PHARMACOGENOMICS 101 FOR HEALTHCARE PROVIDERS

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President, Hawaiʻi Pharmacists Association
ROADMAP

Pharmacogenomics (PGx) Background and Statistics
Nomenclature and Biology
Guidelines & Literature Review
Overlaps in other clinical areas
Phenoconversion
Implementation and Coverage
BACKGROUND & STATISTICS
COST BURDEN OF NON-OPTIMIZED MEDICATION USE

- $528 billion estimated impact of improper medication therapy on U.S. annual healthcare spend

- $200 billion annual cost of treating each of the following diseases that drive pharmacy trend
  - Cardiovascular disease (CVD)
  - Diabetes
  - Cancer

IMPORTANCE OF PGX

• 99% of individuals harbor a genetic variant that may impact medication response\(^1\)

• Every two minutes in the United States a life is lost from non-optimized medication\(^1\)

• Adverse Drug Reactions are the 4th leading cause of death in the US, ahead of pulmonary disease, diabetes, and automobile accidents\(^2\)

• 40 million patients are on 5+ medications and that number is anticipated to double by 2040\(^3\)

2. JAMA 1998;279:1200–120
CURRENT HEALTHCARE LANDSCAPE

• The state of Hawai‘i is short more than 1,000 physicians\textsuperscript{1}

• Doctor shortages are especially severe in the neighbor islands, where there are very few specialists.\textsuperscript{1}

• The trial-and-error prescribing process can negatively affect multiple aspects of patient care
  • Compliance
  • Treatment resistant depression
  • Adverse drug reactions (ADRs)
  • Patient-provider relationship
  • Financially taxing

\textsuperscript{1} Grassroots Institute Hawaii, 2022
Nearly six in 10 (58%) say they have experienced health care delays in the past year.

Source of Data: Community First Access to Care Report. 2022

### FIGURE 2. One Size Does Not Fit All

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Depressants (SSRIs)</td>
<td>38%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes Drugs</td>
<td>43%</td>
</tr>
<tr>
<td>Arthritis Drugs</td>
<td>50%</td>
</tr>
<tr>
<td>Alzheimer's Drugs</td>
<td>70%</td>
</tr>
<tr>
<td>Cancer Drugs</td>
<td>75%</td>
</tr>
</tbody>
</table>

WHERE DOES PGX FIT?

Pharmacogenomics (PGx)
How genetics impact medication

Pharmacokinetics (PK)
How the body affects the medication

Pharmacodynamics (PD)
How medication affects the body
WHAT IS PHARMACOGENOMICS

**Blockbuster** one-size-fits-all approach to drug development and prescribing

**Personalized prescribing** enables selection of the right drug and dose

"Pgx helps to find the right drug, at the right dose, the FIRST time"
HOW DOES PGX WORK?

• Buccal or blood sample taken from patient

• Sample is genotyped for genes and alleles to determine phenotype

• No PGx laboratories in the state of Hawaii, 2-3 week turnaround time

• Genes do NOT change over the course of a lifetime
UK BIOBANK ANALYSIS

- Analysis of 487,409 UK Biobank patients

- >99% of people may have an atypical response to at least one medication

- The average person may have an atypical response to 10 medications

NOMENCLATURE & BIOLOGY
NOMENCLATURE – CYP450 ENZYMES

Gene designated with the abbreviation CYP
Number indicating the gene family
Capital letter indicating the subfamily
Numeral for the individual gene
NOMENCLATURE CONT’D

* (star) alleles – pharmacogenomic haplotype

Normal function/enzyme activity (wild type) denoted by *1

Altered function variant: *2, *3, *4, etc.

Single genes (CYP2C19) have many star alleles (e.g., CYP2C19*2, CYP2C19*3)

Results reported as diplotypes: CYP2C19*1/*17
ENZYME BIOLOGY

Ultrarapid Metabolizer (UM)
- Increased enzyme activity
- Therapeutic Window
- Lack of Response

Normal Metabolizer (NM)
- Normal enzyme activity
- Expected Response

Intermediate Metabolizer (IM)
- Intermediate enzyme activity
- Exaggerated Response

Poor Metabolizer (PM)
- Low or absent enzyme activity
- Adverse Effects

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ACTIVE DRUGS VS. PRODRUGS

Active drug

Active drug

Prodrug

inactive parent

active metabolite

inactive parent
At steady state, we expect:

- **PM** – low-absent enzymatic activity; more likely to experience adverse effects due to high levels of unmetabolized drugs
- **IM** – possibly more adverse effects compared to **NM** due to decreased enzymatic activity
- **NM** – typical response at standard doses
- **UM** – less likely to experience therapeutic effect at standard doses due to increased enzymatic activity
DRUG RESPONSE: PRODRUG

A prodrug is a biologically inactive precursor drug that must undergo chemical conversion before becoming an active pharmacological agent (active metabolite).

