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Gx™ PGx-Pain Test Report

Larry Hung, MD, Laboratory Director
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PATIENT: Doe, John (M)
DOB: 1985-01-01
PATIENT ID: #####

COLLECTED: 01/12/2017
RECEIVED: 03/10/2017
REPORTED: 05/05/2017

SAMPLE TYPE: Saliva
PHYSICIAN: John Doe
PRACTICE: xxxxxx

ACCESSION: LIT-PGXITT289

QUICK SUMMARY

BENZODIAZEPINES	RESULTS
Diazepam (VALIUM®)	✅ Consider label recommended dosage if no contraindication.

GENERAL ANESTHETICS	
Desflurane (SUPRANE®) Isoflurane (FORANE®) Sevoflurane (ULTANE®, SOJOURN®) Succinylcholine (ANECTINE®, QUELICIN®)	✅ Consider label recommended dosage if no contraindication.
Nitrous Oxide (NITRONOX)	⚠ Higher homocysteine levels after anesthesia.

MUSCLE RELAXANTS	
Carisoprodol (SOMA®)	✅ Consider label recommended dosage if no contraindication.

NSAIDS	
Celecoxib (CELEBREX®) Diclofenac (VOLTAREN®, CATAFLAM®)	⚠ Increased likelihood of acute coronary syndrome.

OPIOIDS	
Buprenorphine (SUBUTEX®)	✅ Consider label recommended dosage if no contraindication.
Codeine (TYLENOL® #3) Hydrocodone (LORTAB®, VICODIN®) Oxycodone (OXYCONTIN®, PERCOCET®) Tramadol (ULTRAM®)	⛔ Patient is an ultrarapid metabolizer of narcotic analgesics and has an increased risk of toxicity. Consider alternative analgesics such as morphine or a nonopioid.

IMPORTANT

This Quick Summary provides a brief overview of the predicted response of the patient. This information is based solely on the genotype information and is not based on a complete patient profile. Detection or absence of variants does not replace the need for therapeutic monitoring. Physicians should consider the information contained in the Details section, as well as consider current prescriptions, family history, presenting symptoms, and other factors before making any clinical or therapeutic decisions.

✅ No negative assertions based on genotype.

⚠ Genotype may present increased risk or decreased effectiveness; prescribe with caution.

⛔ Genotype may present increased risk or decreased effectiveness; select alternative drug.

GENE SUMMARY

GENE	GENOTYPE	PHENOTYPE
CYP2D6	*2/*2xN	⛔ Ultrarapid Metabolizer
CYP2C19	*1/*17	⚠ Rapid Metabolizer
CYP2C9	*1/*1	✅ Extensive (Normal) Metabolizer
CYP3A4	*1/*1	✅ Extensive (Normal) Metabolizer

