Personalized Medicine for Everyone: Best Practices for Utilizing Pharmacogenomics Programs at Scale

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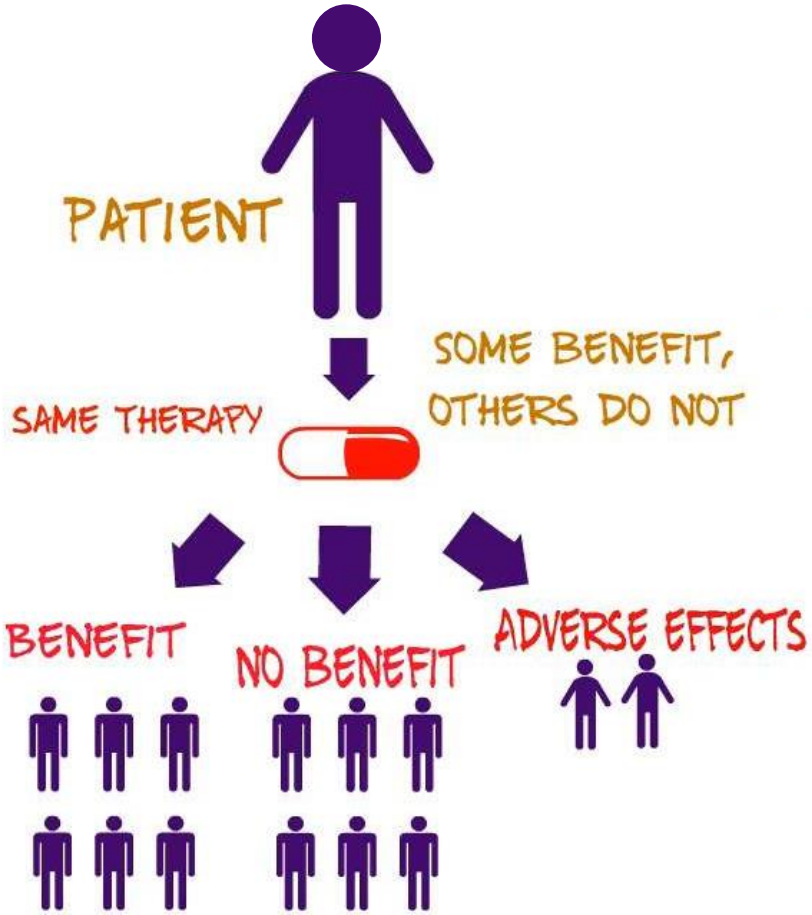
Current Standard of Care

Consider a time that you administered a drug, or took a drug, with a desired outcome in mind and that it didn't work.

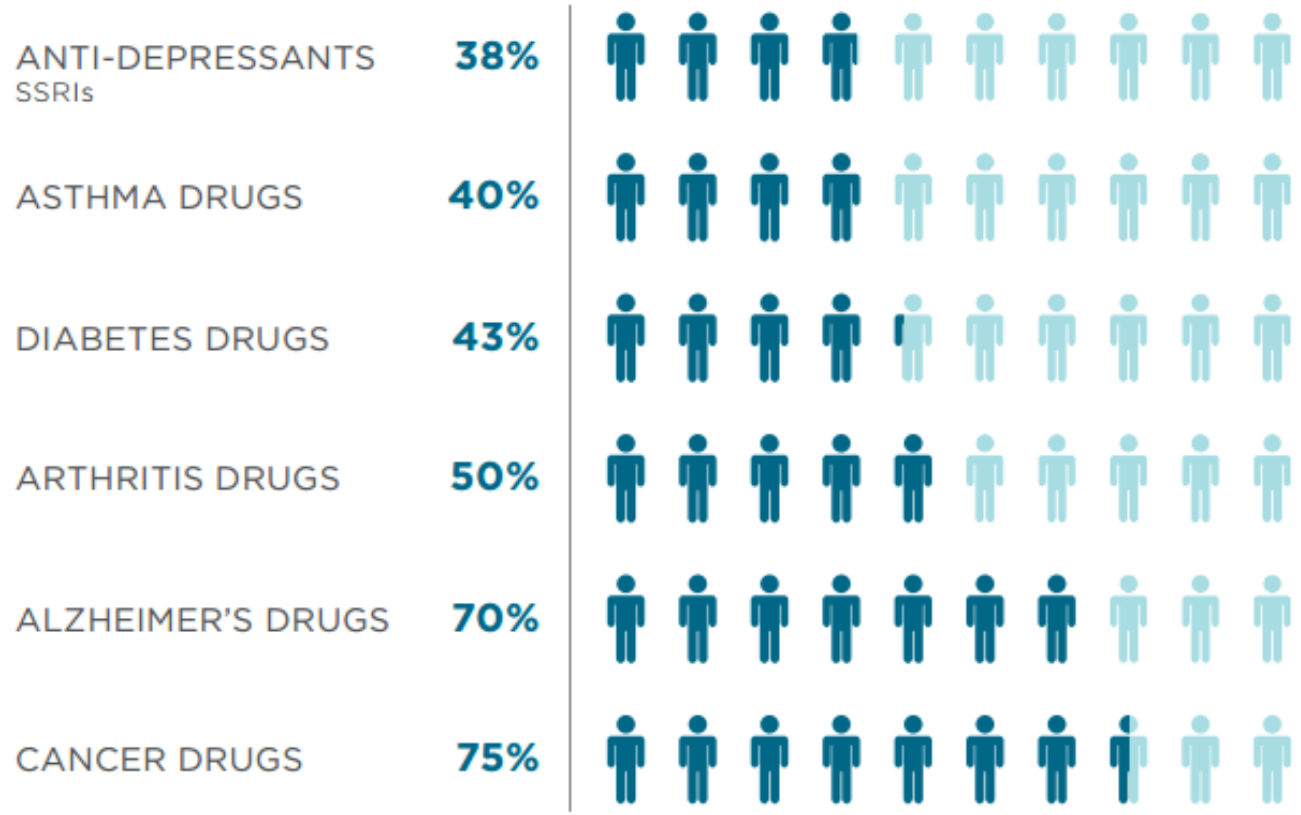
OR

Consider a time that you administered a drug, or took a drug, and had an unexpected or adverse reaction to the drug.

