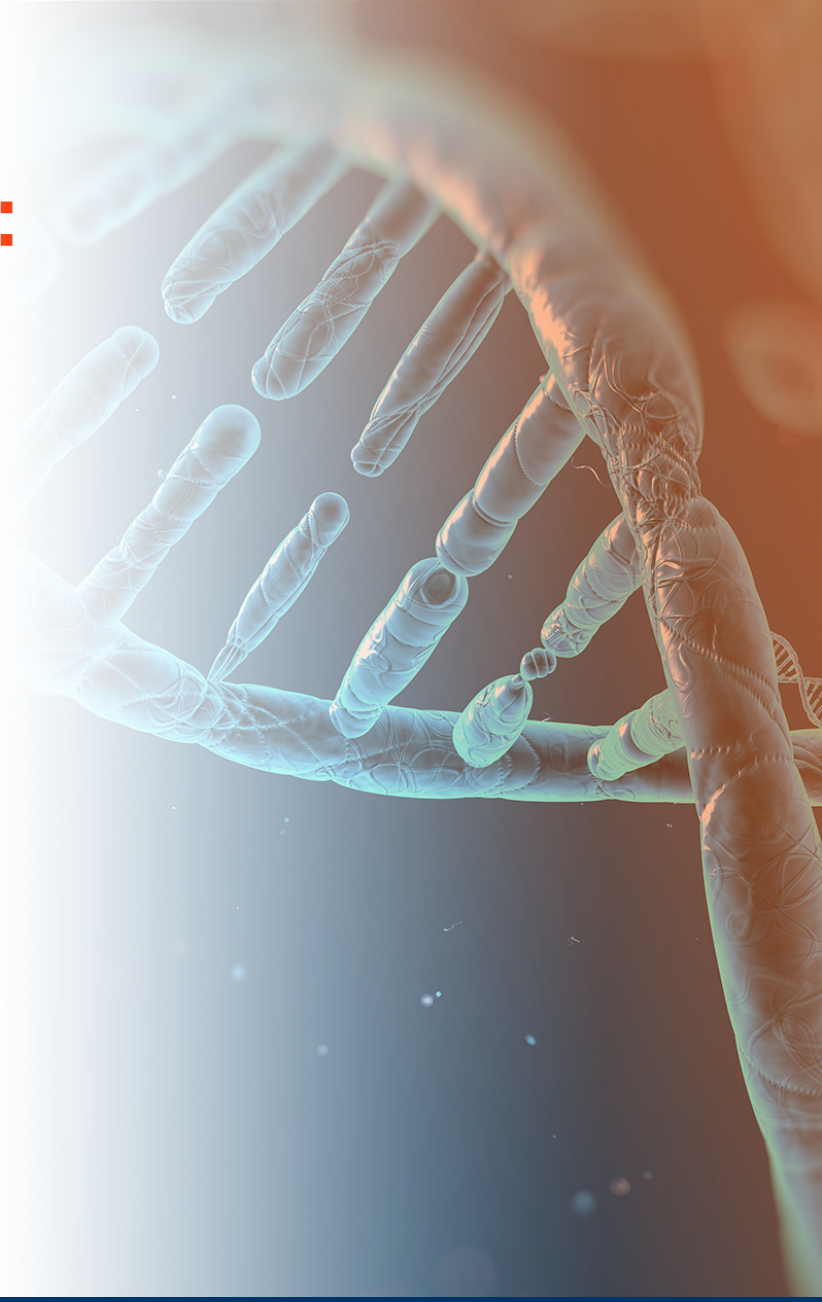
UF Health Precision Medicine Program: Lessons Learned After a Decade of Clinical Pharmacogenomics Implementation



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Clinical Professor

Associate Director, UF Health Precision Medicine Program

Director, Graduate Program in Precision Medicine, Clinical Fellowship and PGY2 Pharmacogenomics Residency

University of Florida College of Pharmacy

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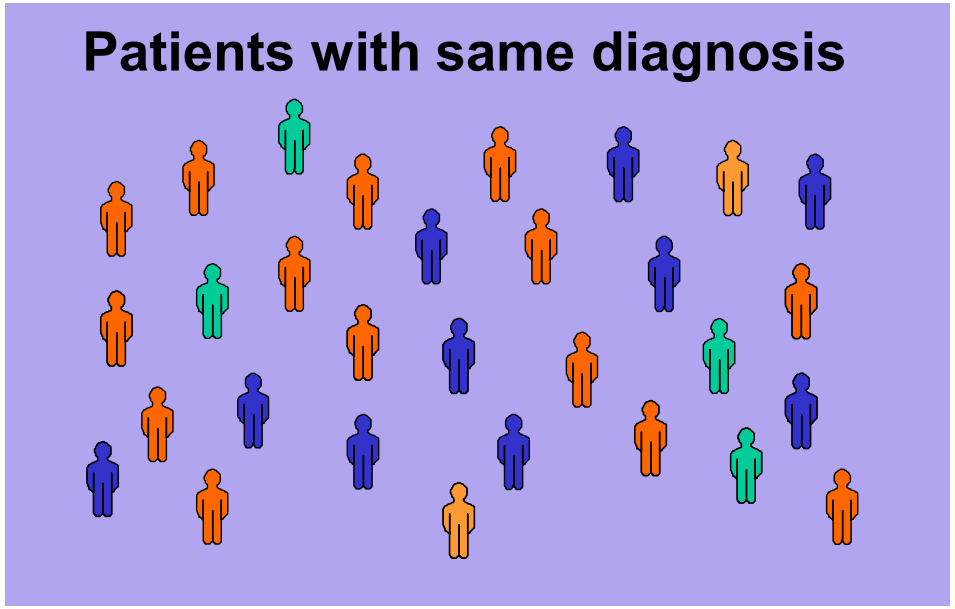
Clinical Potential of Pharmacogenetics



Evans and Johnson 2001 PMID 11701642

Achieving the Clinical Potential of Pharmacogenomics

- Discovery of genetic variants influencing drug response
- Developing evidence base and tools for clinical use of pharmacogenetics
- Clinical implementation of pharmacogenetics
- Documentation of impact on clinical outcomes
- Pharmacists have and will continue to play critical roles in each of these steps

Clinical Pharmacogenetics Implementation Consortium

- TPMT, NUDT15
  - MP, TG, azathioprine
- CYP2D6
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs, tamoxifen, SSRIs, ondansetron, tropisetron, atomoxetine
- CYP2C19
  - TCAs, clopidogrel, voriconazole, SSRIs, PPIs
- CYP2C9
  - Warfarin/coumarins, phenytoin, NSAIDs (in progress)
- HLA-B
  - Allopurinol, CBZ, oxcarbazepine, abacavir, phenytoin

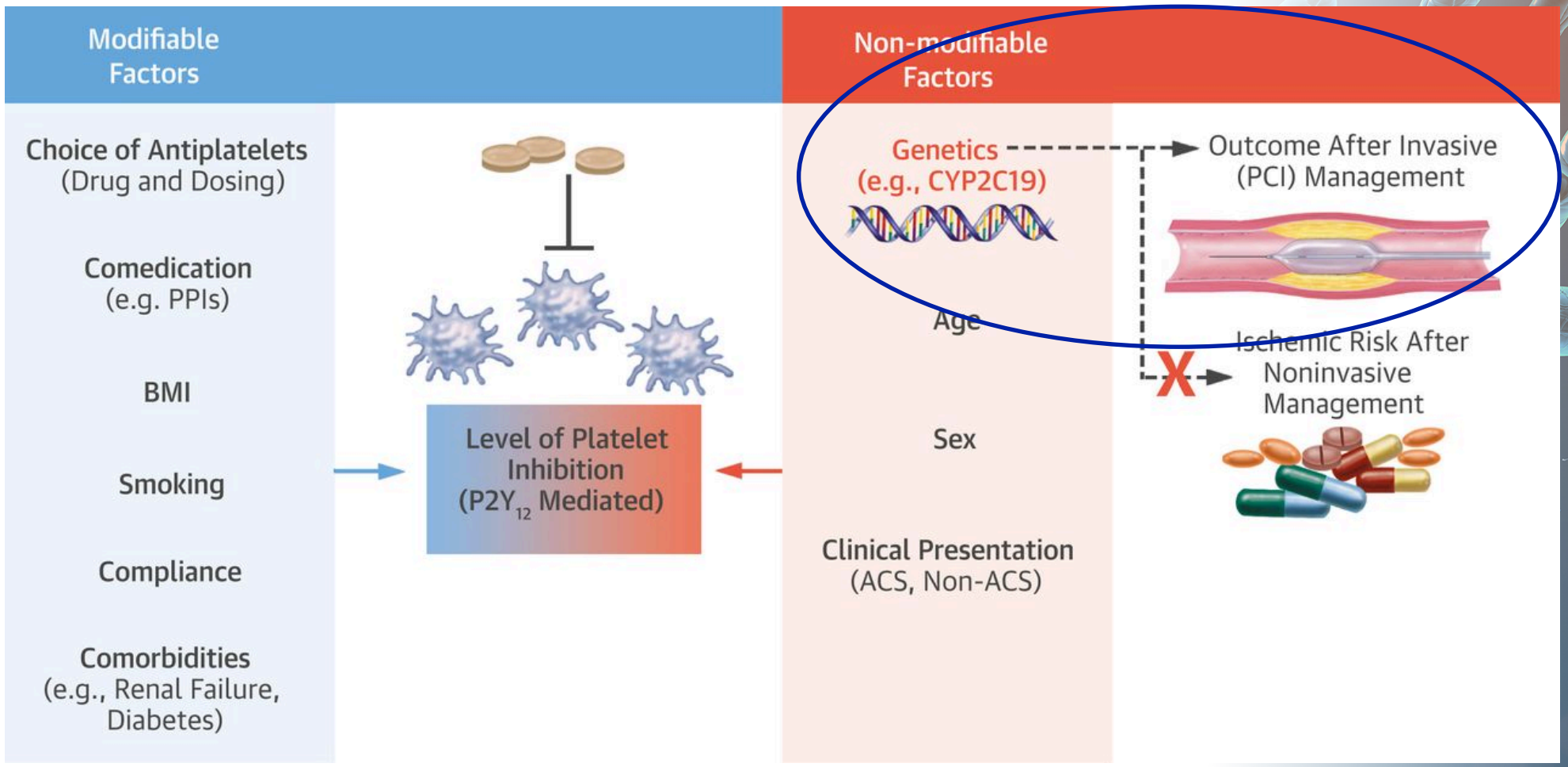
- VKORC1
  - Warfarin/coumarins
- CYP4F2
  - Warfarin/coumarins
- CFTR
  - Ivacaftor
- HLA-A
  - CBZ
- G6PD
  - Rasburicase
- UGT1A1
  - Atazanavir
- SLCO1B1
  - Simvastatin

