Table S1: Pharmacogenetic testing processes.

	Testing Platform	Gene Tested	Alleles Tested[4]
UF Health Pathology Laboratory[1]	Luminex xTAG *CYP2D6* Kit v3 (Luminex Corporation, Austin, TX)	*CYP2D6* [3]	*2, *3, *4, *5, *6, *7, *8, *9, *10 *11, *15, *17, *29, *35, *41, *CYP2D6* gene rearrangements associated with the deletion (*5) and duplication genotypes
	eSensor XT-8 (GenMark Diagnostics, Carlsbad, CA)	*CYP2C19* [3]	*2, *3, *4, *5, *6, *7, *8, *9, *10, *13, *17
	GatorPGx panel [2] QuantStudio 12K Flex Real Time PCR System (Applied Biosystems by Life Technologies, Carlsbad, CA)	*CYP2D6*	*2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *17, *29, *41,* rs1135840, *CYP2D6* gene rearrangements associated with the deletion (*5) and duplication genotypes
		CYP2C19	*2, *3, *4, *6, *8, *10, *17
		CYP3A5	*3, *6, *7
		CYP2C9	*2, *3, *5, *6, *8, *11
		CYP2C9 cluster	rs12777823
		CYP4F2	V433M
		VKORC1	c.-1639G>A
		TPMT	*2, *3A, *3B, *3C
		NUDT15	*3
		SLCO1B1	*5

[1] College of American Pathologists-accredited and Clinical Laboratory Improvement Amendments-licensed (CAP/CLIA) clinical laboratory in Gainesville, Florida.

[2] The pharmacist collected buccal samples from the patient for testing on the QuantStudio platform. GatorPGx panel was launched in July 2019.

[3] Upon clinic launch in September 2017, an offsite phlebotomist collected blood samples from the patient for *CYP2D6* and *CYP2C19* testing on the Luminex and GenMark platforms, respectively. At this time, the Luminex platform was validated for blood and buccal samples for *CYP2D6* testing, however, the GenMark platform was only validated for blood sample collection for *CYP2C19* testing. Once the GenMark platform was validated for buccal samples in October 2017, the pharmacist began collecting buccal brush samples from the patient during the first visit for both *CYP2C19* and *CYP2D6* testing.

[4] *CYP2C19* and *CYP2D6* genotypes were translated into phenotypes based on guidance at the time from the Clinical Pharmacogenetics Implementation Consortium (CPIC).[1]

Table S2: CYP2D6 phenotype translation.[2,3]

Step 1: Determined patient's activity score from *CYP2D6* genotype by determining the activity score of each allele present and adding the score together. In the case where a duplication was present, the total score was calculated twice, once with one allele duplicated and once with the other allele duplicated to account for both possibilities (resulting in a ranged phenotype).[1]	
Allele	**Activity Score**
**3, *4, *5, *6, *7, *8, *11, *15*	0
**9, *10, *17, *29, *41*	0.5
**1, *2, *35*	1
Step 2: Determined if patient was taking a CYP2D6 inhibitor [2,4], and multiplied the activity score calculated from step 1 by the applicable factor shown below. If patient was prescribed multiple inhibitors, the strongest inhibitor was used in this calculation.	
CYP2D6 inhibitor	**Multiple activity score by:**
Strong inhibitor[2]	0
Moderate inhibitor	0.5
Weak inhibitor	N/A
Step 3: Determined patient's phenotype from the calculated activity score from step 2 as shown below.	
Calculated Activity Score	**CYP2D6 Phenotype[3]**
>2	UM
1->2	NM-UM
1-2	NM
0.25-0.75	IM
0.5-2	IM-NM
0	PM

UM: ultra-rapid metabolizer; NM-UM: normal to ultra-rapid metabolizer; NM: normal metabolizer; IM: intermediate metabolizer; IM-NM: intermediate to normal metabolizer; PM: poor metabolizer.

[1] Ranged CYP2D6 phenotypes were possible because the assay used did not indicate the exact number of alleles present or which allele was duplicated. For instance, *CYP2D6*1/*4* duplication would translate to CYP2D6 normal to ultra-rapid metabolizer (NM-UM), because this genotype could result in a NM phenotype if the patient's **41* allele was duplicated and a UM phenotype if the patient's **1* allele was duplicated. Patients with a CYP2D6 NM-UM phenotype were treated conservatively as possible UM.

[2] Based on information the pharmacist collected from the patient on their history of response to current and/or past CYP2D6 substrates, the above translation method was not used if the patient with a total activity score >2 was taking a strong inhibitor and appeared to have a predicted phenotype other than PM (in light of being unable to determine exact number of *CYP2D6* copies). In this scenario, the pharmacist instead estimated the CYP2D6 phenotype based on clinical picture, assuming that patient did not undergo complete phenoconversion to PM. For example, if a patient who was taking bupropion (strong CYP2D6 inhibitor) and hydrocodone/ acetaminophen

(CYP2D6 substrate) reported having an exaggerated response to hydrocodone (e.g., severe opioid-induced pruritis and 50% reduction in pain) instead of the expected lack of pain relief common with PM, the pharmacist would estimate a phenotype of CYP2D6 NM-UM for the patient in this case. If CYP2D6 phenotype prediction was not possible based on patient's clinical picture, the phenotype was denoted as "Indeterminate".

[3] This *CYP2D6* genotype to phenotype translation represents the guidance at the time (i.e., September 2017-2019) from CPIC [1], prior to their translation standardization with the Dutch Pharmacogenetics Working Group (DPWG) [5].

Table S3: Patients' current and planned medications[1] that could be guided by *CYP2C19* and *CYP2D6* testing, along with number of recommendations suggesting that physicians consider a change in medication/dose and number of accepted recommendations.

Current/ Planned Medications[1]	Medication Class	Medications	Number of genotype-guided[1] medications (n=123)	Number of recommendations[2] (n=62)	Number of accepted recommendations (n=54)
Current	**Medications impacted by *CYP2C19***				
	SSRI	citalopram	1	0	N/A
		escitalopram	7	2	2
		sertraline	10	5	4
	PPI	dexlansoprazole	1	0	N/A
		esomeprazole	3	4	4
		omeprazole	22	11	9
		pantoprazole	15	10	8
		rabeprazole	1	0	N/A
	Antiplatelet	clopidogrel	1	0	N/A
	Medications impacted by *CYP2D6*				
	Antipsychotic	aripiprazole	2	1	1
	SNRI	venlafaxine	7	2	2
	SSRI	paroxetine	1	1	1
	Opioid	tramadol	7	2	2
		hydrocodone/ APAP	2	2	2
		hydrocodone/ homatropine	1	0	N/A
		oxycodone (IR/ER)	4	1	1
		oxycodone/ acetaminophen	3	1	0
	5HT3 Receptor Antagonist	ondansetron	6	0	N/A
Planned	**Medications impacted by *CYP2C19* or *CYP2D6***				
	Antidepressant/ Antipsychotic	—	28	20	18
	PPI	—	1	0	N/A

5HT3: serotonin type 3; PGx: pharmacogenetic; PPI proton pump inhibitor; SNRI serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

[1] Current/ planned medications that could be impacted by *CYP2C19* and/or *CYP2D6* per CPIC and/or DPWG guidelines [3,6-9]: SSRIs except fluoxetine, venlafaxine, aripiprazole, PPIs, opioids (i.e., codeine, tramadol, hydrocodone, oxycodone), clopidogrel, ondansetron.

[2] Excluded 2 patients with recommendations who were lost to follow-up with their physician.

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