Current Standard of Care



Percentage of the patient population for which a particular drug in a class is ineffective

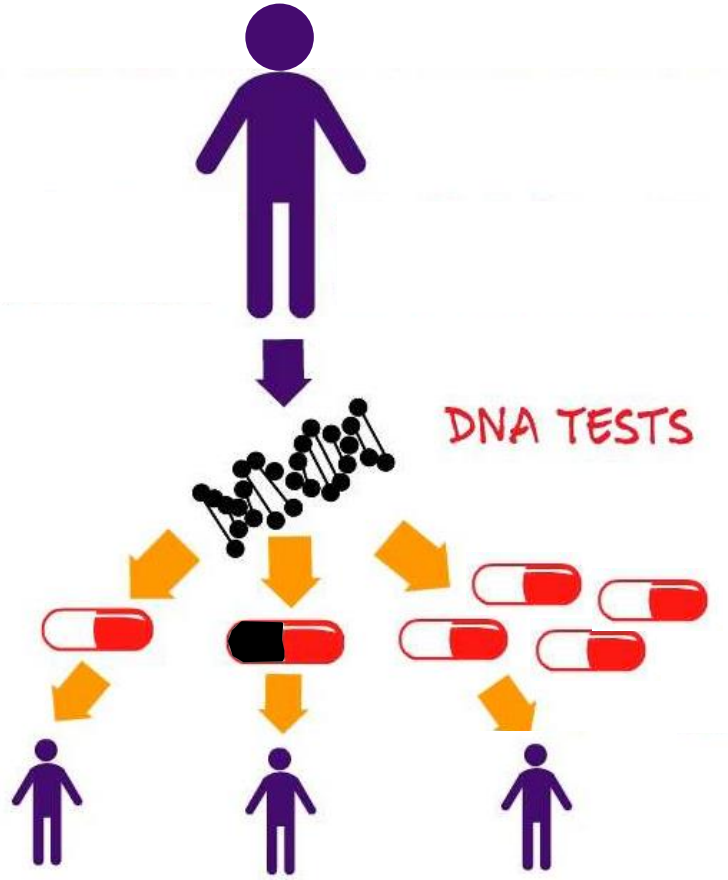


Source: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine," Volume 7, Issue 5, 1 May 2001, pages 201-204.

Future of Care

Genotyping or Genetic Sequencing allows physicians and healthcare providers to tailor medicine specifically to the patient.

Goal: Maximize therapeutic effect, minimize adverse effects



Nomenclature

Personalized Medicine

Precision Medicine

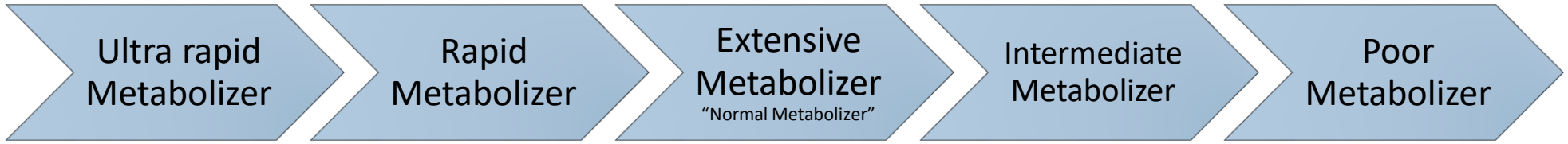
Pharmacogenomics (PGx)