- IFNL3 (IL28B)
  - Interferon
- CYP3A5
  - Tacrolimus
- CYP2B6
  - Efavirenz
- RYR1, CACNA1S
  - Inhaled anesthetics
- mRNR1 (in progress)
  - Aminoglycosides
- DPYD
  - 5FU, capecitabine, tegafur

https://cpicpgx.org/guidelines/

UF Health Personalized Medicine Program Launched June 25, 2012

Clopidogrel Pilot: Clinical Implementation

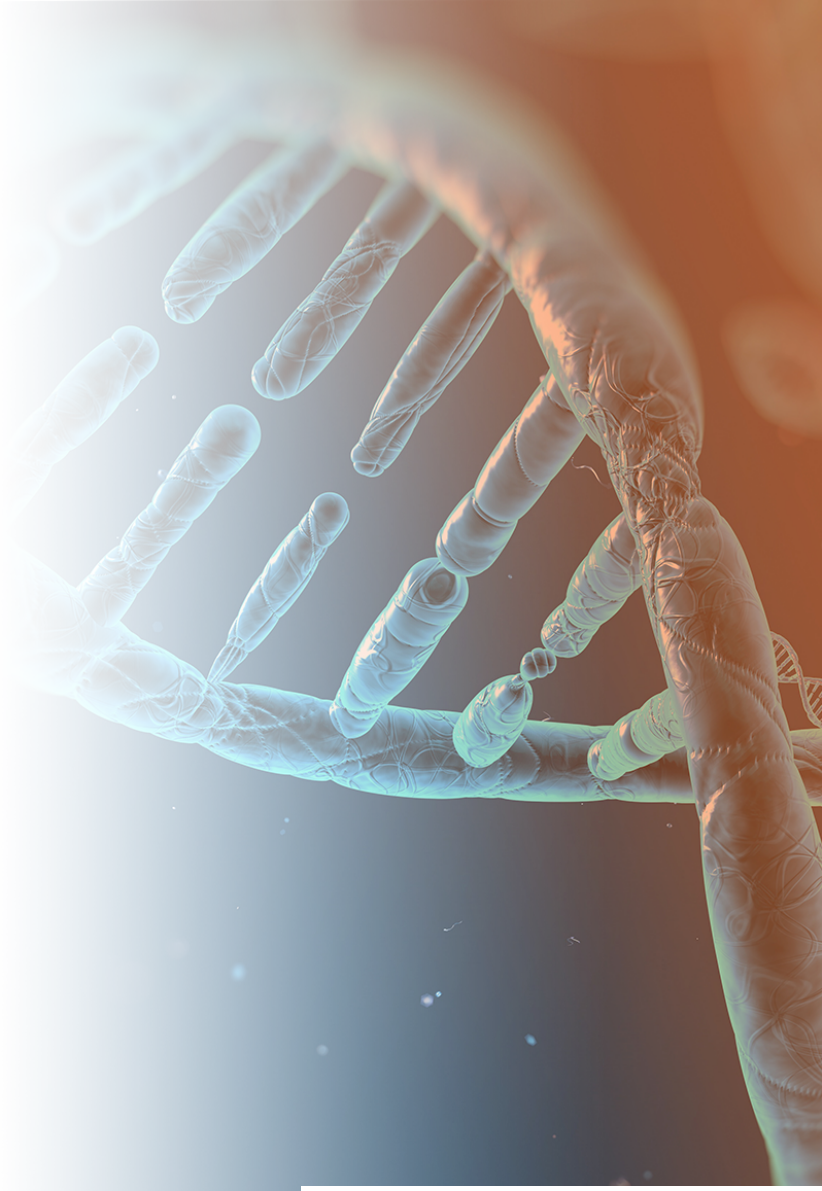


Sibbing D et al. JACC. 2016;67(8):948.

Clopidogrel Pilot: Clinical Implementation

- CYP2C19 genotype test added as standard of care for patients in cath lab
  - CYP2C19 pre-selected on order sets
  - CYP2C19 genotype moves to EHR in all patients, independent of treatment with clopidogrel

- N = 1,097 patients genotyped



Weitzel KW et al. 2014. Clinical pharmacogenetics implementation: Approaches, successes, and challenges. *Am J Med Genet Part C Semin Med Genet* 166C: 56– 67

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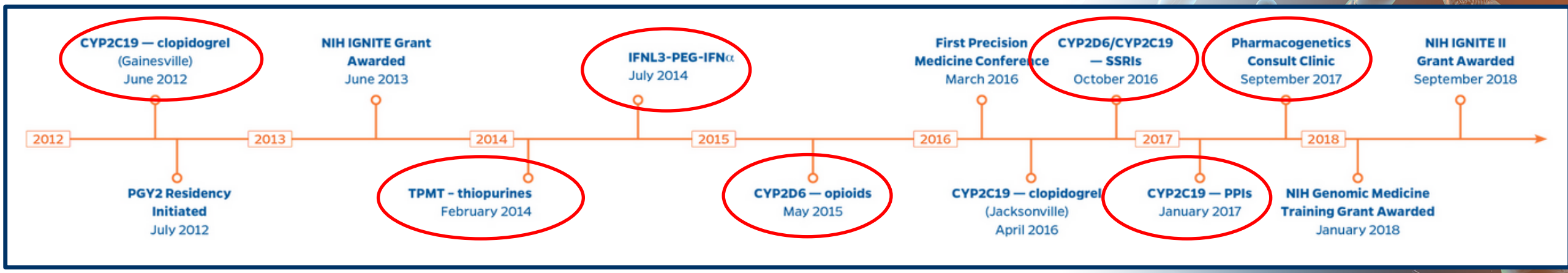
UF Health Precision Medicine Program

- Pharmacist-led multidisciplinary team within the College of Pharmacy



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https://precisionmedicine.ufhealth.org/

IGNITE
Implementing GeNomics In practicE

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Research Implementation

- Clinical trials
- Inpatient or outpatient setting
- Consultation and recommendations occur per research protocol

UF Health Genotype Consults

- Any setting
- Any pharmacogene
- Follow up with note placed in chart for provider

Primary Care PGx Clinic

- Outpatient
- Internal Medicine
- 2-visit model with pharmacist
- Billing for visit
- Patient education

Clinical Decision Support

Patient and Provider Education

Pathology/ Return of Results

Communication and Documentation

Reimbursement

Monitoring and Follow Up

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Implementing GeNomics In practicE

Available In-House Pharmacogenetic Tests

	Lab Number	Gene(s)	Medications
Single Tests	LAB2103048	CYP2D6	SSRIs, opioids, ondansetron, tamoxifen
	LAB5169	CYP2C19	SSRIs, PPIs, clopidogrel, voriconazole
	LAB5291	TPMT	Thiopurines
Panel test – "Gator PGx"	LAB12305000*	CYP2C9	Warfarin, NSAIDs
		SLCO1B1	Simvastatin
		CYP4F2	Warfarin
		CYP2C cluster	Warfarin
		CYP3A5	Tacrolimus
		CYP2D6	See above
		CYP2C19	See above

PPIs: Proton Pump Inhibitors; SSRIs: Selective Serotonin Reuptake Inhibitors;
NSAIDs: Nonsteroidal anti-inflammatory drug

*Only available out-patient

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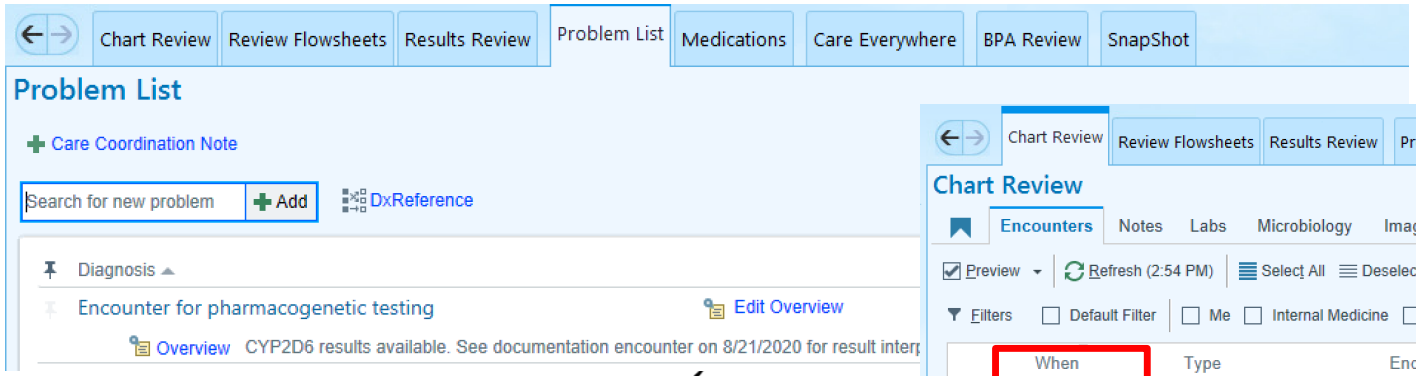
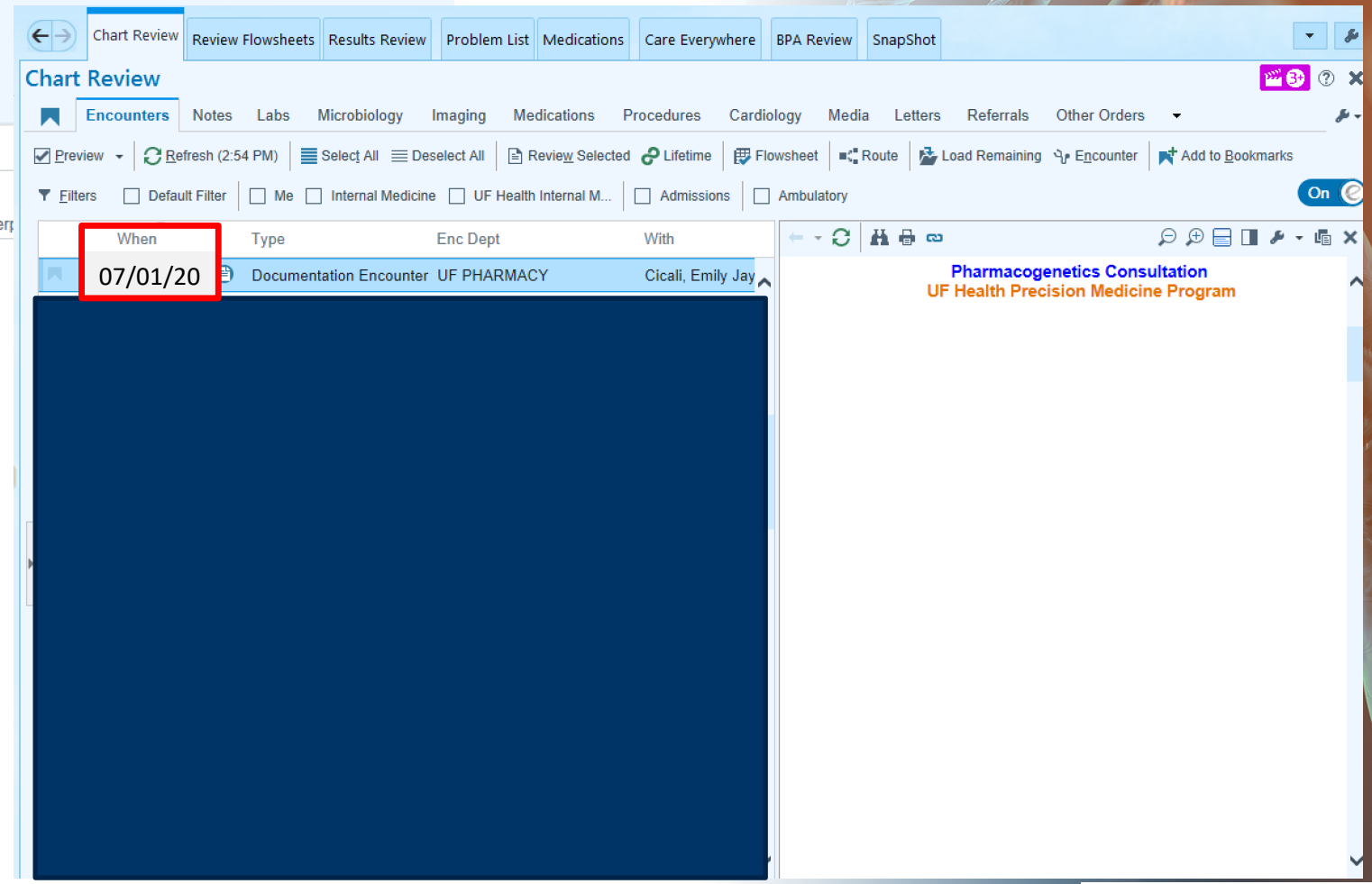
When Results Returned – Consult Note