At steady state, we expect:

- **UM** – more likely to experience adverse effects due increased/rapid formation of active metabolites
- **NM** – typical response at standard doses, possibly more adverse effects
- **IM** – typical response at standard doses; possibly less therapeutic effects
- **PM** – less likely to experience therapeutic effect since the inactive parent compound is not been converted to the active form
GUIDELINE REVIEW
PGX INFORMATION RESOURCES

<table>
<thead>
<tr>
<th>CPIC</th>
<th>PharmGKB</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pharmacogenetics Implementation Consortium</td>
<td>Data aggregate resource that identifies consistent genetic variant-drug response interactions.</td>
<td>The FDA publishes information on pharmacogenomic associations in three categories:</td>
</tr>
<tr>
<td>Guideline actionable drug-gene pairs.</td>
<td></td>
<td>1. Sufficient scientific evidence for therapeutic management</td>
</tr>
<tr>
<td>Endorsed by multiple medical societies.</td>
<td></td>
<td>2. Potential impact on safety</td>
</tr>
<tr>
<td>Indexed as guidelines in PubMed.</td>
<td></td>
<td>3. Potential impact on pharmacokinetic properties only</td>
</tr>
</tbody>
</table>
CPIC LEVELS OF EVIDENCE

Gene(s)/drug(s)

Gene already subject to CPIC guideline
- Actionable in other professional society guidelines
- Nominated by CPIC member or recommended by external group (e.g. FDA, EMA)

Gene not yet subject to CPIC guideline
- PharmGKB Annotation level 1A, 1B, 2A or 2B
- Mentioned in professional society guidelines but not actionable

Evaluate alternatives, evidence
- CPIC level A or B: Prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe
- CPIC level C: No prescribing change based on genetics; alternatives are unclear or evidence is weak but testing is common or gene is CPIC level A or B for other drugs
- CPIC level D: PharmGKB annotation only; no prescribing action recommended; alternatives unclear or evidence is weak; testing is rare

https://cpicpgx.org/prioritization/
<table>
<thead>
<tr>
<th>CPIC level</th>
<th>Clinical context</th>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Genetic information should be used to change prescribing of affected drug.</td>
<td>Preponderance of evidence is high or moderate in favor of changing prescribing.</td>
<td>At least one moderate or strong action (change in prescribing) recommended.</td>
</tr>
<tr>
<td>A/B</td>
<td>Preliminary review indicates it is likely that the definitive CPIC level will be either A or B.</td>
<td>Full evidence review needed to assess level of evidence, but prescribing actionability is likely.</td>
<td>Full review by expert guideline group to assign strength of recommendation.</td>
</tr>
<tr>
<td>B</td>
<td>Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing.</td>
<td>Preponderance of evidence is weak with little conflicting data.</td>
<td>At least one optional action (change in prescribing) is recommended.</td>
</tr>
<tr>
<td>B/C</td>
<td>Preliminary review indicates it is likely that the definitive CPIC level will be either B or C.</td>
<td>Prescribing actionability based on genetics is not clear without further evidence review.</td>
<td>Full review by expert guideline group to assess strength of recommendation.</td>
</tr>
<tr>
<td>C</td>
<td>There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical, or (c) few published studies or mostly weak evidence and clinical actions are unclear.</td>
<td>Evidence levels can vary.</td>
<td>No prescribing actions are recommended.</td>
</tr>
<tr>
<td>C/D</td>
<td>Preliminary review indicates it is likely that the definitive CPIC level will be either C or D.</td>
<td>Evidence levels can vary.</td>
<td>No prescribing actions are recommended.</td>
</tr>
<tr>
<td>D</td>
<td>There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.</td>
<td>Evidence levels can vary.</td>
<td>No prescribing actions are recommended.</td>
</tr>
</tbody>
</table>

https://cpicpgx.org/prioritization/
List of drugs impacted by pharmacogenomics according to the FDA and Clinical Pharmacogenetics Implementation Consortium (CPIC)\(^1,2\)