Genotyping

Genetic Sequencing

Genotype

Phenotype

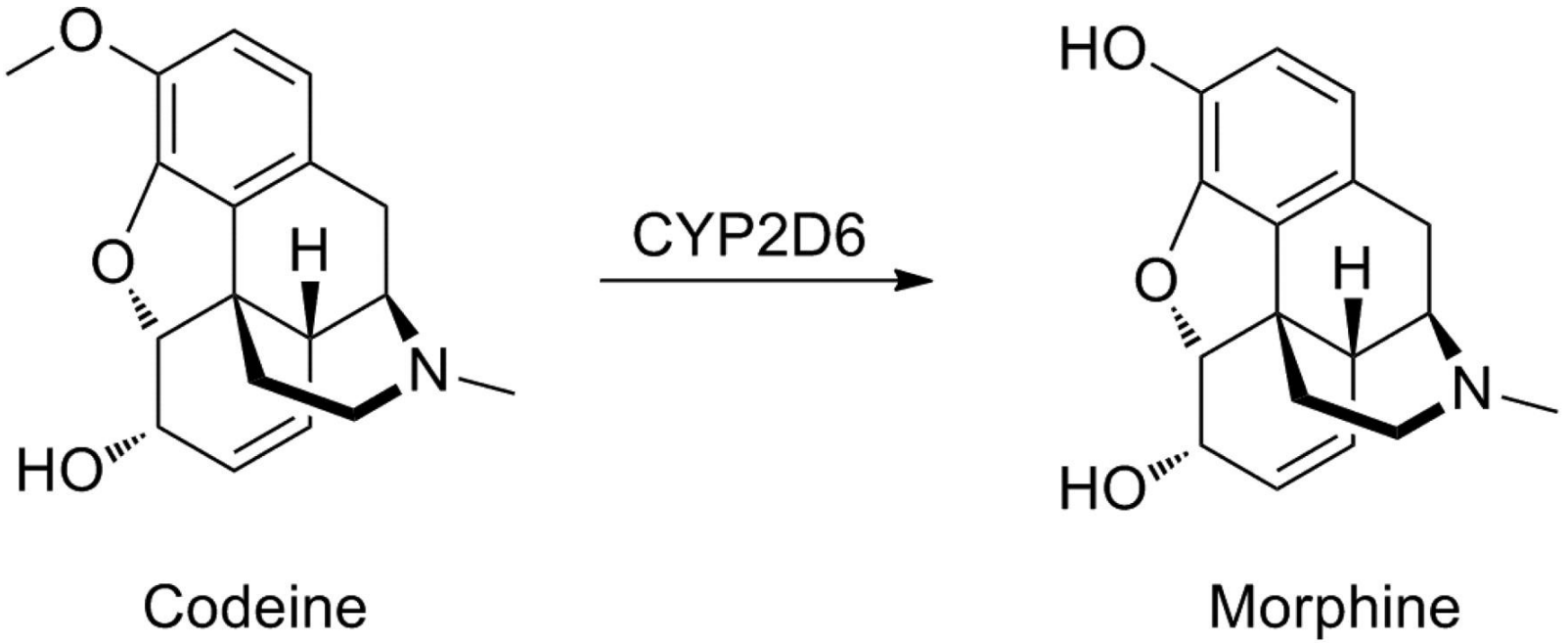


Missed Opportunity for Precision Medicine

Rani Jamieson

Tariq Jamieson

Missed Opportunity for Precision Medicine



Codeine

Morphine

Rani Jamieson

Ultra Rapid Metabolizer

Other Opportunities for Precision Medicine

TABLE: MOST COMMONLY PRESCRIBED DRUGS OF 2011 FOUND IN THE FDA'S "TABLE OF PHARMACOGENOMIC BIOMARKERS IN DRUG LABELS"

Drug	Top 200 Rank (number of prescriptions dispensed in 2011)[a,b]	Therapeutic Area	Biomarker	Label Section(s)
Amitriptyline	120 (6,782,000)	Psychiatry	CYP2D6	Precautions
Atorvastatin	5 (40,812,000)	Metabolic and endocrinology	LDLR	Indications and Usage, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Carisoprodol	148 (6,077,000)	Musculoskeletal	CYP2C19	Clinical Pharmacology, Use in Special Populations
Carvedilol	86 (14,542,000)	Cardiovascular	CYP2D6	Drug Interactions, Clinical Pharmacology, Dosage and Administration, Use in Special Populations
Citalopram	67 (19,508,000)	Psychiatry	CYP2C19/ CYP2D6	Drug Interactions Warnings
Clopidogrel	7 (28,139,000)	Cardiovascular	CYP2C19	Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Diazepam	105 (12,159,000)	Psychiatry	CYP2C19	Drug Interactions, Clinical Pharmacology
Fluoxetine	65 (16,921,000)	Psychiatry	CYP2D6	Warnings, Precautions, Clinical Pharmacology
Metoprolol	40 (59,597,000)	Cardiovascular	CYP2D6	Precautions, Clinical Pharmacology
Omeprazole	21 (57,826,000)	Gastroenterology	CYP2C19	Dosage and Administration, Warnings and Precautions, Drug Interactions
Pantoprazole	193 (9,299,000)	Gastroenterology	CYP2C19	Clinical Pharmacology, Drug Interactions, Use in Special Populations
Paroxetine	143 (6,169,000)	Psychiatry	CYP2D6	Clinical Pharmacology, Drug Interactions
Pravastatin	38 (14,667,000)	Cardiovascular	Apoε2	Clinical Studies, Use in Special Populations
Risperidone	157 (5,782,000)	Psychiatry	CYP2D6	Drug Interactions, Clinical Pharmacology
Tramadol	25 (25,609,000)	Analgesics	CYP2D6	Clinical Pharmacology
Venlafaxine	75 (9,586,000)	Psychiatry	CYP2D6	Drug Interactions
Warfarin	35 (28,573,000)	Hematology	CYP2C9/ VKORC1	Clinical Pharmacology, Dosage and Administration, Precautions

[a]Highest ranking; [b]Combined all manufacturers

Apoε2 = apolipoprotein epsilon2; CYP = cytochrome P450; LDLR = low-density lipoprotein receptor; VKORC1 = vitamin K epoxide reductase complex subunit 1.

Using the Clinical Pharmacogenomics Implementation Consortium (CPIC) Guidelines

https://cpicpgx.org/

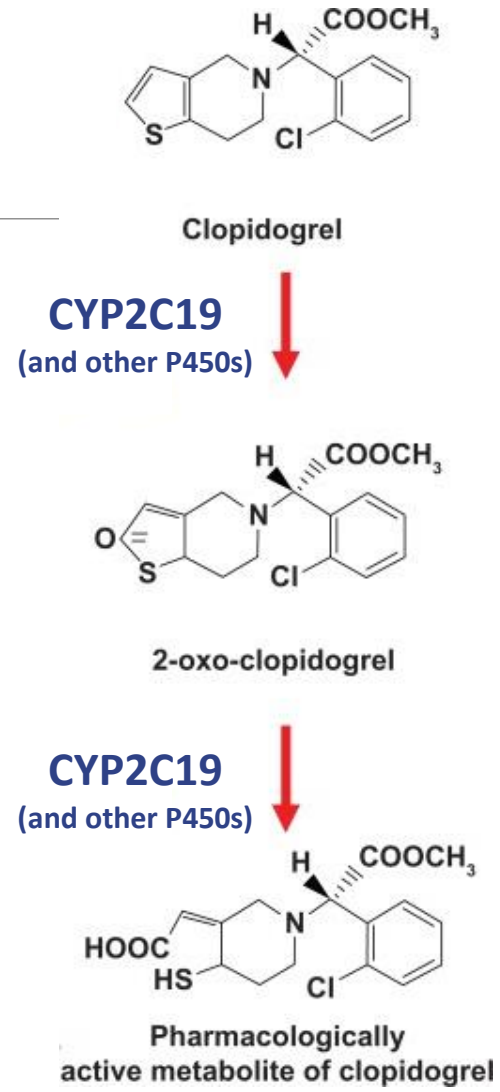
CPIC®
Clinical Pharmacogenetics Implementation Consortium

