Pharmacogenomics Applied to Chronic Pain Treatment in Primary Care (PGx-ACT) trial: A Largely Virtual Randomized Trial

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Background

- *CYP2D6* variation is associated with reduced bioactivation of tramadol, codeine, and hydrocodone.
- A prior non-randomized trial identified provision of CYP2D6-guided recommendations was associated with improved pain intensity among CYP2D6 intermediate and poor metabolizers prescribed tramadol, codeine, and hydrocodone (PMID: 30670877)
- Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) provide recommendations for codeine and tramadol based on *CYP2D6* genotype (PMID: 33387367)

Primary Objective

Identify the effects of providing pharmacogenomic (PGx) results and recommendations for patients with chronic pain who are treated in primary care clinics vs. standard care.

Methods

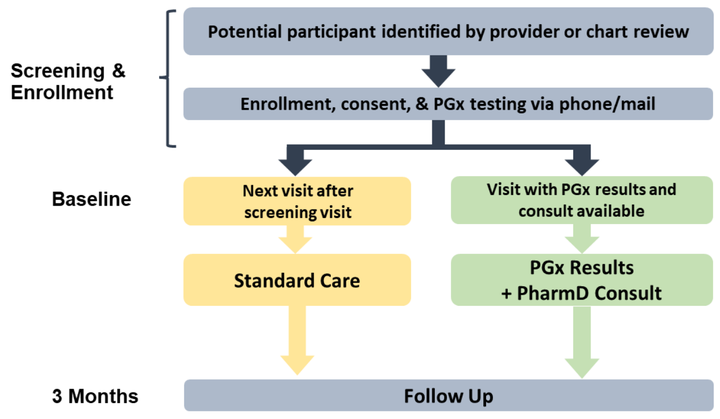
Population

- Adults with chronic pain (≥ 3 months) treated with either tramadol, codeine, or hydrocodone (TCH)
- Enrolled 01/2021 – 12/2022 from primary care practice sites at MedStar Health, a large, mid-Atlantic, health system
- Opioid had to be prescribed by a provider within the health system.

Design

- Open-label, prospective, trial randomized participants to a PGx-guided care or standard care arm (NCT04685304)
- No required in-person activities beyond usual care

Figure 1: Trial Design



Intervention

- All prescribing decisions were at the discretion of the treating providers
- PGx test: Kailos Genetics performed targeted next-generation sequencing on select genes (below) in a Clinical Laboratory Improvement Amendments (CLIA) certified lab. Phenotypes defined per CPIC
  - *CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, SLCO1B1, TPMT, VKORC1*
  - A separate PCR-based assay assessed *CYP2D6* copy number variation
- PharmD consult: Pharmacist sent a consultation note to relevant treating providers, which included result interpretation and therapeutic recommendations (Table 1)
- CDS alerts: Interruptive alerts recommended alternative therapy to providers placing an order for tramadol or codeine for a CYP2D6 PM and UM phenotypes per genotype
- Phenoconversion: Moderate and strong CYP2D6 inhibitors, as defined by the FDA convert NMs to IMs and PMs, respectively.
  - Strong CYP2D6 inhibitors: bupropion, fluoxetine, paroxetine, quinidine, terbinafine
  - Moderate CYP2D6 inhibitors: cinacalcet, duloxetine, fluvoxamine, mirabegron
- Standard Care: the study did not comment on care for participants in the standard care arm

Table 1: PGx-guided Recommendations

Phenotype	Recommendations Provided
IM	If TCH provides inadequate pain relief, 1) DC TCH and 2) prescribe non-opioid analgesic or different opioid (e.g. oxycodone)
	If TCH provides adequate pain relief, 1) continue or 2) replace with non-opioid analgesic
PM or UM	DC TCH
IM or PM	If phenoconverted, consider discontinuing CYP2D6 inhibitor and continue TCH
NM	Use per standard care

Endpoints

- Primary: change in pain intensity PROMIS T-score among CYP2D6 IM/PMs between baseline and 3 months
- Secondary: - all among CYP2D6 IM/PMs between baseline and 3 months - proportion with a ≥ 30% improvement in pain intensity (i.e., clinically meaningful improvement), MME prescribed, pharmacotherapy concordant with PGx-guided recommendations

Statistical Analysis

- Original sample size determination: 400 study subjects are needed to enroll to provide 80% power, with alpha=0.05, to detect an effect size of 0.5 (as in PMID 30670877). Assuming 80% complete follow up and 40% are eligible for the primary analysis (i.e., CYP2D6 IM or PM per genotype and concomitant medications)
- Adjusted sample size determination: increased effect size to 0.6 after additional analysis of the previous trial identified the effect size was 0.6. The primary analysis will have 80% power to detect an effect size of 0.6 at an alpha of 0.05 when 90 subjects with IM/PM status complete the trial.
- Primary analysis: penalized regression using elastic-net methods.
- Secondary analyses: Comparisons between arms used a two-sample t-test, chi-square analysis, or Fisher's exact test, as appropriate
  - PGx-aligned care (i.e., concordance) as used in post hoc analysis: prescribing that aligns with IM/PM recommendations in Table 1.
- Approved by IRB at MedStar Health Research Institute