**Behavioral health**
- amitriptyline
- aripiprazole
- atomoxetine
- brexpiprazole
citalopram
desipramine
doxepin
escitalopram
fluvoxamine
imipramine
mirtazapine
nortriptyline
paroxetine
propranolol
risperidone
sertraline
trimipramine
venlafaxine
vortioxetine

**Cardiology**
- atorvastatin
clopipramine
rosuvastatin
simvastatin
warfarin

**Hematology/oncology**
- belinostat
capcitabine
eliglustat
fluorouracil
irinotecan
mercaptopurine
tamoxifen
thioguanine

**Gastroenterology**
- dexlansoprazole
esomeprazole
lansoprazole
omeprazole
ondansetron
pantoprazole
rabeprazole

**Pain management**
- celecoxib
codeine
flurbiprofen
ibuprofen
meloxicam
methadone
oxycodone
pizicam
tramadol

**Infectious disease**
- abacavir
atazanavir
efavirenz
nevirapine
voriconazole

**Neurology**
- phenytoin
siponimod
pimozide

**Rheumatology**
- azathioprine
dextromethorphan

**Ear, eye, nose, throat**

| Same set of genes affect most medications |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>3.2%</td>
</tr>
<tr>
<td>NUDT15</td>
<td>3.2%</td>
</tr>
<tr>
<td>HLA-B*15:02</td>
<td>3.2%</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>41.1%</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10.5%</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>16.9%</td>
</tr>
<tr>
<td>DPYD</td>
<td>2.4%</td>
</tr>
<tr>
<td>HLA-B*57:01</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

And many more...

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LITERATURE REVIEW
“Knowingly placed Plavix patients at grave risk of serious injury or death in order to substantially increase their profits.”

Engaged in “immoral, unethical, oppressive or unscrupulous” acts, by choosing not to warn about the risks and benefits of Plavix and instead “burying their heads in the sand.”

Deprived consumers of the right to make informed choices about the use of Plavix
• CYP2C19 *2 or *3 carriers have reduced hepatic 2C19 activity, lowering conversion of clopidogrel to its active metabolite, increasing the likelihood of acute stent thrombosis after angioplasty.

• Plavix trial participants were white/European with *2 and *3 allele frequency of ~10–20%.

• The population of Hawaii is 42% East Asian, 24% White, 10% Pacific Islander.

• *2 variant frequency is 23–45% in East Asians and 40–77% in Pacific Islanders.

• Nearly double cardiovascular death rate as a percentage of patients suffering an AMI (native Hawaiians, 273 total deaths/year or 4.8% vs. White/European, 307 deaths/year, 2.5%).

• Hawaii DA claims that clopidogrel manufacturers knew about the relevant genetic variances prior to the black box warning.

Hawaii's mental health crisis growing as demand surges

Hawaii’s Mental Health Care Crisis

The lack of psychiatrists is a particular problem for people who rely on the state’s public health insurance for low-income residents.

Hawaii News

Kaiser’s mental health shortage puts patient safety at risk, national agency finds

The Current Access to Psychiatric Care Problem in Hawaii

The mental health needs of individuals across our state continue to outweigh the capacity of our mental health system. According to a Report on Findings from the Hawaii Physician Workforce

Psychiatrist shortage hot topic again at legislature

Does Hawaii Have Enough Psychiatrists? Assessing Mental Health Workforce Versus Demand in the Aloha State

Psychiatry and mental health counseling are, far and away, the two professional areas needed most, according to providers. Though medical service needs abound due to widespread shortages in a number of medical specialties.
PGX IN DEPRESSION & ANXIETY

- PGx testing showed an increase in the number of patients with Major Depressive Disorder (MDD) who responded to antidepressant therapy

- Remission rates also improved
  - 35% PGx vs. 13% standard of care

- NNT = 3
  - Patients with severe depression to respond to treatment after 12 weeks
COST EFFECTIVENESS OF PGX GUIDED TREATMENT FOR MAJOR DEPRESSION

• Evaluation of effectiveness and cost analysis from a payor perspective of pharmacogenomic testing in adult patients with newly diagnosed MDD

• Patients who had undergone pharmacogenomic testing were 11% less likely to stop pharmacotherapy and 57% less likely to stop because of adverse effects.