- Pharmacogene tested
- Date of consult note



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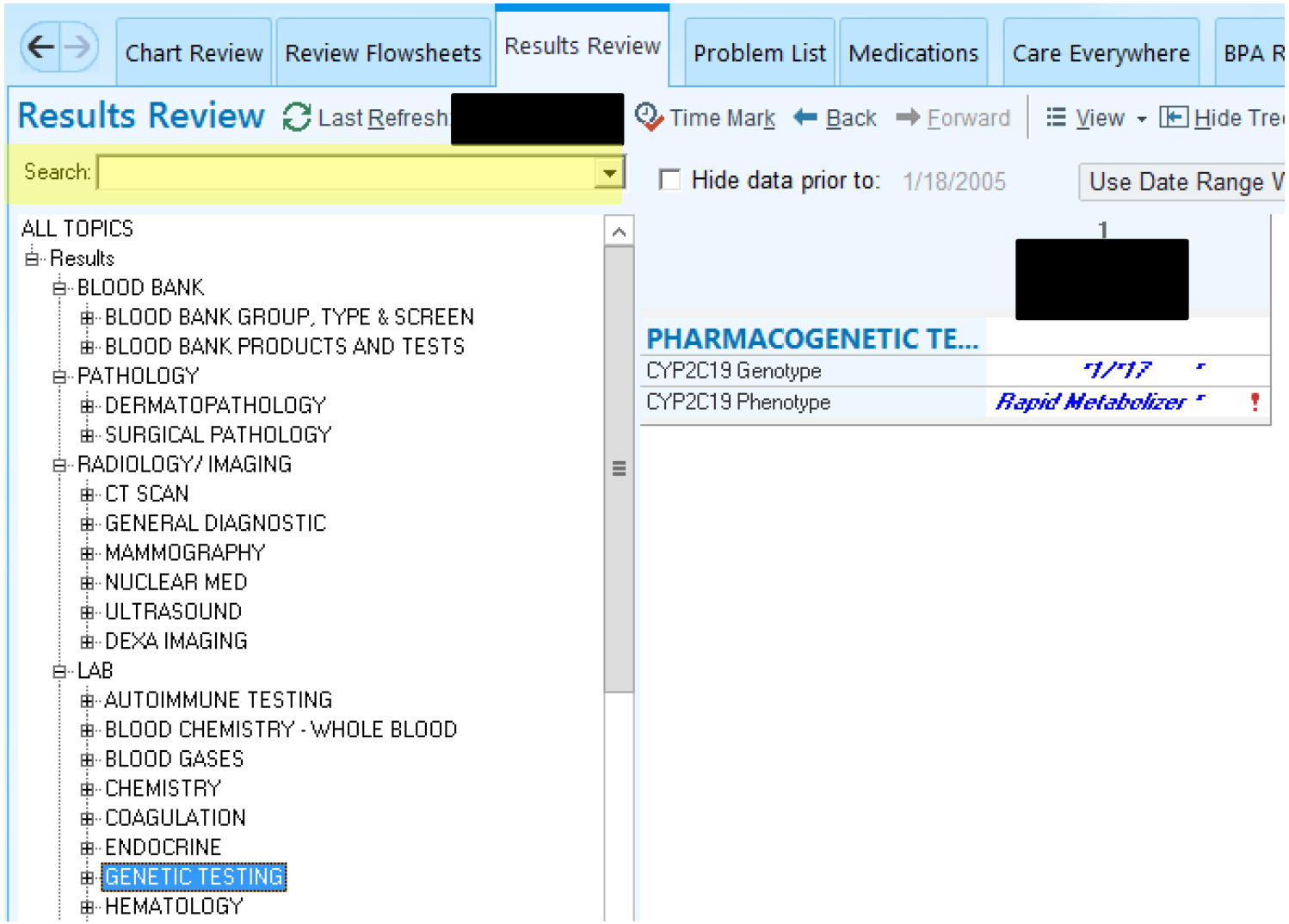
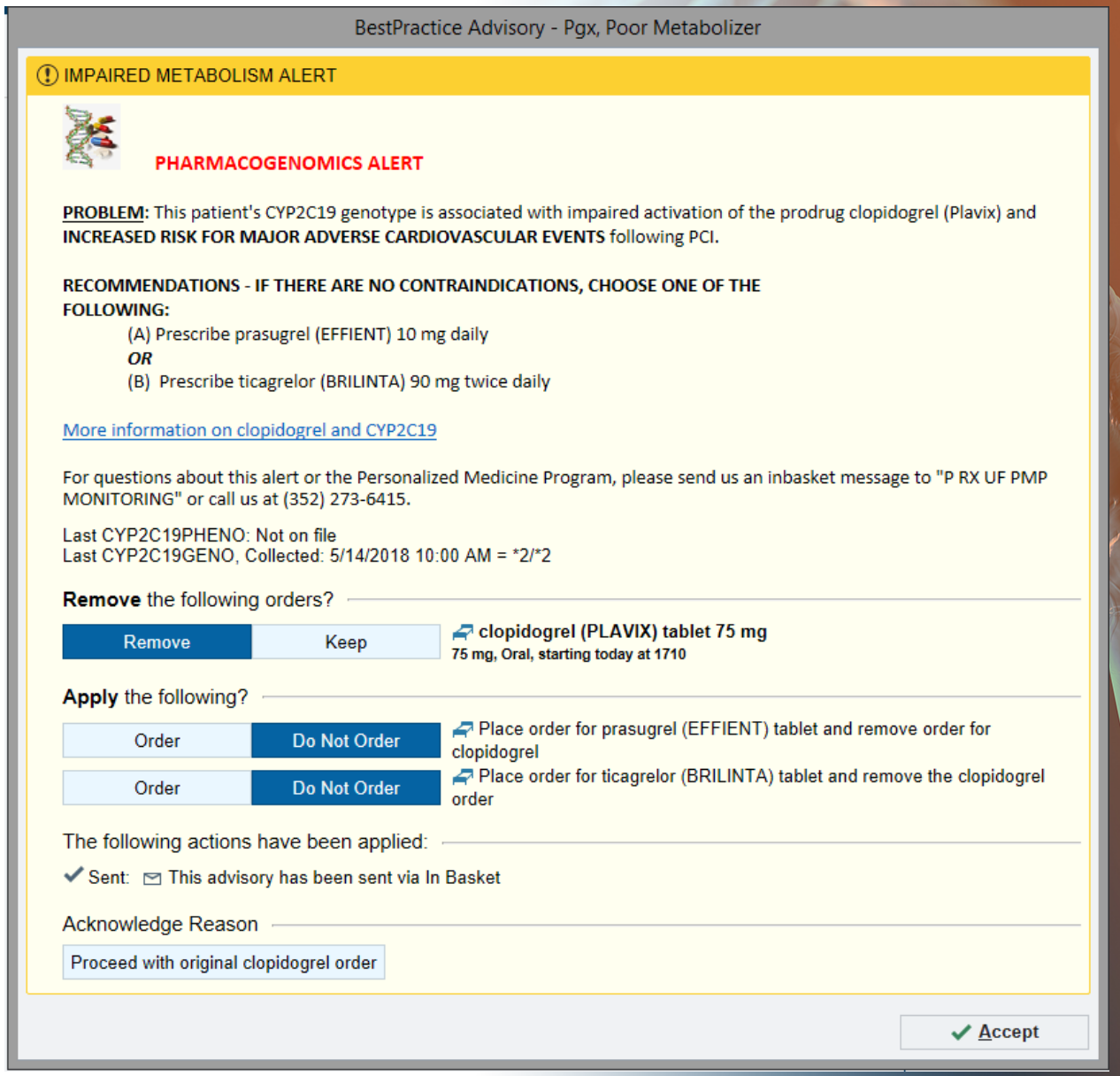
Where Test Results Live



Best Practice Advisories (BPA)

- CYP2C19-clopidogrel
- CYP2D6-Opioids
- CYP2C19-Proton Pump Inhibitors
- CYP2D6/CYP2C19 - Selective Serotonin Reuptake Inhibitors
- CYP2C19-Voriconazole
- CYP2D6-Ondansetron
- TPMT/NUDT15- Thiopurines



Patients Genotyped (2011 – present)

Demographics	Total Patients* (n=5,980)
Age**, mean± SD	57 ± 18
Male‡, n(%)	3,224 (54)
Caucasian, n(%)	4,308 (72)
African American, n(%)	1,275 (21)
Hispanic or Latino, n (%)	224 (4)

*Approx. 500 patients were genotyped for IL-28B that are not yet included in this data
**Age only available for 5,794 patients
‡ Sex only available for 5,966 patients

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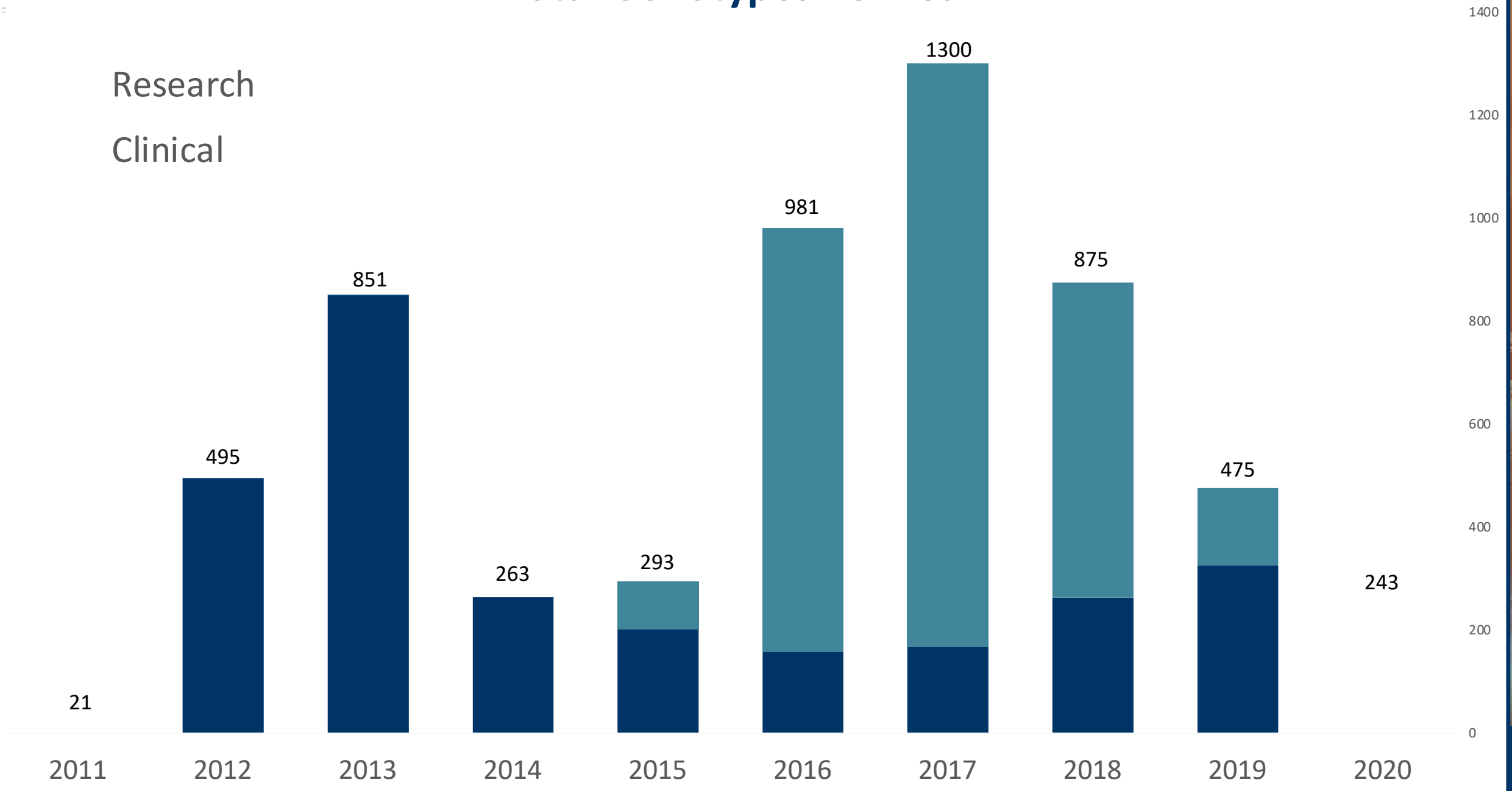
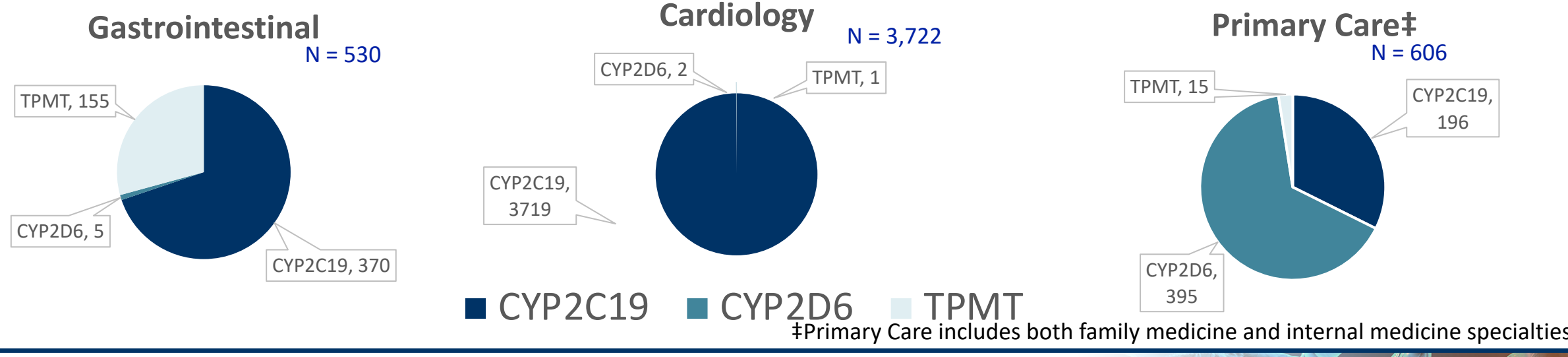
Total Genotypes Per Year