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Buprenorphine	CYP3A4 *1/*1	*Extensive (normal) metabolizer.*	Evidence ★
	The patient is predicted to be an extensive (normal) CYP3A4 metabolizer. Buprenorphine is metabolized by N-dealkylation via CYP3A4 into norbuprenorphine. Although CYP3A4 is the major enzyme responsible for buprenorphine metabolism, chemical inhibition of CYP3A4 does not appear to significantly affect buprenorphine concentrations. Caution is recommended when co-administering buprenorphine with drugs that affect CYP3A4 activity. Examples of CYP3A4 inhibitors include protease inhibitors, macrolide antibiotics, chloramphenicol, azole antifungals and nefazodone.		
Carisoprodol	CYP2C19 *1/*17	*Rapid metabolizer.*	Evidence ★★★
	Consider label recommended dosage of Carisoprodol if no contraindication.		
Celecoxib	CYP2C9 *1/*1	*Extensive (normal) metabolizer.*	Evidence ★★★
	Consider label recommended dosage of Celecoxib if no contraindication.		
	AGT rs699 A/A (WT)		Evidence ★
	Patients with this genotype may have increased likelihood of acute coronary syndrome when exposed to NSAIDs compared to patients with the homozygous genotype.		
Codeine	CYP2D6 *2/*2 Allele Duplication	*Ultrarapid metabolizer.*	Evidence ★★★
	The genotype predicts that the patient is an Ultrarapid Metabolizer for Codeine. Patient may have increased formation of morphine following codeine administration, leading to higher risk of toxicity. FDA WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism. CPIC Dosing Guidelines recommend avoiding codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopiod. Consider avoiding tramadol. In a patient identified as a CYP2D6 ultrarapid metabolizer, the choice of an alternative analgesic should be made to avoid the risk of severe toxicity associated with a 'normal' dose of codeine. That is, it may be preferable to use an analgesic other than the CYP2D6 substrate tramadol in ultrarapid metabolizers. The Dutch Pharmacogenetics Working Group Guideline suggests selecting an alternative drug (e.g., acetaminophen, NSAID, morphine-not tramadol or oxycodone) or be alert to ADE. Clinical effect: death; arrhythmia; unanticipated myelosuppression.		
Desflurane	RYR1 rs118192170 T/T (WT) RYR1 rs118192162 A/A (WT) RYR1 rs118192175 C/C (WT) RYR1 rs118192176 G/G (WT) RYR1 rs121918593 G/G (WT) RYR1 rs121918594 G/G (WT) RYR1 rs121918595 C/C (WT)	RYR1 rs121918592 G/G (WT) RYR1 rs118192172 C/C (WT) RYR1 rs118192163 G/G (WT) RYR1 rs118192177 C/C (WT) RYR1 rs28933397 C/C (WT) RYR1 rs118192167 A/A (WT) RYR1 rs118192161 C/C (WT)	Evidence ★
	Consider label recommended dosage of Desflurane if no contraindication.		
Diazepam	CYP2C19 *1/*17	*Rapid metabolizer.*	Evidence ★
	The patient is a rarapid metabolizer of diazepam and should have increased metabolism of diazepam (lower AUC and higher clearance of diazepam) compared to poor metabolizers. The patient should emerge from anesthesia more rapidly than poor metabolizers.		
Diclofenac	CYP2C9 *1/*1	*Extensive (normal) metabolizer.*	Evidence ★★
	Consider label recommended dosage of Diclofenac if no contraindication.		
	AGT rs699 A/A (WT)		Evidence ★
	Patients with this genotype may have increased likelihood of acute coronary syndrome when exposed to NSAIDs compared to patients with the homozygous genotype.		

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Hydrocodone	CYP2D6 *2/*2 Allele Duplication — *Ultrarapid metabolizer.*		Evidence ★★★
	The genotype predicts that the patient is an Ultrarapid Metabolizer for Hydrocodone. This may lead to increased formation of hydromorphone following Hydrocodone administration, leading to a higher risk of toxicity. The CPIC codeine guidelines suggest avoiding use of analgesics metabolized by CYP2D6 (such as Codeine, Hydrocodone, Oxycodeine, Tramadol). Consider alternative analgesics such as morphine or a non-opioid.		
Isoflurane	RYR1 rs118192170 T/T (WT)	RYR1 rs121918592 G/G (WT)	Evidence ★
	RYR1 rs118192162 A/A (WT)	RYR1 rs118192172 C/C (WT)	
	RYR1 rs118192175 C/C (WT)	RYR1 rs118192163 G/G (WT)	
	RYR1 rs118192176 G/G (WT)	RYR1 rs118192177 C/C (WT)	
	RYR1 rs121918593 G/G (WT)	RYR1 rs28933397 C/C (WT)	
	RYR1 rs121918594 G/G (WT)	RYR1 rs118192167 A/A (WT)	
	RYR1 rs121918595 C/C (WT)	RYR1 rs118192161 C/C (WT)	
	Consider label recommended dosage of Isoflurane if no contraindication.		
Nitrous Oxide	MTHFR rs1801133 A/A (HOM)		Evidence ★
	Patients with the homozygous rs1801133 genotype who undergo elective surgery with nitrous oxide anesthesia may have higher plasma total homocysteine concentrations.		
	MTHFR rs1801131 T/T (WT)		Evidence ★
	Consider label recommended dosage of Nitrous Oxide if no contraindication.		
Oxycodone	CYP2D6 *2/*2 Allele Duplication — *Ultrarapid metabolizer.*		Evidence ★★
	The genotype predicts that the patient is an Ultrarapid Metabolizer for Oxycodone. Consider using an alternate drug rather than oxycodone (not codeine or tramadol), or be alert to adverse drug events. The Dutch Pharmacogenetics Working Group Guideline indicates that there is insufficient data to allow calculation of dose adjustment, and recommends selecting an alternate drug - not tramadol or codeine - or be alert to ADEs (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention). Minor clinical effect: QTc prolongation (<450 ms men, <470 ms women); INR increase < 4.5. Kinetic effect.		
Sevoflurane	RYR1 rs118192170 T/T (WT)	RYR1 rs121918592 G/G (WT)	Evidence ★
	RYR1 rs118192162 A/A (WT)	RYR1 rs118192172 C/C (WT)	
	RYR1 rs118192175 C/C (WT)	RYR1 rs118192163 G/G (WT)	
	RYR1 rs118192176 G/G (WT)	RYR1 rs118192177 C/C (WT)	
	RYR1 rs121918593 G/G (WT)	RYR1 rs28933397 C/C (WT)	
	RYR1 rs121918594 G/G (WT)	RYR1 rs118192167 A/A (WT)	
	RYR1 rs121918595 C/C (WT)	RYR1 rs118192161 C/C (WT)	
	Consider label recommended dosage of Sevoflurane if no contraindication.		
Succinylcholine	RYR1 rs118192170 T/T (WT)	RYR1 rs121918592 G/G (WT)	Evidence ★
	RYR1 rs118192162 A/A (WT)	RYR1 rs118192172 C/C (WT)	
	RYR1 rs118192175 C/C (WT)	RYR1 rs118192163 G/G (WT)	
	RYR1 rs118192176 G/G (WT)	RYR1 rs118192177 C/C (WT)	
	RYR1 rs121918593 G/G (WT)	RYR1 rs28933397 C/C (WT)	
	RYR1 rs121918594 G/G (WT)	RYR1 rs118192167 A/A (WT)	
	RYR1 rs121918595 C/C (WT)	RYR1 rs118192161 C/C (WT)	
	Consider label recommended dosage of Succinylcholine if no contraindication.		