• Taken together, the overall cost savings from a public payer perspective was estimated to be $956 million over the 20-year time horizon, or a cost savings of $4926 per patient.
PGX IN ONCOLOGY

• There are over 400 FDA drug labels related to pharmacogenomics. Over 40% are for cancer medications. ¹

• Cancer patients have complex medication regimens and those ‘accessory’ medications can also be impacted by pharmacogenomics. ²

¹ Table of pharmacogenomic biomarkers in drug labeling. U. S FDA.
ONCOLOGY: CASE REPORT

• March 2019: Lynn S had first dose of IV 5-FU. Less than 1 month later, Lynn had passed, but not from cancer.

• 1 in 20 people of European ancestry produce insufficient DYPD.

• Without DYPD 5-FU stays in the body and results in toxicity with concentration increases of up to 200%

• Carriers of pathogenic DPYD gene variants had a 25.6 times - increased risk of treatment related death (95% CI, 12.1 53.9; p < .001)

• The current CPIC guidelines recommends to reduce the dose of fluoropyrimidines by 25-50% (from the full standard dose) in DPYD Intermediate Metabolizers.

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• 1 in 20 people of European ancestry produce insufficient DYPD.

• Without DYPD 5-FU stays in the body and results in toxicity with concentration increases of up 200%.

"Her last weeks were agony," Chris says. "Her entire digestive tract was burnt, as if by acid. She had constant nausea and diarrhea and couldn't process food. No one warned us this might happen. Yet as I know now, Lynn's death was avoidable."

IMPLEMENTING COMPREHENSIVE PHARMACOGENOMICS IN A COMMUNITY PRIMARY CARE SETTING

PGx services were implemented in 30 primary care clinics. Discrete data results were returned directly into the EMR/CDST for review by PGx-certified ambulatory care pharmacists. Recommendations were discussed and implemented as a collaborative effort.

Results
• Of 422 unique interactions, 213 (50.5%) were pharmacogenomic and 124 were actionable, with a change to therapy recommended.

• Of the 124 actionable interactions, 82% of the time a change in medication was recommended.

• The underlying reasons for recommending therapy alterations were most commonly ineffective therapy (43%), adverse drug reaction prevented (34%), or adverse drug reaction observed (13%).
Figure 1. Type and reasons for PGx interventions implemented by pharmacists following PGx testing.
TESTING CONSIDERATIONS
# TESTING CONSIDERATIONS

<table>
<thead>
<tr>
<th>Timing</th>
<th>Scope</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive “just in time”</td>
<td>Single gene “targeted panel”</td>
<td>Presentation of Clinical Decision Support Tools and information “lights vs. letters”</td>
</tr>
<tr>
<td>Proactive “just in case”</td>
<td>Multi gene “broad panel”</td>
<td>Is the evidence for each recommendation available?</td>
</tr>
<tr>
<td>Turn around time and implication</td>
<td>Breadth of evidence in decision making process</td>
<td>Is the lab within a billable network?</td>
</tr>
</tbody>
</table>
Limiting PGx testing to a single clinical area might lead to missed actionable drug-gene interactions and potential patient harm.

~60% of patients were taking medications that could have a PGx interaction in more than 1 clinical area.

Clinical areas included behavioral health, cardiology, pain management, hematology and oncology, infectious disease, gastroenterology, urology, transplant, reproductive & sexual health, neurology, rheumatology, and endocrinology.

Of patients with a PIP score greater than 0, 1 in 3 were found to have an immediate, evidence-based actionable drug-gene interaction.

Proportion of patients with high-impact PGx medications by number of clinical areas impacted (n=30,471)

- 1 clinical area impacted (41.4%)
- 2 clinical areas impacted (32.2%)
- 3 clinical areas impacted (18.4%)
- 4 clinical areas impacted (6.8%)
- 5+ clinical areas impacted (1.1%)
COMPARISON OF TARGETED VS. EXPANDED PGX TESTING: WHAT ARE WE MISSING?

Recognized Drug-Gene Interactions by Panel

- Expanded Panel: 100%
- 14 Gene - Mental Health: 27%
- Dual Gene (2C19/2D6): 11.23%
- Single Gene (2C19): 4.56%

Targeted PGx testing for limited genes or by specialty may miss or not report significant portions of PGx gene-drug interactions.