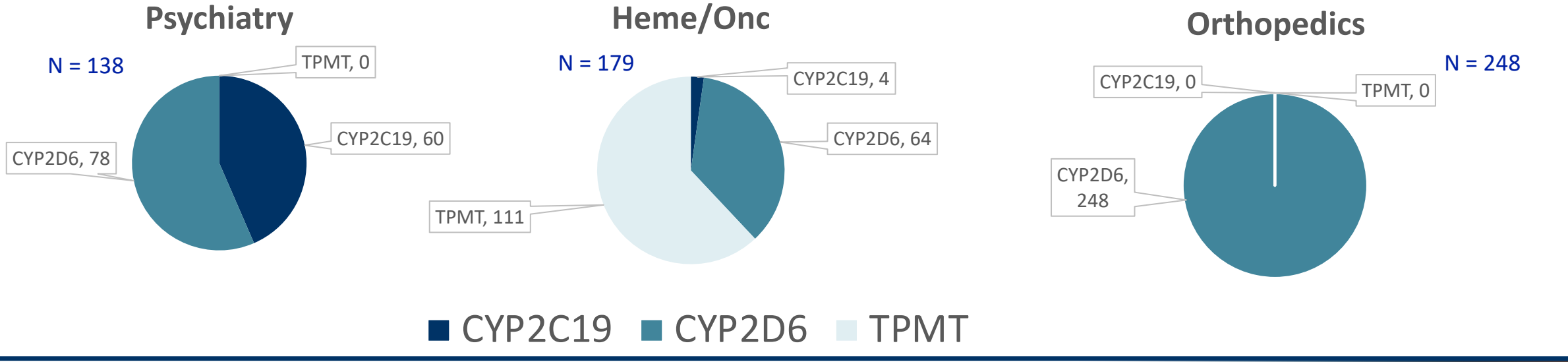


Genotype ordering per service (n>500)



‡Primary Care includes both family medicine and internal medicine specialties

Genotype ordering per service (100>n<500)



Lessons Learned

- Consistency
- Scalability
- Efficiency

Cicali EJ, et al. *Clin Pharmacol Ther*. 2020;107: S57. (PII-079).

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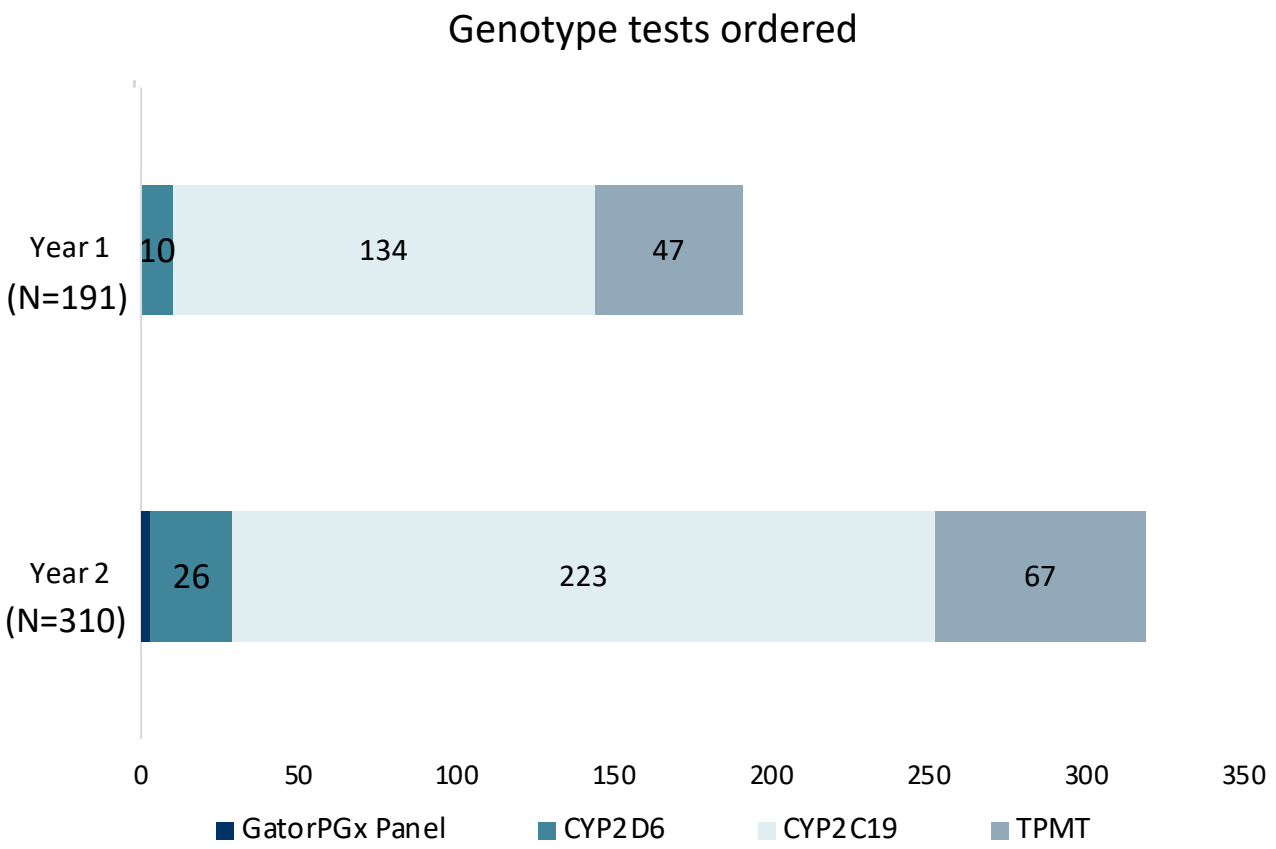
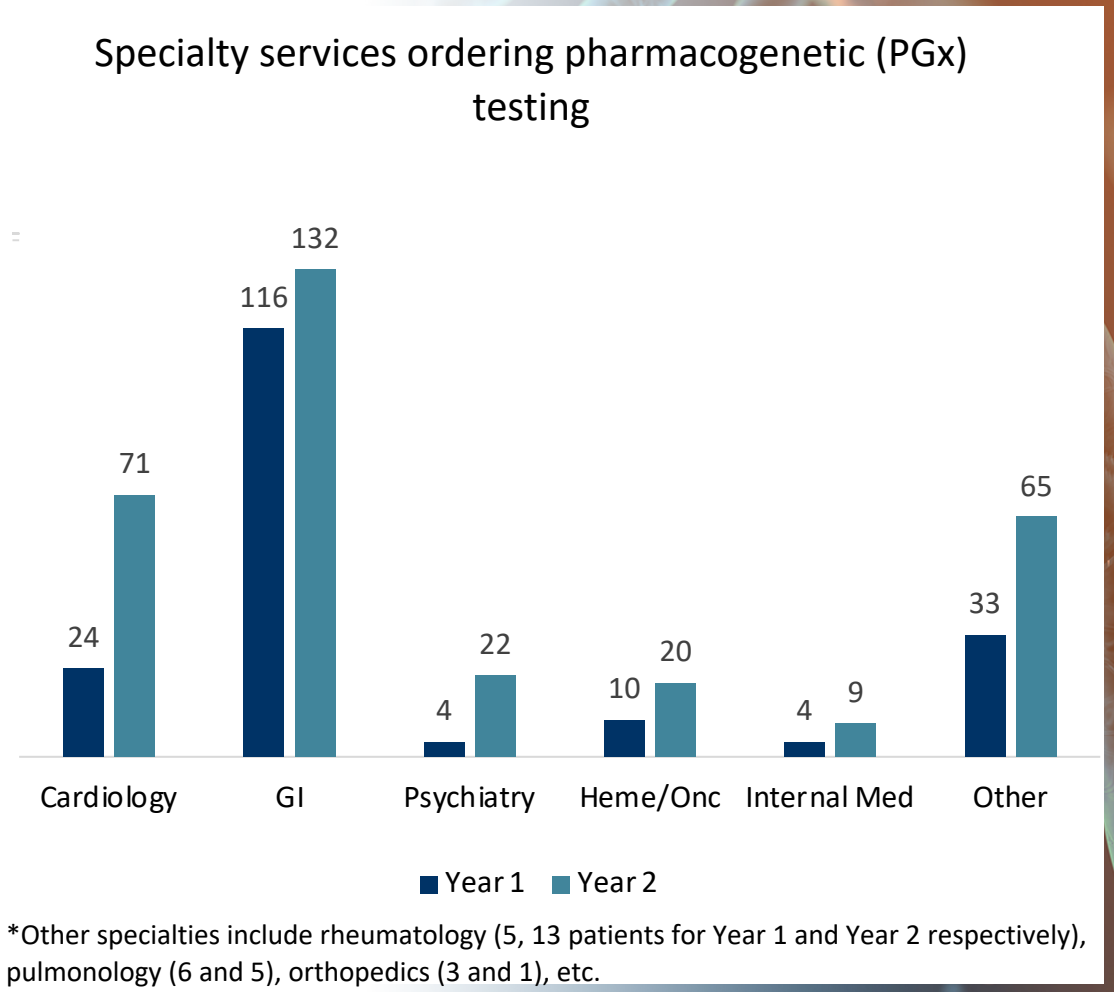
Comparison of the Last Two Years

- **Year 1** (July 1st, 2018- June 30th, 2019)
  - Clinical consult notes upon request

- **Year 2** (July 1st, 2019- June 30th, 2020)
  - Clinical consult notes for all test results