Results

Figure 2: CONSORT Diagram

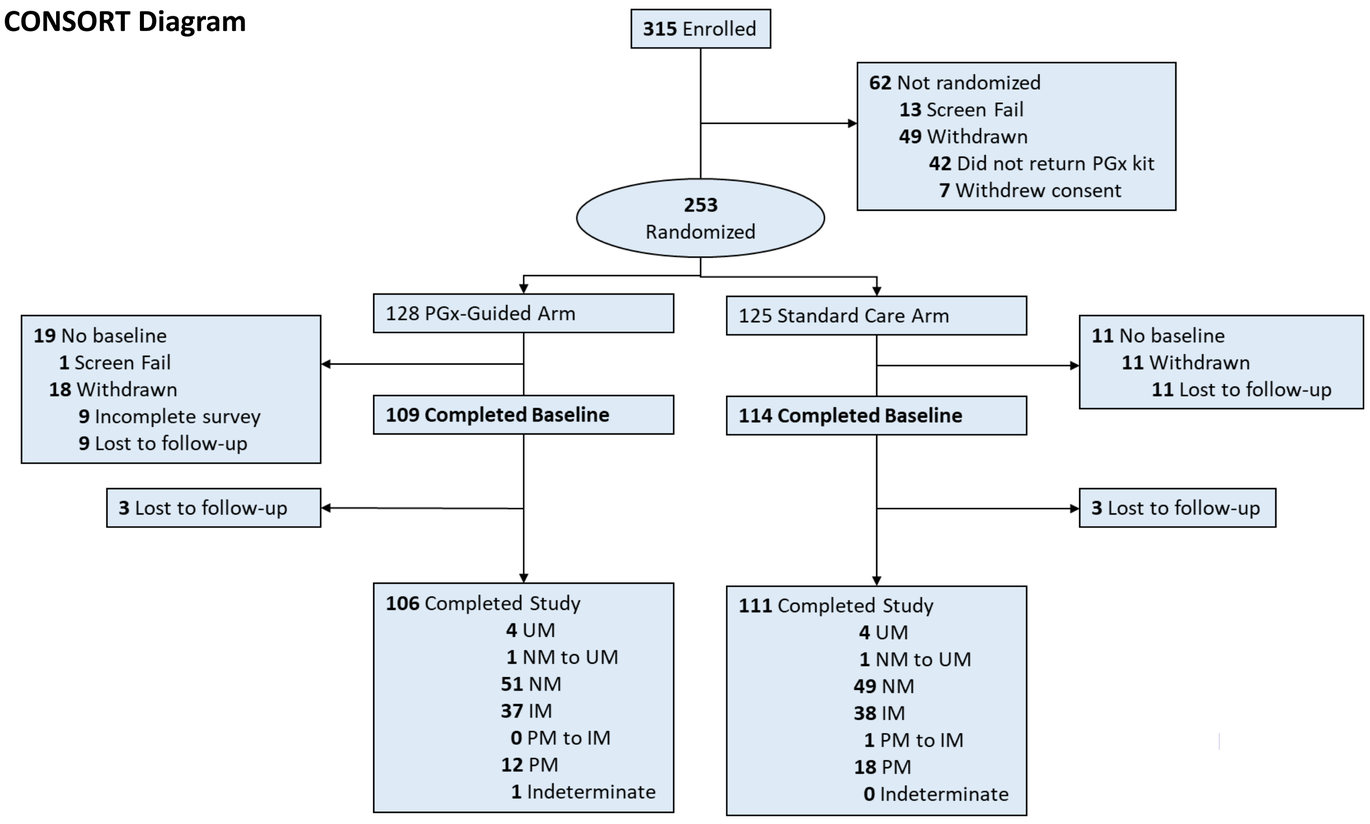


Table 2: Baseline Characteristics

Baseline Characteristics	PGx-Guided Care (n=109)	Standard Care (n=114)	P-value
Age, years	66.5 (59, 71)	64.1 (57, 72)	0.72
Sex, female[1]	82 (75)	82 (72)	0.58
Self-reported race[2]			
White	58 (53)	60 (53)	0.33
Black or AA	39 (36)	46 (40)	
Multiple races	6 (6)	2 (2)	
Native American or Alaska Native	1 (1)	1 (1)	
Native Hawaiian or other Pacific Islander	0 (0)	2 (2)	
Asian Indian	0 (0)	1 (1)	
Prefer not to say	5 (5)	2 (2)	
Ethnicity			
Hispanic or Latinx	2 (2)	1 (1)	0.76
Non-Hispanic or Latinx	101 (93)	105 (92)	
Prefer not to say	6 (6)	8 (7)	
Pain Management Indication[3]			
Back pain	64 (59)	73 (64)	0.42
Arthritis	58 (53)	49 (43)	0.13
Musculoskeletal	17 (16)	14 (12)	0.47
Duration of Pain			0.82
< 1 year	5 (5)	4 (4)	
1 – 5 years	26 (24)	31 (27)	
> 5 years	78 (72)	79 (69)	
Pain Intensity	7 (5, 8)	7 (5, 8)	0.91
Baseline Opioid Use[4]			
Tramadol	86 (79)	90 (79)	0.99
Hydrocodone/ acetaminophen	11 (10)	14 (12)	0.60
Codeine/acetaminophen	13 (12)	10 (9)	0.44
Two opioids	4 (4)	6 (5)	0.57
MME Prescribed	10 (10, 20)	15 (10, 20)	0.79