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Tramadol	CYP2D6 *2/*2 Allele Duplication	*Ultrarapid metabolizer.*	Evidence ★★

The genotype predicts that the patient is an Ultra Metabolizer for Tramadol. The Dutch Pharmacogentics Working Group Guideline recommends reducing dose by 30% and be alert to ADEs (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) or select alternative drug (e.g., acetaminophen, NSAID, morphine-not oxycodone or codeine). Clinical effect: long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); INR 4.5-6.0; neutropenia 1.0-1.5x10^9/l; leucopenia 2.0-3.0x10^9/l; thrombocytopenia 50-75x10^9/l.

KEY FOR VARIANT-DRUG COMBINATION EVIDENCE

★★★ Replicated in multiple studies with statistical significance and strong effect size.
★★ Replicated in multiple studies with and without statistical significance and effect size may be minimal.
★ Not yet replicated or replicated but lacking clear evidence of an association.
Notable information is available and special considerations may be of interest when prescribing for this genotype.
Literature does not indicate additional risks, benefits, or prescription changes to consider for this genotype.

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REPORTED GENOTYPES

This panel performs genotyping analysis on key genes and variant hot-spot regions, focused on analyzing loci documented as altering the effectiveness of drug metabolism. Key genotyping results include the following:

AGT
rs699:A/A Wild

CYP2C19
CYP2C19 *1/*17
rs4244285:G/G Wild
rs4986893:G/G Wild
rs28399504:A/A Wild
rs56337013:C/C Wild
rs72552267:G/G Wild
rs72558186:T/T Wild
rs41291556:T/T Wild
rs17884712:G/G Wild
rs6413438:C/C Wild
rs55640102:A/A Wild
rs12248560:C/T Het

CYP2C9
CYP2C9 *1/*1
rs1799853:C/C Wild
rs1057910:A/A Wild

CYP2D6
CYP2D6 *2/*2xN
Allele Duplication
rs16947:A/A Wild
rs1135840:G/G Wild
rs35742686:T/T Wild
rs1135824:T/T Wild
rs1065852:G/G Wild
rs3892097:C/C Wild
rs5030655:A/A Wild
rs5030867:T/T Wild
rs5030865:C/C Wild
rs5030656:CTT/CTT Wild
rs5030863:C/C Wild
rs5030862:C/C Wild
rs72549357:C/C Wild
rs28371706:G/G Wild
rs59421388:C/C Wild
rs769258:C/C Wild
rs28371725:C/C Wild
rs28371696:C/C Wild
rs28371717:C/C Wild