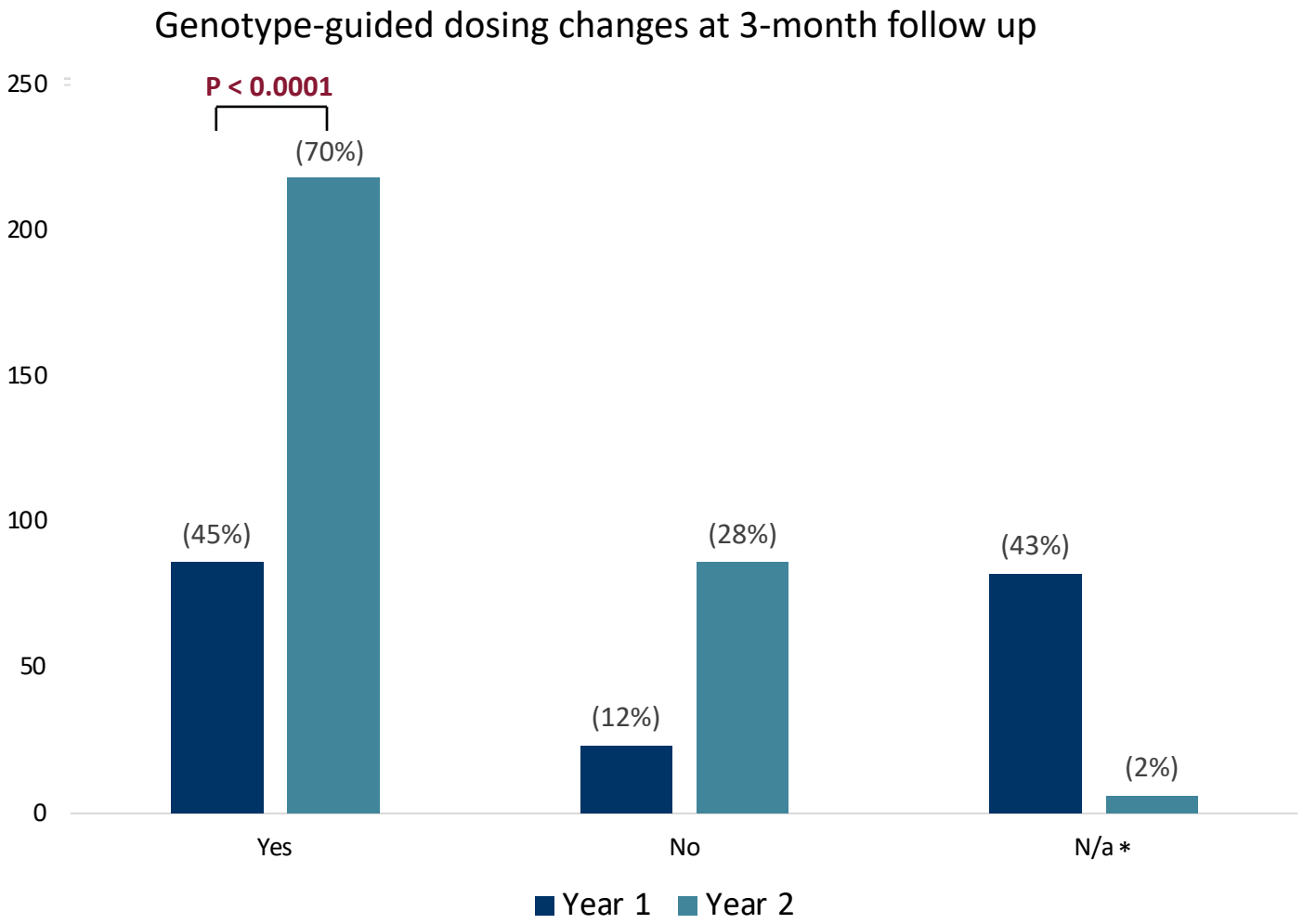
Genotype Tests Ordered





*Other specialties include rheumatology (5, 13 patients for Year 1 and Year 2 respectively), pulmonology (6 and 5), orthopedics (3 and 1), etc.

Medication Changes Consistent With Genotype



*N/A indicates patients deceased, patients lost to follow up or patients not on any drug informed by the PGx test ordered.

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A Systematic Approach to Information Management and Communication

	Patient-Specific Clinical Data	Test Result Display	Medications included in clinical interpretation	Impact of Other Genes on Drug Therapy Recommendation	Phenoconversion Effects (if applicable)	Drug Therapy Recommendation(s)
Pathology Report	Identifying information only	Diplotype (primary) Phenotype	All drugs that meet evidence threshold	None	General disclaimer	None
Clinical Decision Support	Identifying information Genotype-Drug pair that triggers alert	Phenotype	Trigger drug- or drug class that meets evidence threshold	Advisory if other genotype available Informational if genotype not available	None	Targeted to specific gene-drug pair; Advisory with Immediate Actionability
Provider Report (e.g., consult note)	HPI Current Medications Allergies Interacting Medications	Phenotype (primary) Diplotype	Customized for patient's current medications that have pgx implications; +/- all relevant drugs for specific area (e.g., supportive care)	Advisory if other genotype available Informational if genotype not available	Integrated with genotype for drug therapy recommendations based on clinical phenotype	All current medications Potential future use of relevant medications Advisory with actionability when clinically appropriate
Patient Education	Identifying information only	Phenotype (primary) Diplotype	All drugs that meet evidence threshold	Informational	General disclaimer	None

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Central Database/Matrix of All Clinical Recommendations and Trigger Rules for BPAs

CYP2D6 Diplotype	CYP2D6 Phenotype	Relevant Medications	Problem Statement	BPA text Recommendation
CYP2D6 *X/*X	CYP2D6 UM	Codeine Tramadol Hydrocodone Oxycodone	This patient's CYP2D6 genotype is associated with production of excess amounts of active forms of tramadol, codeine, hydrocodone, and oxycodone. This patient is at risk for **ADVERSE EVENTS** such as **RESPIRATORY DEPRESSION OR DEATH** with these medications, even at low doses.	(A) Avoid tramadol, codeine, hydrocodone, and oxycodone and consider a **non-opioid** analgesic instead. **OR** (B) If an opioid analgesic is indicated, consider an alternative opioid such as morphine, hydromorphone, or oxymorphone, that is not affected by CYP2D6 metabolizer status
CYP2D6 *X/*X	CYP2D6 NM-UM	Codeine Tramadol Hydrocodone Oxycodone	This patient's CYP2D6 genotype is associated with production of excess amounts of active forms of tramadol, codeine, hydrocodone, and oxycodone. This patient is at risk for **ADVERSE EVENTS** such as **RESPIRATORY DEPRESSION OR DEATH** with these medications, even at low doses.	(A) Avoid tramadol, codeine, hydrocodone, and oxycodone and consider a **non-opioid** analgesic instead. **OR** (B) If an opioid analgesic is indicated, consider an alternative opioid such as morphine, hydromorphone, or oxymorphone, that is not affected by CYP2D6 metabolizer status
CYP2D6 *X/*X	CYP2D6 NM	Codeine Tramadol Hydrocodone Oxycodone	N/A	N/A
CYP2D6 *X/*X	CYP2D6 IM	Codeine Tramadol Hydrocodone	This patient's CYP2D6 genotype is associated with decreased production of active forms of tramadol, codeine, hydrocodone, and to a lesser extent, oxycodone. This patient may get **LITTLE TO NO PAIN RELIEF** with these medications.	(A) Avoid tramadol, codeine, and hydrocodone and consider a **non-opioid** analgesic instead. **OR** (B) If an opioid analgesic is indicated, consider an alternative opioid such as morphine, hydromorphone, or oxymorphone, that is not affected by CYP2D6 metabolizer status
CYP2D6 *X/*X	CYP2D6 PM	Codeine Tramadol Hydrocodone	This patient's CYP2D6 genotype is associated with significantly decreased production of active forms of tramadol, codeine, hydrocodone, and to a lesser extent, oxycodone. This patient may get **LITTLE TO NO PAIN RELIEF** with these medications.	(A) Avoid tramadol, codeine, and hydrocodone and consider a **non-opioid** analgesic instead. **OR** (B) If an opioid analgesic is indicated, consider an alternative opioid such as morphine, hydromorphone, or oxymorphone, that is not affected by CYP2D6 metabolizer status

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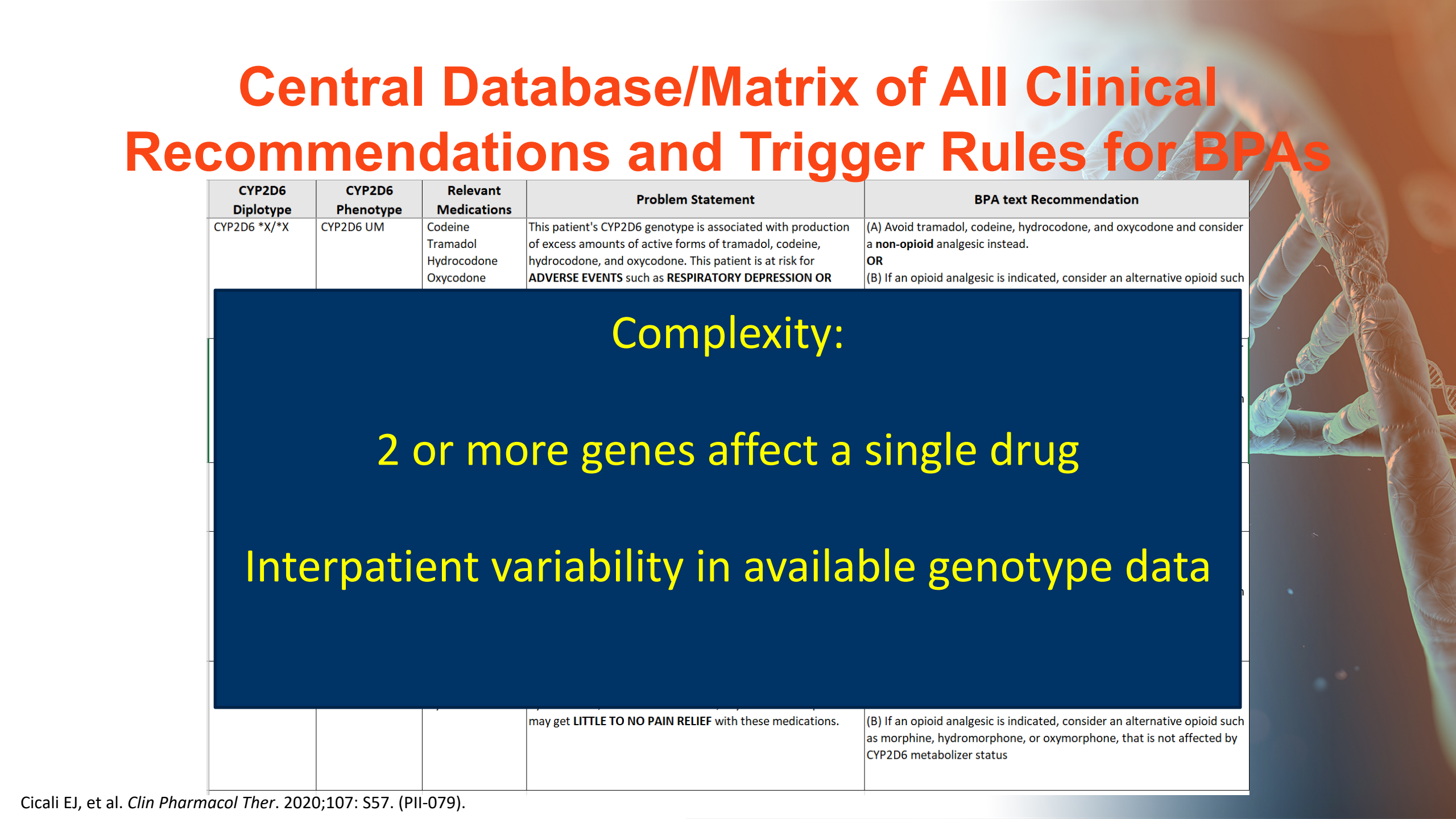
			may get **LITTLE TO NO PAIN RELIEF** with these medications.	(B) If an opioid analgesic is indicated, consider an alternative opioid such as morphine, hydromorphone, or oxymorphone, that is not affected by CYP2D6 metabolizer status

Complexity:

2 or more genes affect a single drug

Interpatient variability in available genotype data



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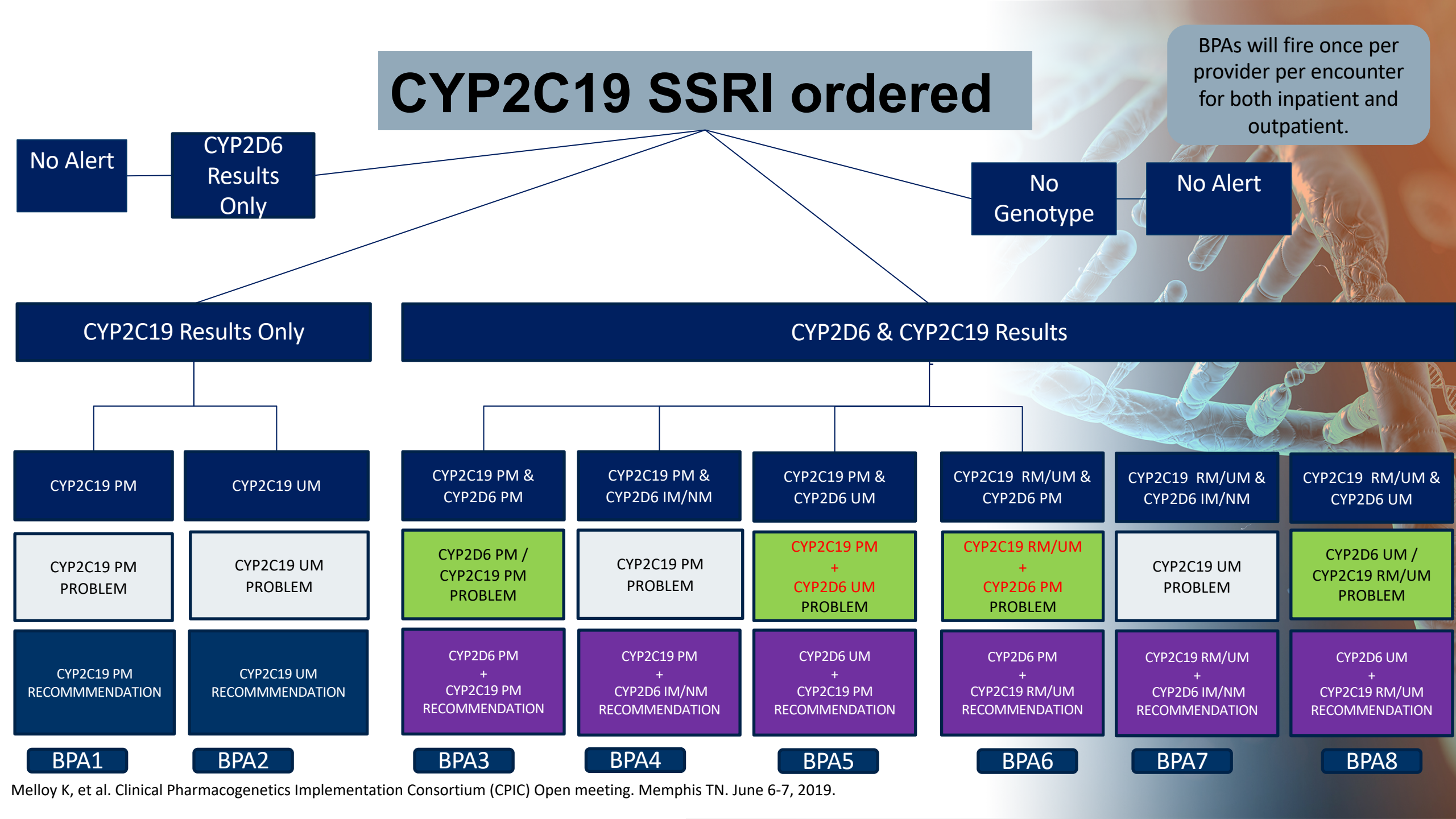
CYP2C19 SSRI ordered

BPAs will fire once per provider per encounter for both inpatient and outpatient.



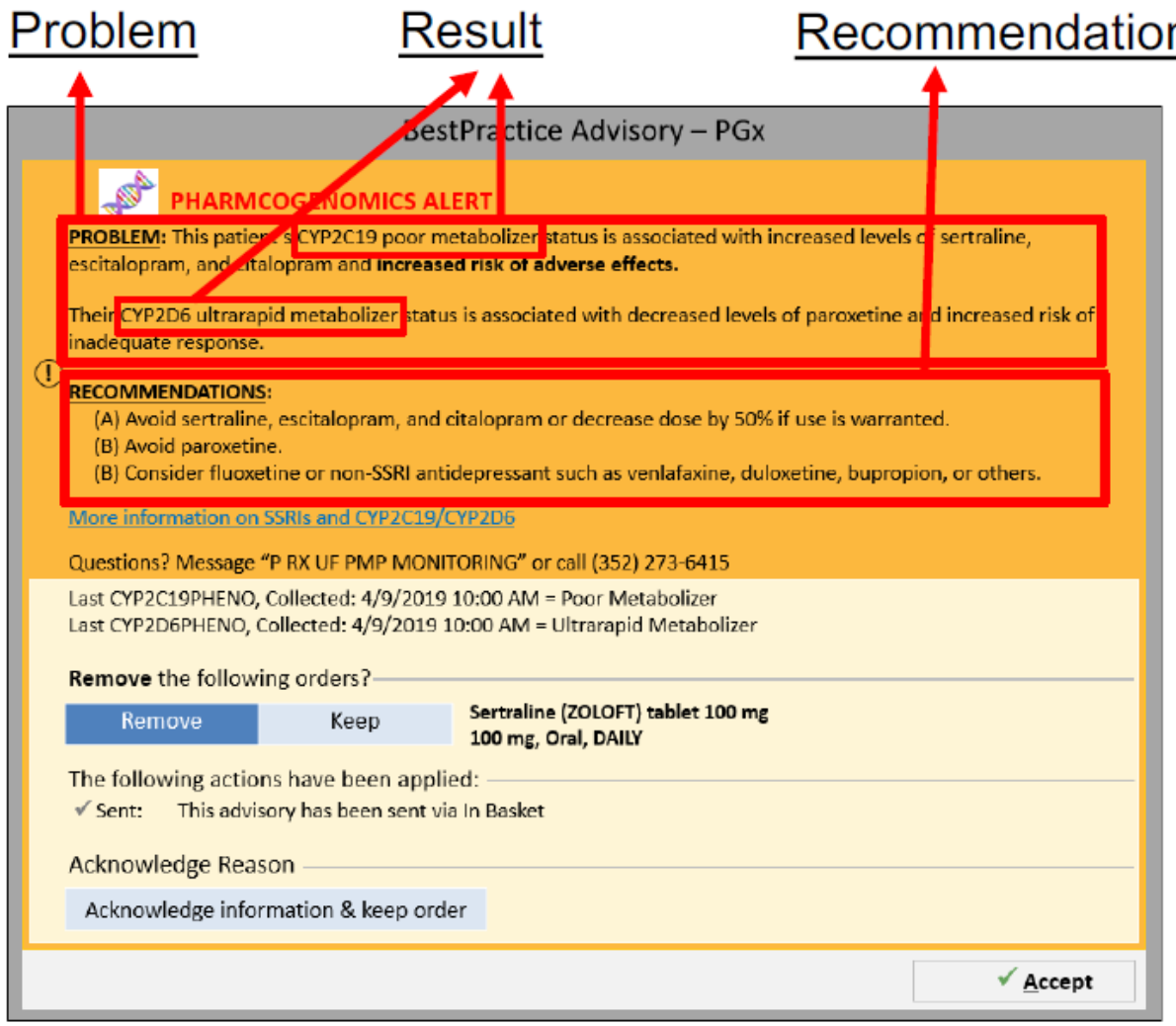
Melloy K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Open meeting. Memphis TN. June 6-7, 2019.

Multi-Gene/Drug Scenarios

CYP2D6 Diplotyp	CYP2D6 Phenotyp	CYP2C19 Diplotyp	CYP2C19 Phenotype	Relevant Medicatior	Problem Statement	BPA Text (Both Genes)
CYP2D6 *X/*X	CYP2D6 PM	CYP2C19 *X/*X	CYP2C19 PM	sertraline, escitalopram, citalopram, paroxetine, fluvoxamine	This patient's CYP2D6 and CYP2C19 poor metabolizer statuses are associated with increased levels of sertraline, escitalopram, citalopram, paroxetine, and fluvoxamine and **increased risk of adverse effects**	(A) Avoid sertraline, escitalopram, citalopram, paroxetine, and fluvoxamine or decrease dose by 50% if use is warranted. (B) Consider non-SSRI antidepressant such as desvenlafaxine, duloxetine, bupropion, or others.
CYP2D6 *X/*X	CYP2D6 UM	CYP2C19 *X/*X	CYP2C19 PM	sertraline, escitalopram, citalopram	This patient's CYP2C19 poor metabolizer status is associated with increased levels of sertraline, escitalopram, and citalopram and increased risk of adverse effects. Their CYP2D6 ultra rapid metabolizer status is associated with decreased levels of paroxetine and increased risk of inadequate response	(A) Avoid sertraline, escitalopram, and citalopram or decrease dose by 50% if use is warranted. (B) Avoid paroxetine. (C) Consider fluoxetine or non-SSRI antidepressant such as venlafaxine, duloxetine, bupropion, or others.
	CYP2D6 UM	CYP2C19 *X/*X	CYP2C19 PM	paroxetine	This patient's CYP2D6 ultra rapid metabolizer status is associated with decreased levels of paroxetine and increased risk of inadequate response. Their CYP2C19 poor metabolizer status is associated with increased levels of sertraline, escitalopram, and citalopram and increased risk of adverse effects	(A) Avoid paroxetine . (B) Avoid sertraline, escitalopram, and citalopram or decrease dose by 50% if use is warranted. © Consider fluoxetine or non-SSRI antidepressant such as venlafaxine, duloxetine, bupropion, or others.
CYP2D6 *X/*X	CYP2D6 PM	CYP2C19 *X/*X	CYP2C19 RM/UM	sertraline, escitalopram, citalopram	This patient's CYP2C19 rapid or ultra rapid metabolizer status is associated with decreased levels of sertraline, escitalopram, and citalopram and increased risk of inadequate response. Their CYP2D6 poor metabolizer status is associated with increased levels of paroxetine and fluvoxamine and increased risk of adverse effects	(A) Avoid escitalopram, citalopram, and potentially sertraline. (B) Avoid paroxetine and fluvoxamine or decrease dose by 50% if use is warranted. (C) Consider non-SSRI antidepressant such as desvenlafaxine, duloxetine, bupropion, or others.

Melloy K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Open meeting. Memphis TN. June 6-7, 2019.

Figure 2. Example of updated SSRI BPA incorporating both the CYP2C19 and CYP2D6 phenotype.