[1] No patients identified as intersex or other.
[2] No patients identified as Japanese, Korean, Vietnamese, or other Asian.
[3] Top 3 most prevalent indications are shown. Patients may have more than one indication.
[4] One patient in the PGx-guided group was prescribed two enrollment opioids (codeine, tramadol)

Table 3: CYP2D6 Activity among Participants that Completed the Trial (n=217)

CYP2D6 Activity Score			Phenotype	
	Per Genotype	Per Genotype & DDI at baseline		
	n (%)	n (%)		n (%)
0	6 (3)	30 (14)	PM	30 (14)
0 to 0.5	0 (0)	1 (0.5)	IM or PM	1 (0.5)
0 to 1	1 (0.5)	0 (0)		
0.25	2 (1)	3 (1)	IM	75 (35)
0.5	14 (6)	18 (8)		
0.75	2 (1)	7 (3)		
1	58 (27)	47 (22)		
1.25	6 (3)	6 (3)	NM	100 (46)
1.5	53 (24)	40 (18)		
2	63 (29)	54 (25)		
1.5 or more	0 (0)	2 (1)	NM or UM	4 (2)
2 or more	2 (1)	2 (1)		
3 or more	9 (4)	6 (3)	UM	6 (3)
Unknown	1 (0.5)	1 (0.5)	Unknown	1 (0.5)

Phenoconversion

- 33 (18%) of NMs per genotype were phenoconverted to IM or PM
- Most common CYP2D6 inhibitors: duloxetine (18), bupropion (16), fluoxetine (8), mirabegron (5), paroxetine (3)

Table 4: Clinical Outcomes in CYP2D6 IM/PMs

	PGx-Guided n = 49	Standard Care N = 57	P-value
Primary outcome			
Change in pain intensity[1]	-1.1 ± 5.6	-1.5 ± 7.3	0.66[2]
Secondary outcome			
Proportion with a ≥ 30% improvement in pain intensity	8 (16%)	10 (18%)	0.87

[1] Per change in PROMIS T-score between baseline and 3 months
[2]Adjusted for baseline sleep t-score, baseline social t-score, baseline fatigue t-score, baseline anxiety t-score, Hx of hypertension, Hx of previous injury, Hx of anxiety.

Table 5: Prescribing Outcomes in CYP2D6 IM/PMs

	PGx-Guided n = 49	Standard Care N = 57	P -value
Proportion with PGx-aligned care	34 (69%)	36 (63%)	0.50
MME Prescribed	-1.7 ± 13	-0.94 ± 13	0.76

Table 6: Post hoc Analysis in CYP2D6 IM/PMs

	PGx-aligned care	Unaligned care	P-value
	N = 70	N = 36	
Pain intensity	-1.8 ± 6.4	-0.22 ± 6.6	0.072
Among those with ≥ 1 analgesic medication change	N = 31	N = 36	
Change in pain intensity	-2.7 ± 7.1	-0.22 ± 6.6	0.0495
MME prescribed	-8.5 ± 16	2.8 ± 13	< 0.001

Implementation Metrics

- 17 (16%) of 109 patients in the PGx-guided arm had their PGx results mentioned in the providers note at the baseline visit
- Median time between:
  - Enrollment and PGx result return: 38 (30, 49) days
  - PGx result return and PGx consult note upload: 9 (5.5, 18) days
  - PGx consult note upload and baseline visit: 31 (8, 66) days
- 238 of 249 (96%) samples returned used one sample collection to generate PGx results

Limitations

- Unblinded
- Pragmatic intervention came at the cost of reduced utilization
- Limited population to those already prescribed tramadol, codeine, or hydrocodone

Conclusion

- An asynchronous PGx Consult Note with supporting CDS alerts was not an effective implementation strategy for this population
- When prescribing aligned with PGx results, it resulted in improved pain symptoms and reduced MME prescribed
- Future efforts should identify effective implementation strategies for integration of PGx results into opioid prescribing

Abbreviations - IM: Intermediate Metabolizer; NM: Normal Metabolizer; PM: Poor Metabolizer; UM: Ultrarapid Metabolizer. CDS: Clinical decision support; DDI: drug-drug interaction; MME: Morphine milliequivalent; PROMIS: Patient-Reported Outcomes Measurement Information System; PGx: Pharmacogenomics. TCH: tramadol, codeine, or hydrocodone.

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