CYP3A4
CYP3A4 *1/*1
rs12721627:G/G Wild
rs12721629:G/G Wild
rs4987161:A/A Wild
rs72552799:C/C Wild
rs67784355:G/G Wild
rs4986909:G/G Wild
rs35599367:G/G Wild

MTHFR
rs1801133:A/A Hom
rs1801131:T/T Wild

RYR1
rs118192161:C/C Wild
rs121918592:G/G Wild
rs118192162:A/A Wild
rs118192172:C/C Wild
rs118192175:C/C Wild
rs118192163:G/G Wild
rs118192176:G/G Wild
rs118192177:C/C Wild
rs121918593:G/G Wild
rs28933397:C/C Wild
rs121918594:G/G Wild
rs118192167:A/A Wild
rs121918595:C/C Wild
rs118192170:T/T Wild

Reported genotype calls are all displayed with respect to the positive DNA strand. Variants indicated as homozygous (Hom) or heterozygous (Het) differ from the GRCh37/hg19 reference sequence (Wild). This report is limited to the following star-alleles: CYP2D6: *1, *2, *3, *3B, *4, *5, *6, *6C, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *29, *33, *35A, *41, *45A & *46. CYP2C19: *1, *2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *12 & *17. CYP2C9: *1, *2 & *3. CYP3A5: *1 & *3. CYP3A4: *1, *8, *11, *12, *13, *16, *17 & *22. TPMT: *1, *2, *3A, *3B, *3C & *4. DPYD: *1, *2, *4, *5, *13 & rs67376798A. Any genotype identified as a default star-allele (CYP2D6 *2, CYP2C19 *1, CYP2C9 *1, CYP3A5 *3, CYP3A4 *1, TPMT *1, DPYD *1) indicates the absence only of the other alleles listed and does not imply that other variants in the gene are absent. Full allele deletions and duplications are only analyzed for the CYP2D6 gene. This test does not report polymorphisms other than those specifically listed, and mutations in other genes associated with drug metabolism will not be detected. Rare diagnostic errors may occur if variations occur in primer site locations.

DISCLAIMER

The information presented on this report is provided as supplementary health information. The results presented are intended for use by a physician, pharmacist or other healthcare professional to advise a patient on the use of prescribed medications. This test is not a 510k cleared test, but managed by CMS and FDA under the Clinical Laboratory Improvement Amendment (CLIA) as a LDT. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided. Results are dependent on adequate specimen collection and processing.

METHODOLOGY

Genomic DNA is extracted from dry buccal swabs using magnetic particle processing. DNA from patient samples are amplified with primers specific for AGT, CYP2C19, CYP2C9, CYP2D6, CYP3A4, MTHFR & RYR1 using Nested Patch PCR (Varley, et. al.). Positive and negative controls are used with each run. Patient samples, positive, and negative controls are sequenced using a MiSeq (Illumina). Sequences are analyzed using alignment and base call algorithms with Kailos Blue Software for the presence or absence of single nucleotide base changes, insertions and deletions. LR-PCR utilized for confirmation of CYP2D6 duplications and deletions. Results and recommendations are compiled as part of a medical report.

Genetic testing was performed in the Kailos Genetics CLIA facility at 601 Genome Way; Huntsville, Al. 35806. CLIA#: 01D2016114. Medical Director: Ronald McGlennen MD, FCAP, FACMG, ABMG.

This report was reviewed and approved for release by CLIA Lab Manager & Supervisor: Michele R. Erickson-Johnson, PhD, MB (ASCP)^{CM}

REFERENCES

M.V. Relling, T.E. Klein. "CPIC: Clincial Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network." Clinical Pharmacology & Therapeutics (2011) 89(3): 464-467.

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J.J. Swen, M. Nijenhuis, A. de Boer, L. Grandia, A.H. Maitland-van der Zee, H. Mulder, G.A. Rongen, R.H. van Schaik, T. Schalekamp, D.J. Touw, J. van der Weide, B. Wilffert, V.H. Deneer, H.J. Guchelaar. "Pharmacogenetics: from bench to byte--an update of guidelines." Clinical Pharmacology & Therapeutics (2011) 89(5): 662-673.

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