This can lead to potential patient harm from the missed interactions and subsequent failed therapies and/or adverse reactions.

*J Am Pharm Assn* 2023 May;63(3):939-945
IMPLICATIONS IN HAWAI’I

• A large majority of drug research is done on those of European ancestry (Caucasian)
  • According to the NIH: 70-81%

• In 2019, 25% of Hawaii’s population was multiracial. Only 2.8% of the US population was multiracial. The United States was three-fourths Caucasian Alone, there was no majority race in Hawaii

• Asian American and Pacific Islanders (AAPI) have significantly different medication processing pathways than Caucasians and are more at risk for medication related complications
<table>
<thead>
<tr>
<th>Drug</th>
<th>Select gene and phenotype</th>
<th>Frequency in Asian subgroups</th>
<th>Increase in Asians having risk phenotype&lt;sup&gt;a,c&lt;/sup&gt;</th>
<th>Side effect/toxicity</th>
<th>CPIC recommended action if found to have an at-risk genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19 poor and intermediate metabolizer</td>
<td>0.62 (East Asians)</td>
<td>2.1x</td>
<td>Decreased antiplatelet activity (lack of efficacy)</td>
<td>Consider prescribing an alternative agent such as prasugrel or ticagrelor</td>
</tr>
<tr>
<td>Warfarin</td>
<td>VKORC rs9923231 SNP carrier</td>
<td>0.88 (East Asians)</td>
<td>2.1x</td>
<td>Excessive anticoagulation (supratherapeutic)</td>
<td>Lower dose to maintain target concentration</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>CYP2D6 intermediate or poor metabolizer</td>
<td>0.87 (East Asians)</td>
<td>1.2x for intermediate metabolizer</td>
<td>Lower drug concentrations; increased risk of cancer recurrence</td>
<td>Consider alternative hormonal therapy, such as aromatase inhibitor</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>HLA-B*5801 carrier</td>
<td>0.05 (East and Central Asians)</td>
<td>6.7x</td>
<td>Significantly increased risk of SCARs, such as SJS and TENS</td>
<td>Do not use allopurinol; may consider an alternative agent, such as febuxostat</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B*15:02 carrier</td>
<td>0.069 (East and Central Asians)</td>
<td>172x</td>
<td>Increased risk of SJS and TENS</td>
<td>Do not use carbamazepine; may consider an alternative agent</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>HLA-B*15:02 carrier</td>
<td>0.069 (East and Central Asians)</td>
<td>172x</td>
<td>Increased risk of SJS and TENS</td>
<td>Do not use oxcarbazepine; may consider an alternative agent</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>HLA-B*15:02 carrier</td>
<td>0.069 (East and Central Asians)</td>
<td>172x</td>
<td>Increased risk of SJS and TENS</td>
<td>Do not use phenytoin; may consider an alternative agent</td>
</tr>
<tr>
<td>Selective</td>
<td>CYP2C19 poor metabolizer</td>
<td>0.62 (East Asians)</td>
<td>5.8x</td>
<td>Potential for arrhythmia at supratherapeutic doses (QT prolongation for citalopram)</td>
<td>Consider 50% dose reduction and monitor response; consider alternative agent</td>
</tr>
<tr>
<td>Serotonin Reuptake inhibitors&lt;sup&gt;g&lt;/sup&gt;</td>
<td>CYP2C19 poor metabolizer</td>
<td>0.62 (East Asians)</td>
<td>5.8x</td>
<td>Potential for suboptimal response</td>
<td>Consider alternative drug not metabolized by CYP2C19, such as secondary amines nortriptyline and desipramine, or 50% dose reduction</td>
</tr>
<tr>
<td>Tricyclic</td>
<td>CYP2C19 poor metabolizer</td>
<td>0.62 (East Asians)</td>
<td>5.8x</td>
<td>Potential for suboptimal response</td>
<td>Consider alternative drug not metabolized by CYP2C19, such as secondary amines nortriptyline and desipramine, or 50% dose reduction</td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiopurines</td>
<td>NUDT15 intermediate or poor metabolizer</td>
<td>0.009</td>
<td>620x increase in East Asian for poor metabolizer</td>
<td>Increased risk of myelosuppression</td>
<td>Consider alternative drug class in nonmalignant conditions; use reduced dose of thiopurines in malignant conditions</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>CYP2C19 poor metabolizer</td>
<td>0.15</td>
<td>5.8x increase in East Asians</td>
<td>Potential for hepatotoxicity, visual disturbances, and neurologic dysfunction</td>
<td>Consider alternative agent such as liposomal amphotericin B or posaconazole</td>
</tr>
</tbody>
</table>
PHENOCONVERSION: THE ACHILLES HEEL OF PGX
• Phenocoverstion: the mismatch between the clinically observed phenotype and the genetically determined phenotype. We want to look at both drug-drug and drug-gene interaction.