Clopidogrel Example

Patient admitted to the ED for ACS and undergoes PCI. Following the procedure the patient is placed on antiplatelet therapy to prevent future clot formation.

How to choose the correct antiplatelet therapy?

https://cpicpgx.org/



Special Considerations in Elderly Populations

Polydrug Use

Confusion/Memory Loss about therapy regimens

Difficulty in communicating therapy regimens

Elderly populations have complex pharmacokinetics

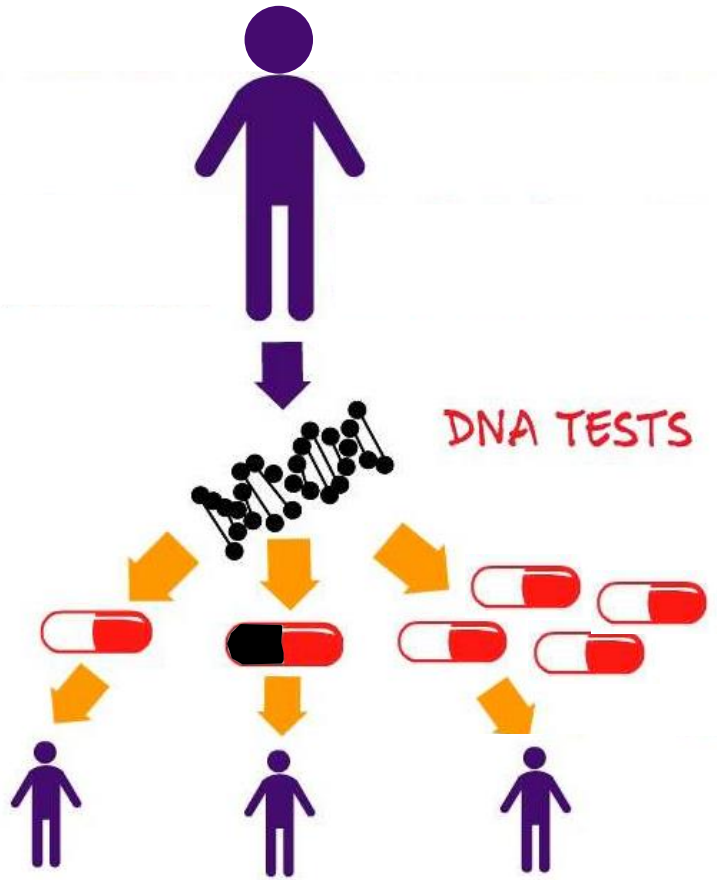
Conclusions

Precision medicine enhances patient care by:

- ensuring best drug selection for the patient
- ensuring best drug dosing for the patient

Limited Use of Precision Medicine in Current Healthcare

- The process required to translate genetic information into a clinical actions.
- Providing recommendations for selecting the drug/gene pairs to implement.
- Test cost, test reimbursement or other economic issues.
- Electronic medical record use.



Clin Pharmacol Ther. 2011 Mar;89(3):464-7.