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Metrics

- Monitor:
  - Pharmacogenetic tests ordered
  - BPAs that fire
  - Action taken when BPAs fire
  - Recommendations followed
  - Reimbursement

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Metrics

- Monitor:
  - Pharmacogenetic tests ordered
  - BPAs that fire
  - Action taken when BPAs fire
  - Recommendations followed
  - Reimbursement
- Upkeep:
  - Return of results
  - Documentation
- Identify education needs

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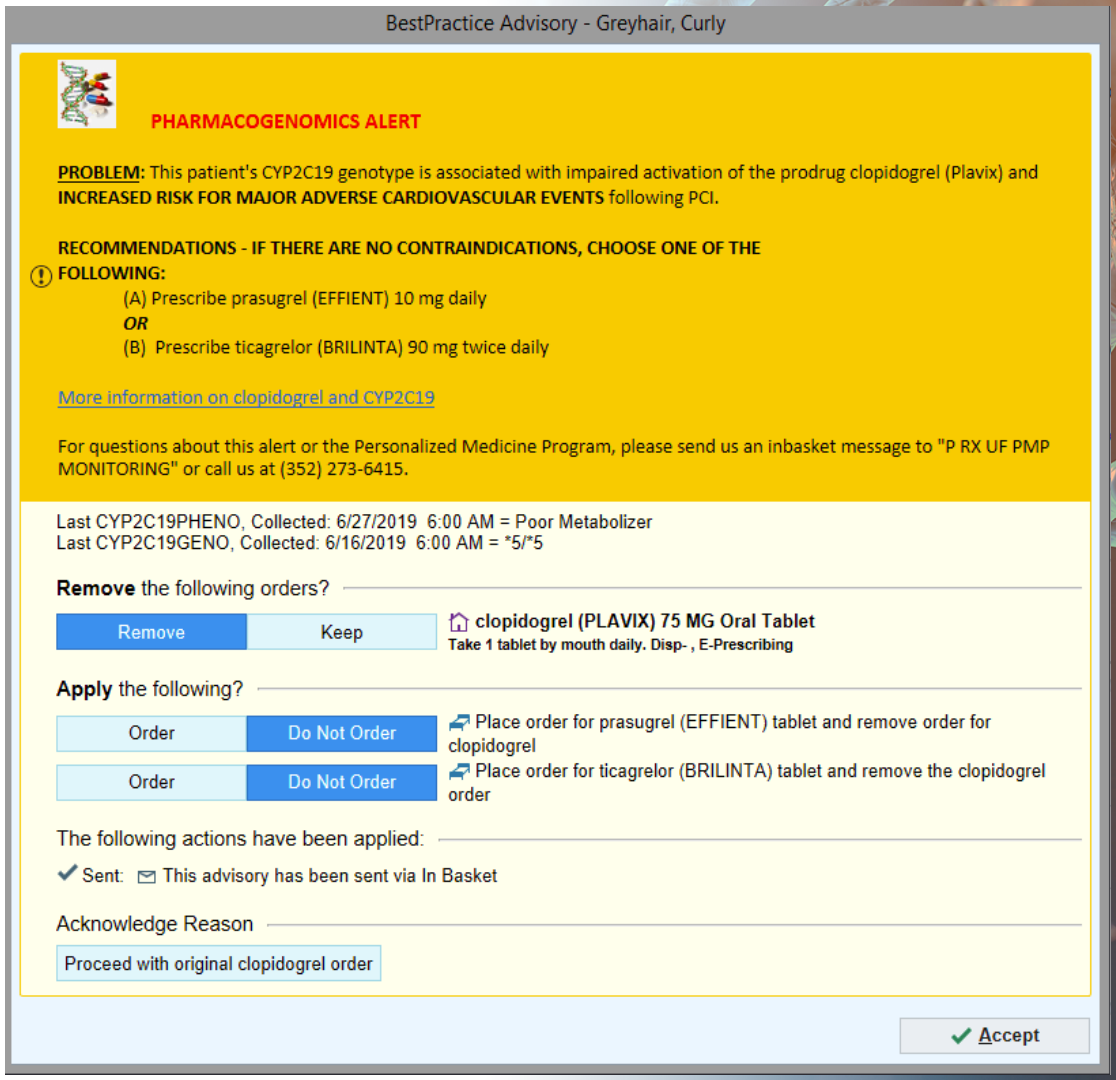
Improve quality of BPA data collection for research and quality improvement from

May 2020 – present

N = 180 BPA Fires

- 25% CYP2C19 RM/UM - Proton Pump Inhibitors
- 24% CYP2C19 IM – Clopidogrel
- 15% no TPMT genotype - Thiopurines



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- Scalability
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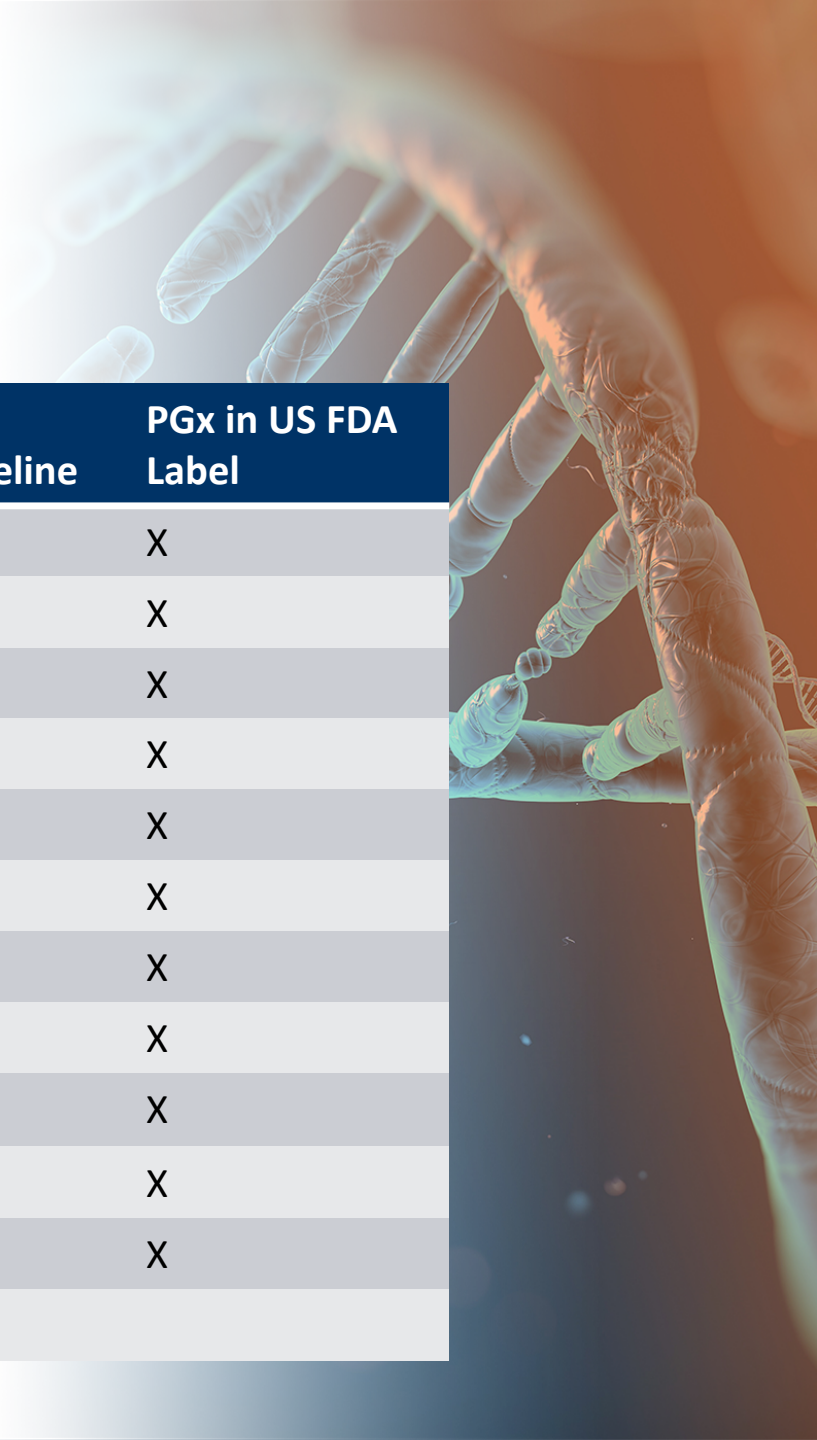
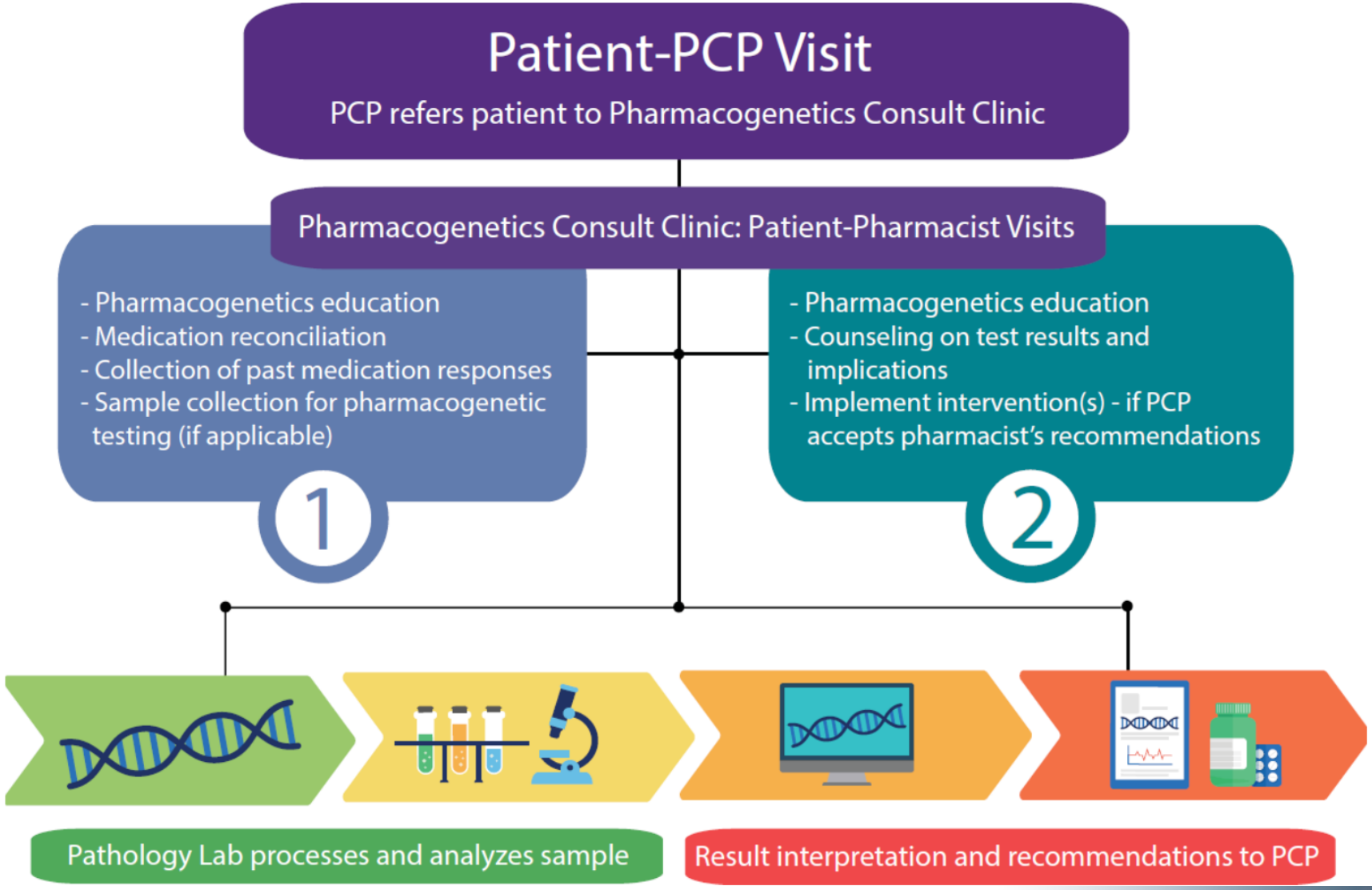
Pharmacogenomics in Primary Care



Medication(s)	Gene	CPIC Guideline	PGx in US FDA Label
Codeine/Tramadol	*CYP2D6*	X	X
Celecoxib	*CYP2C9*	X	X
SSRIs	*CYP2C19* and *CYP2D6*	X	X
Venlafaxine	*CYP2D6*		X
Proton Pump Inhibitors	*CYP2C19*	X	X
Clopidogrel	*CYP2C19*	X	X
Simvastatin	*SLCO1B1*	X	X
Aripiprazole, risperidone	*CYP2D6*		X
Carbamazepine, Oxcarbazepine, Phenytoin	*CYP2C9, HLA-A, HLA-B*	X	X
Atomoxetine	*CYP2D6*	X	X
Ondansetron	*CYP2D6*	X	X
Tamoxifen	*CYP2D6*	X	

Table adapted from: K Wiisanen et al. *Pharmacogenomics*. 2019;20:1103.



