dosage and administration.

- Opana [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc.; 2006.

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Piroxicam
Feldene®

Normal Piroxicam Exposure (CYP2C9: Normal Metabolizer) — ACTIONABLE

Rheumatoid Arthritis and Osteoarthritis: Piroxicam therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when piroxicam is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.
- Feldene [package insert]. New York City, NY: Pfizer; 2019.

Sufentanil
Sufenta®

Normal Response to Sufentanil — INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Sufentanil is primarily metabolized by CYP3A4 and so should be used with caution when prescribed with CYP3A4 inhibitors or inducers.

- SUFENTANIL CITRATE- sufentanil citrate injection, solution [package insert]. Lake Forest, IL: Hospira, Inc. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=283510. Rev Oct 2017.

Sulindac
Clinoril®

Normal Response to Sulindac — INFORMATIVE

Pharmacogenetic guidance: Sulindac is primarily eliminated by glucuronidation which is catalyzed by several isoforms including UGT1A3, UGT1A9 and UGT2B7. The role of CYP2C9 in sulindac metabolism is of minor relevance. No genetically guided drug selection or dosing recommendations are available.

- Clinoril [package insert]. South Granville, NSW, Australia: Merck Sharp & Dohme Pty., Ltd; 2010.

Tapentadol
Nucynta®

Normal Response to Tapentadol — INFORMATIVE

No genetically guided drug selection or dosing recommendations are available. Tapentadol is not metabolized by CYPs, and genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Tapentadol can be prescribed at standard label-recommended dosage and administration.

- Nucynta [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013.

Platinum Diagnostics LLC

PATIENT INFORMATION

NAME: **Emily Issick**
ACC #: 120NPYM
DOB: 1/15/1997
SEX: F

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Test Details

Gene	Results	Phenotype	Alleles Tested
COMT	Val158Met A/G	**Intermediate COMT Activity**	Val158Met
CYP1A2	*1A/*1F	**Normal Metabolizer - Higher Inducibility**	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W
CYP2B6	*1/*4	**Rapid Metabolizer**	*4, *5, *6, *7, *9, *18, *18.002, *22
CYP2C19	*17/*17	**Ultra-Rapid Metabolizer**	*2, *3, *4A, *4B, *5, *6, *7, *8, *9, *10, *17, *35
CYP2C9	*1/*1	**Normal Metabolizer**	*2, *3, *4, *5, *6, *8, *11, *13, *27
CYP2D6	*4/*4	**Poor Metabolizer**	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *29, *31, *35, *40, *41, *42, *49, *59, *114, *5 (gene deletion), XN (gene duplication)
OPRM1	A118G A/A	**Normal OPRM1 Function**	A118G

Approved By: *Gene Geneticist, MD on 2022-Jun-17*

Limitation: This test will not detect all the known alleles that result in altered or inactive tested genes. This test does not account for all individual variations in the individual tested. Absence of a detectable gene mutation does not rule out the possibility that a patient has different phenotypes due to the presence of an undetected polymorphism or due to other factors such as drug-drug interactions, comorbidities and lifestyle habits.

Methodology: Array based assays detect listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Lab Disclaimer: "xxx Laboratories" developed the Genotype test. The performance characteristics of this test were determined by "xxx Laboratories". It has not been cleared or approved by the U.S. Food and Drug Administration.

Translational Software Disclaimer: The information presented on this report is provided as general educational health information. The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of the medications prescribed.

The pharmacogenetic assay involves use of reporting software and genotype-phenotype associations performed by Translational Software (www.translationalsoftware.com). The software has not been evaluated by the Food and Drug Administration. The software, and the report generated by the software, is not intended to diagnose, treat, cure, or prevent any disease. A qualified designee within the lab uses Translational Software to generate and subsequently review the report. The pharmacogenetic report is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome.

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Patient Information Card

This is a summary genetic report for your patient to share with other healthcare providers. The card can be cut out along the dashed line and carried with the patient.

Your Lab
Your Logo

REPORT DETAILS
Name: Emily Issick
DOB: 1/15/1997
ACC #: 120NPYM

Pharmacogenetic Test Summary

COMT	Val158Met A/G	Intermediate COMT Activity
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility
CYP2B6	*1/*4	Rapid Metabolizer
CYP2C19	*17/*17	Ultra-Rapid Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*4/*4	Poor Metabolizer
OPRM1	A118G A/A	Normal OPRM1 Function

For a complete report contact Vanilla PGx 120
www.samplelab.com

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