Resources for Precision Medicine

Certificate Programs

- American Pharmacists Association

Graduate Programs

- Manchester University

Websites

- CPIC Guidelines
- PHRMKGB
- NIH
- Healthcare Provider Competencies for PGx

Joe Spinelli, MedTek21

Promise of PGX

- Right Drug
- Right Dose
- Right Patient

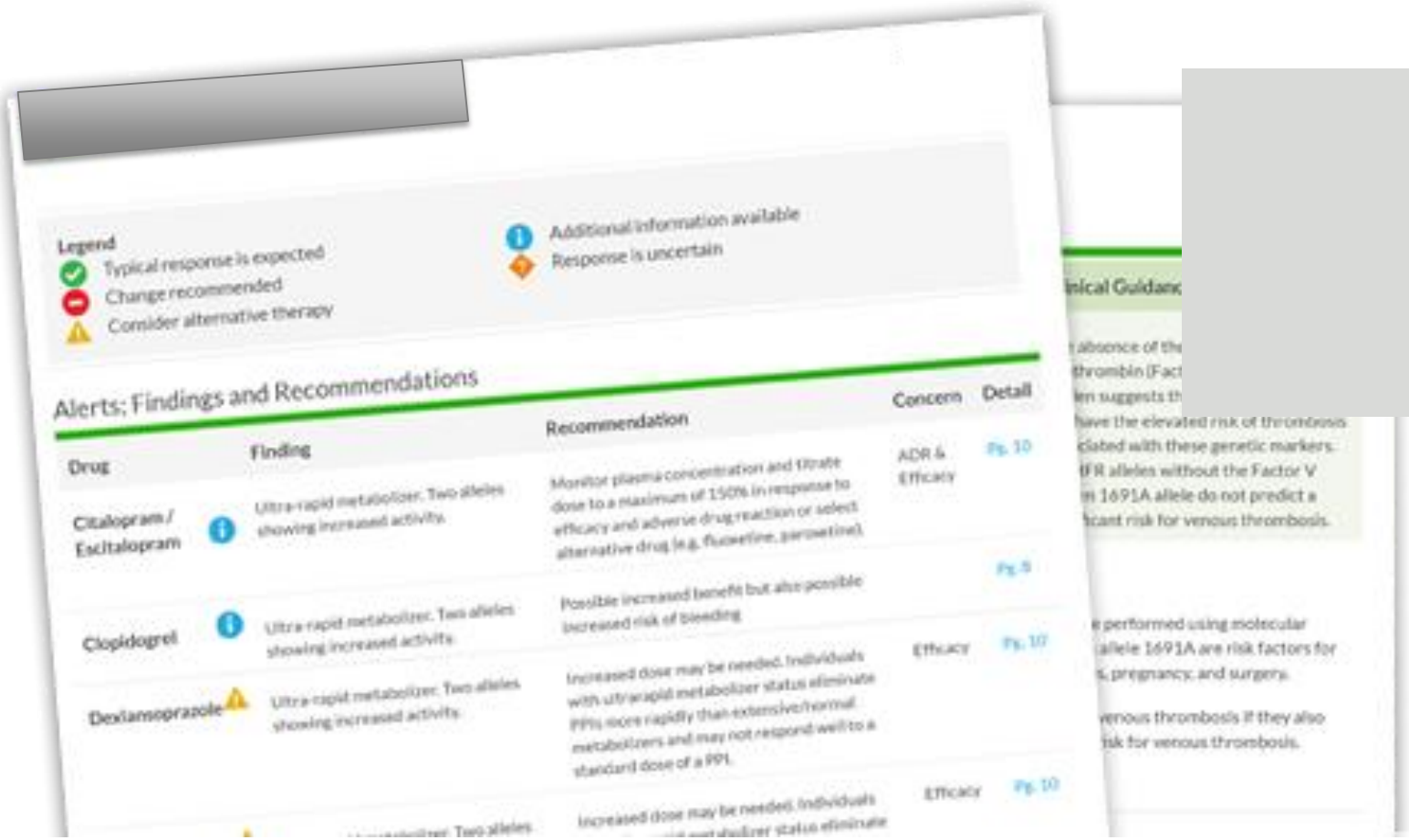
- Proactive
- Reactive
- Within Clinical Workflow

PGX is Here

- 88.1% of clinicians surveyed wish to learn how to use PGX in improvement of care (n=300)

- Examples from over 300 facilities that began software-based programs in 2017

Historical Challenges



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static report!

Key Objectives in PGX Program Design

- Who should be tested?
- How should results be delivered?
- How are new alerts delivered?

Deployment Models

- Pharmacy /Consulting Pharmacy
  - Already providing Drug-to-Drug/Drug-to-Allergy
  - Already Delivering Interventions/Recommendations
  - Existing Workflow
- Care Group
  - Existing care workflows
  - Benefits from care savings/outcomes improvement
- Direct to Patient
  - Limited Scalability/Integration with Clinical Workflows
  - Risk of adherence issue without proper consultation

Key Objectives in PGX Program Design

- Identify key pain points (med costs, hospitalization by class)
- Identifying individuals that should be targeted – risk stratification
- Testing workflows
- Results Delivery/Administration
- Outcomes Tracking