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Build A PGx Business/Practice Model

- Payment for PGx testing and pharmacist clinical services
  - Fee-for-service
  - Capitated and shared-risk, shared-reward systems
  - Blended payment structures
  - MTM billing codes
  - Billing incident-to or in collaboration with physician

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Build A PGx Business/Practice Model

Pre-Implementation
Collaborative Practice Agreement between pharmacist and physician

Patient Identification
At point of care/point of dispensing or provider referral

Billable Visit →

Pharmacist Visit 1
Medication history and buccal swab for PGx testing

PGX Test →

Between Visits
Pharmacist receives result; recommendations to physician

Billable Visit →

Pharmacist Visit 2
Pharmacist reviews recommendations and drug therapy changes

Education
Feedback
Monitoring

Arwood MJ, et al. *J Clin Med*. 2020;9(7):2274.

Build A PGx Business/Practice Model

Table 1. Sample Patient Breakdown by Condition and Payer

Site	Payers	Depression	Chronic Pain	Pain or Depression
Sample Clinic	Medicare	6.5 %	5.5 %	10.1 %
	All	15.8 %	9.7 %	22.6 %

Table 2. Sample Patient Breakdown by Medication and Payer

Site	Payers	Codeine or tramadol	Oxycodone or Hydrocodone	SSRI	TCA	PPI	Any of these Medications
Sample Clinic	Medicare	2.3%	2.8 %	4.3%	0.7 %	7.4 %	13.2 %
	All	4.6 %	6.5 %	12.4 %	1.7 %	16.7 %	33.5 %

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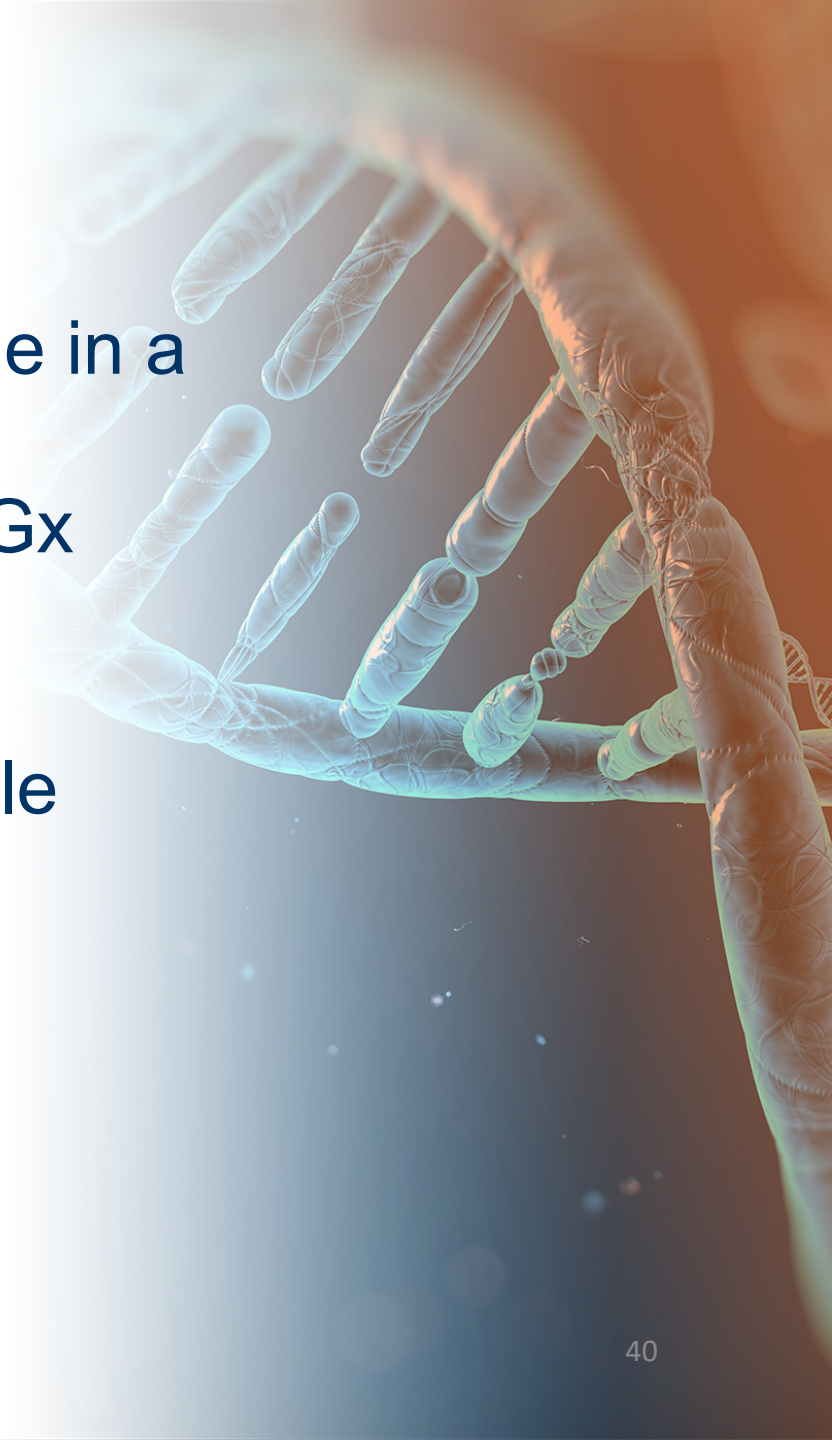
Conclusion

- Pharmacogenetics implementations are feasible in a clinical setting
- Pharmacist leadership is essential in clinical PGx services
- Education is an important catalyst to enable expansion of pharmacogenetics on a large scale
- Lessons learned
  - Consistency
  - Scalability
  - Efficiency



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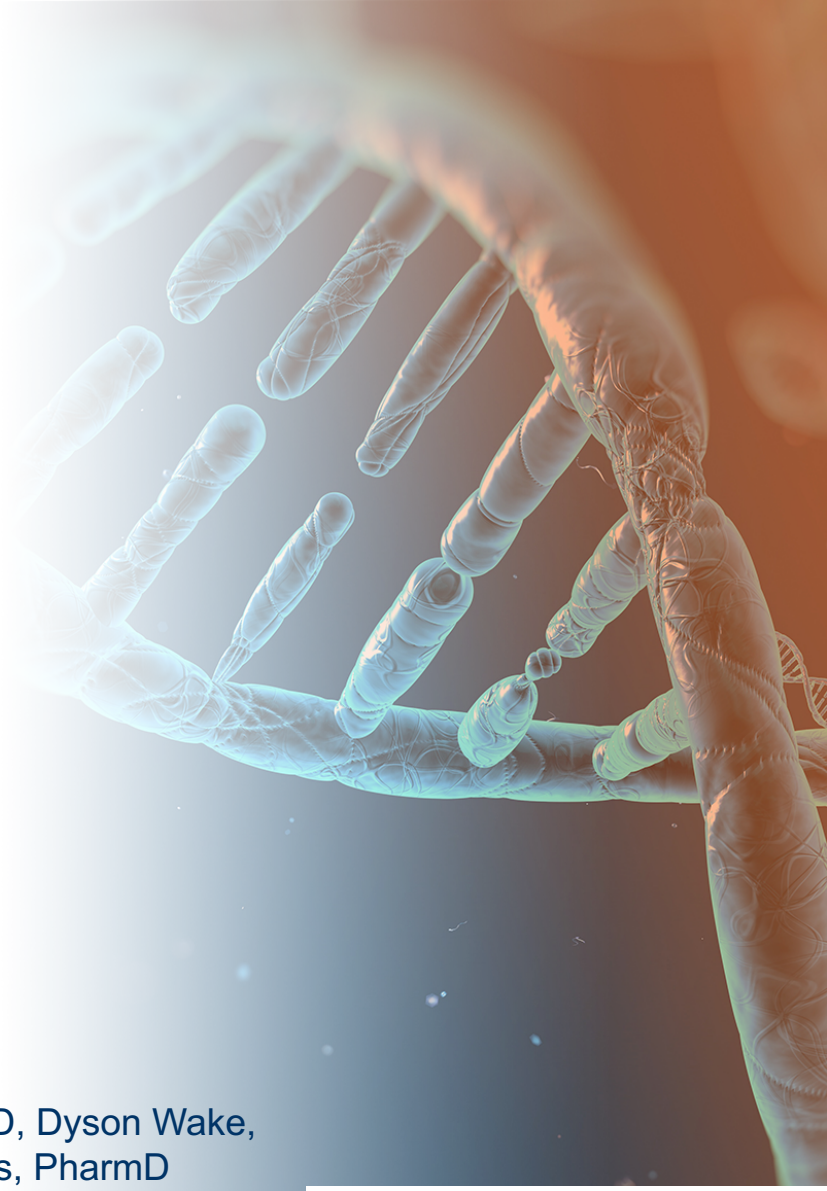

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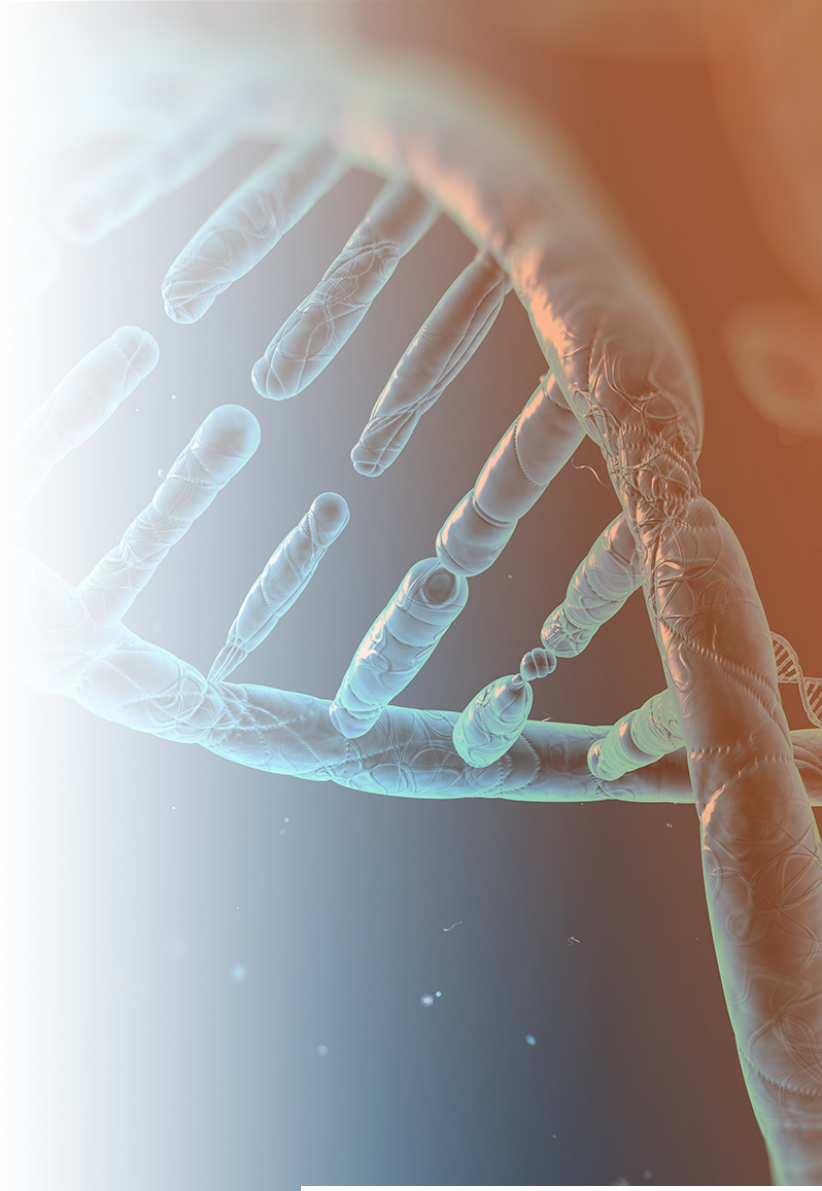

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