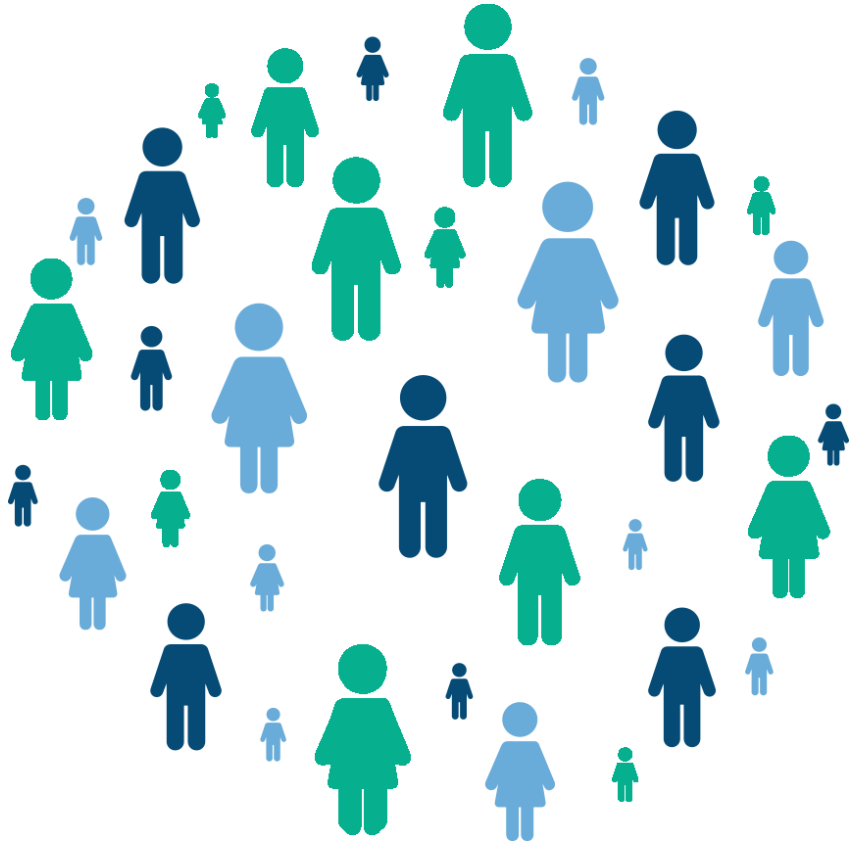
Initial Onboarding

Risks alerted and remediated –

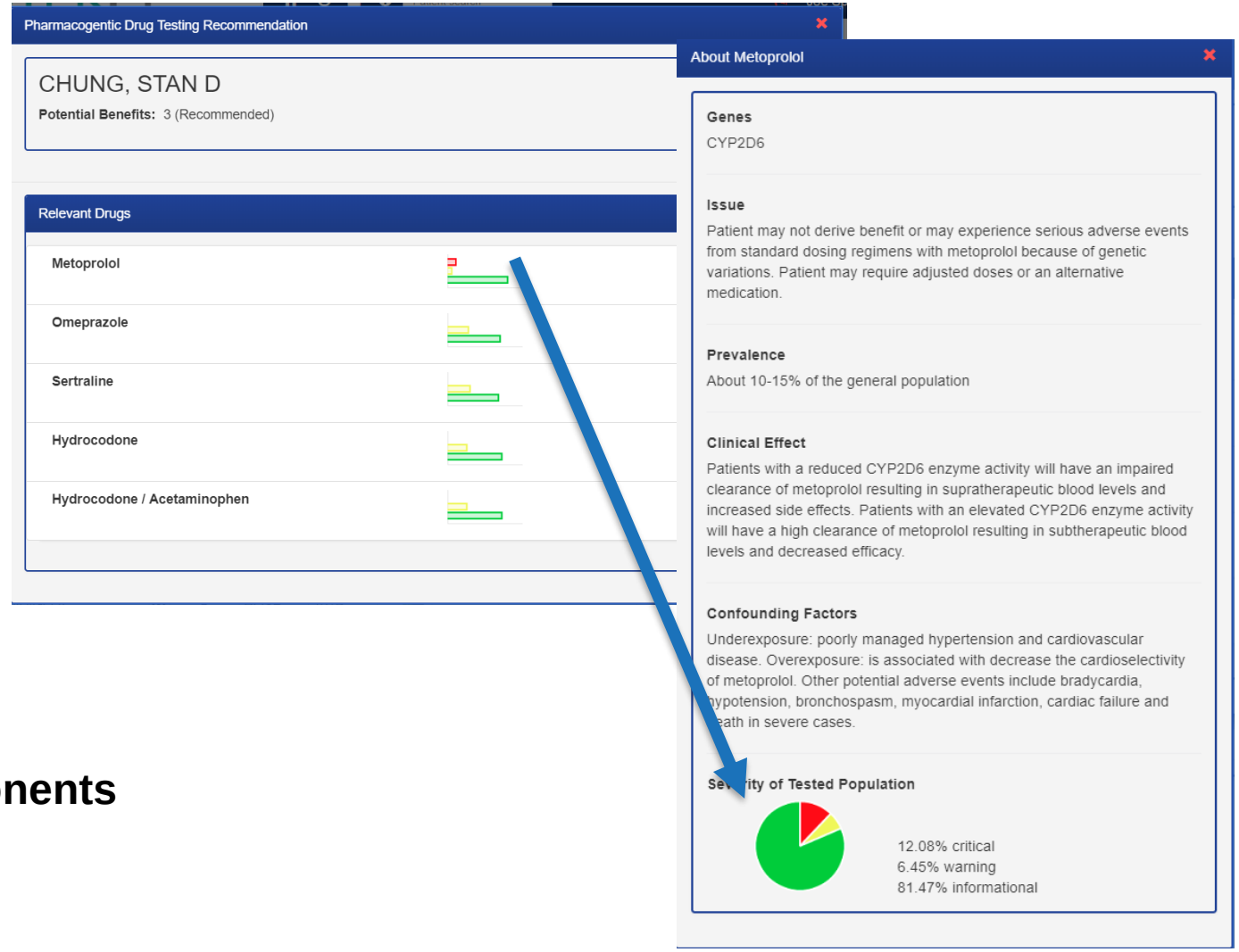
(optional)

Software-Based Risk Stratification

- Current meds that are PGX relevant
- Multiple genomic pathways
- Implications on ROI, program design, incentives

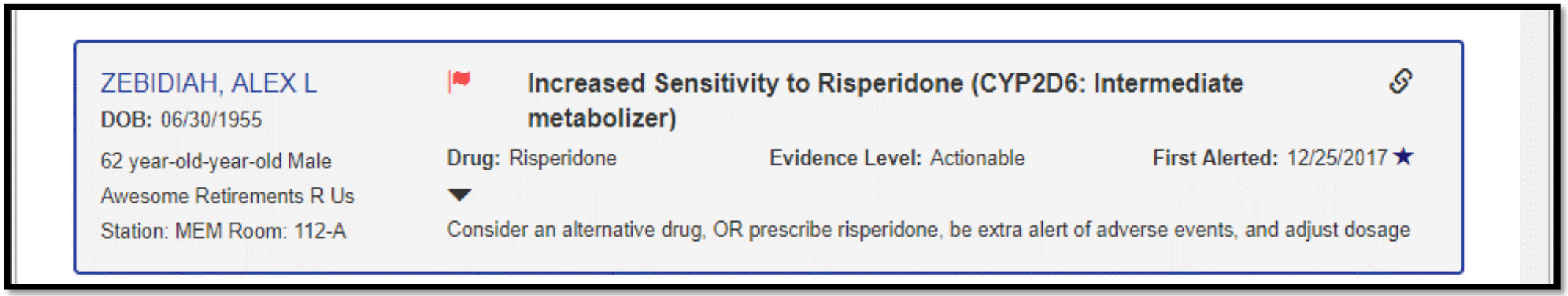


Risk Stratification Example



11 medications
6 PGX relevant
1 med risk, 4 high risk relevant components
Recommended for testing

Alerting Example



- Automatically Generated
- Delivered in Pharmacy Workflow
- Intervention with Patient

Results at Scale

1311 tested patients, High and Moderate Alerts

Drug	Count of High Alerts
Escitalopram	79
Clopidogrel	47
Metoprolol	46
Citalopram	37
Risperidone	35
Tramadol	30
Simvastatin	24
Venlafaxine	15
Paroxetine	13
Haloperidol	8
Amitriptyline	7
Bupropion	6
Codeine	5
Ondansetron	4
Nortriptyline	2
Clomipramine	1
Doxepin	1
Grand Total	**360**
Tested Patients	1,311

Drug	Count of Moderate Alerts
Citalopram	394
Olanzapine	214
Lorazepam	210
Escitalopram	182
Atorvastatin	129
Warfarin	119
Hydrocodone	111
Ondansetron	72
Risperidone	70
Clozapine	66
Omeprazole	66
Sertraline	63
Pantoprazole	60
Clopidogrel	51
Donepezil	41
Bupropion	39
Tizanidine	26
Oxycodone	25
Pravastatin	25
Morphine	23
Top 20	**1,986**
Others	274
Grand Total	**2,260**
Tested Patients	1,311

Real-world alerts - significant issues with behavioral health, blood/cardiac, pain medications

Sample guidance for Escitalopram (Lexapro) – 58 of 79 guidance recommendations At standard label-recommended dosage, escitalopram plasma concentrations levels are expected to be low which may result in a loss of efficacy. ***Consider an alternative medication***. If escitalopram is warranted, consider ***increasing the dose to a maximum of 150%*** and titrate based on the clinical response and tolerability.

Sample guidance for Clopidogrel – 42 of 47 guidance recommendations: ***Consider alternative therapy***.
Examples of alternative drugs: prasugrel (contraindicated in TIA/Stroke patients), ticagrelor, aspirin, aspirin plus dipyridamole.

Patient Case Study

Female in long term care setting

8 PGX-relevant drugs

Patient diagnosis: cardiac arrhythmia, hypertension, coronary artery disease, type 2 diabetes

Director of Nursing believed patient's drugs were not working

5 Actionable warnings (1 severe) to guide improvements in pain management behavioral health

"This patient spends her day sitting in her wheelchair crying" – Director of Nursing

Medications Affected by Patient Genetic Results

Citalopram
Insufficient Response to Citalopram (CYP2C19: Rapid metabolizer) Evidence Level: **Actionable**
At standard label-recommended dosage, citalopram plasma concentrations levels are expected to be low which may result in a loss of efficacy. Consider an alternative medication. If citalopram is warranted, consider increasing the dose to a maximum of 150% and titrate based on the clinical response and tolerability.

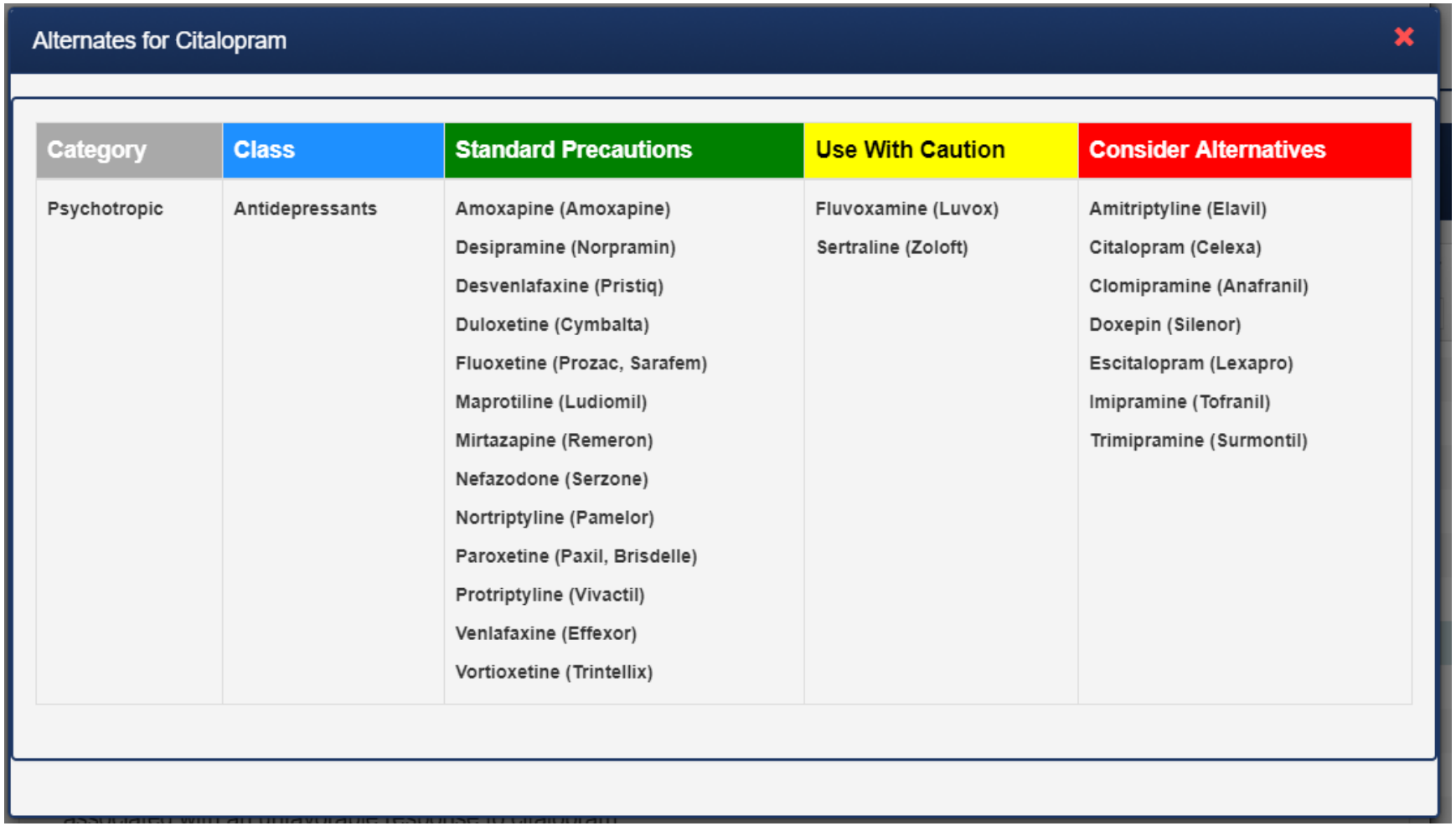
Metoprolol
Increased Sensitivity to Metoprolol (CYP2D6: Intermediate metabolizer) Evidence Level: **Actionable**
Based on the genotype result, this patient may be at risk of excessive beta-blockade when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol, or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, an intermediate metabolizer may require a 50% dose reduction. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol, or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, an intermediate metabolizer may require a 50% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g., bradycardia or cold extremities).

Pantoprazole
Insufficient Response to Pantoprazole (CYP2C19: Rapid metabolizer) Evidence Level: **Actionable**
- Helicobacter pylori eradication: increase dose by 400% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 400%.

Protonix (Pantoprazole)
Insufficient Response to Pantoprazole (CYP2C19: Rapid metabolizer) Evidence Level: **Actionable**
- Helicobacter pylori eradication: increase dose by 400% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 400%.

Tramadol
Possible Non-Responder to Tramadol (CYP2D6: Intermediate metabolizer) Evidence Level: **Actionable**
The patient may need higher doses or may not experience adequate pain relief when taking tramadol. Tramadol dose needs to be individualized and careful weekly titration is recommended. If no response, consider alternative opioids other than codeine, or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available

sample outcomes – behavioral health



Category	Class	Standard Precautions	Use With Caution	Consider Alternatives
Psychotropic	Antidepressants	Amoxapine (Amoxapine) Desipramine (Norpramin) Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Fluoxetine (Prozac, Sarafem) Maprotiline (Ludiomil) Mirtazapine (Remeron) Nefazodone (Serzone) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Venlafaxine (Effexor) Vortioxetine (Trintellix)	Fluvoxamine (Luvox) Sertraline (Zoloft)	Amitriptyline (Elavil) Citalopram (Celexa) Clomipramine (Anafranil) Doxepin (Silenor) Escitalopram (Lexapro) Imipramine (Tofranil) Trimipramine (Surmontil)

sample outcomes – behavioral health

Gene: CYP2C19 - Rapid metabolizer OR Ultrarapid metabolize

Gene: SLC6A4 - S/La OR S/S

Gene: HTR2A - Substitution OR Wild type

Site	PatientCount	HasGene		On Citalopram
Total	2,284	307	13.4%	22

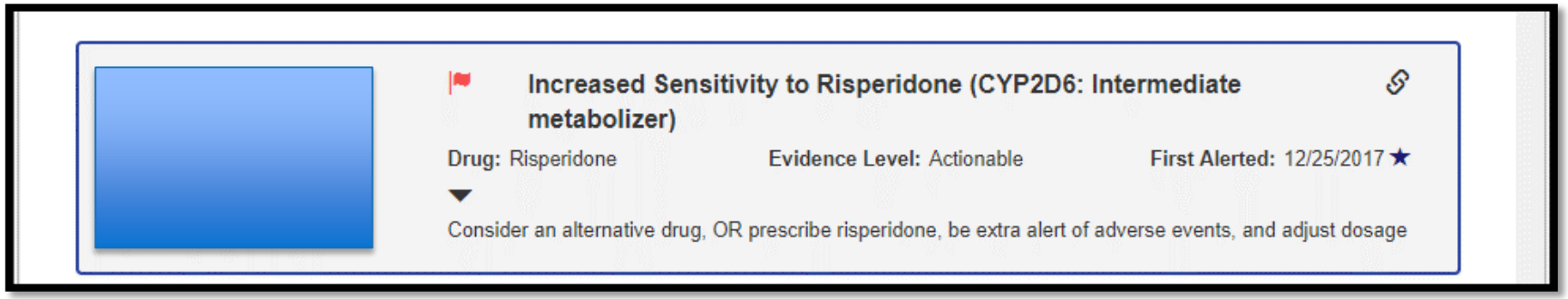
Sample Outcomes - behavioral

Sample Medication Regimen for 12 patients with flag (**no active alerts, use to review standard prescribing guidance)**

- Celexa -> Cymbalta
- Cymbalta
- Remeron -> Celexa -> Remeron
- Cymbalta
- Celexa -> Remeron
- Lexapro
- Cymbalta
- Cymbalta
- Trintellix -> Cymbalta
- Effexor -> Celexa -> Effexor -> Silenor
- Celexa -> Remeron -> Celexa
- Cymbalta

Results Delivery and Administration

- Ensure patient and care provider are notified
- Clinical and genetic counseling resources
- Tracking of interventions through med changes
- Patient Access /Portability



Measuring Benefit

- # of Alerts/Remediated Alerts
- Falls
- Pain Management
- Hospitalizations

Conclusions

- PGX Maximum Benefit – Continuous Monitoring and Alerting
- Leverage Software and Data
- Track the Trackable Outcomes

Thank You / Questions