• Drug-drug-gene interactions (DDGIs) impact 1 in 4 patients on medications with high evidence of PGx interactions.

• 1 in 4 patients on a PGx medication are prescribed an inhibitor or inducer of the respective enzyme.

• Strongly supports the need to account for DDGI in CDSS

• 40 million patients are on 5+ medications; this number is anticipated to double by 2040
Table 4. Ten most common EADGIs (i.e., phenoconversion) with cumulative impact on AUC.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>clopidogrel (metabolite)</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>tramadol</td>
<td>-31–50%</td>
<td>-31–50%</td>
<td>-51–80%</td>
</tr>
<tr>
<td>citalopram</td>
<td>CYP2C19 Rapid Metabolizer</td>
<td>esomeprazole</td>
<td>-31–50%</td>
<td>26–75%</td>
<td>-0–30%</td>
</tr>
<tr>
<td>clopidogrel (metabolite)</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>oxycodone</td>
<td>-31–50%</td>
<td>-31–50%</td>
<td>-51–80%</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>CYP2D6 Intermediate Metabolizer</td>
<td>bupropion</td>
<td>26–75%</td>
<td>26–75%</td>
<td>76–200%</td>
</tr>
<tr>
<td>clopidogrel (metabolite)</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>morphine</td>
<td>-31–50%</td>
<td>-31–50%</td>
<td>-51–80%</td>
</tr>
<tr>
<td>metoprolol</td>
<td>CYP2D6 Intermediate Metabolizer</td>
<td>dronedarone</td>
<td>76–200%</td>
<td>26–75%</td>
<td>&gt;200%</td>
</tr>
<tr>
<td>clopidogrel (metabolite)</td>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>hydrocodone</td>
<td>-31–50%</td>
<td>-31–50%</td>
<td>-51–80%</td>
</tr>
<tr>
<td><strong>clopidogrel (metabolite)</strong></td>
<td><strong>CYP2C19 Poor Metabolizer</strong></td>
<td><strong>tramadol</strong></td>
<td><strong>-51–80%</strong></td>
<td><strong>-31–50%</strong></td>
<td><strong>-81–100%</strong></td>
</tr>
<tr>
<td>amitriptyline</td>
<td>CYP2D6 Poor Metabolizer</td>
<td>bupropion</td>
<td>76–200%</td>
<td>26–75%</td>
<td>&gt;200%</td>
</tr>
<tr>
<td>citalopram</td>
<td>CYP2C19 Rapid Metabolizer</td>
<td>fluvoxamine</td>
<td>-31–50%</td>
<td>26–75%</td>
<td>0–30%</td>
</tr>
</tbody>
</table>

Abbreviation: area under the curve, AUC.
PAYMENT!!
MEDICARE EXPANDED PGX COVERAGE

“PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient’s condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).”

Multigene panels can be performed when (as defined in the policy):

- More than one gene is reasonable and necessary for the safe use of the drug being considered or in use
- More than one drug is in consideration or use that is associated with a gene-drug interaction (includes multi-gene coverage for TCAs and SSRIs)

https://cpicpgx.org/genes-drugs/
The use of pharmacogenetic Multi-Gene Panels (5 or more genes) to guide therapy decisions is proven and medically necessary for antidepressant and antipsychotic medications when all the following criteria are met:

- The individual has a diagnosis of major depressive disorder or generalized anxiety disorder; and
- The individual has failed at least one prior medication to treat their condition; an
- The Multi-Gene Panel has no more than 15 relevant genes.

More than one gene is reasonable and necessary for the safe use of the drug being considered or in use.

<table>
<thead>
<tr>
<th>CPT Codes*</th>
<th>Required Clinical Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>0173U</td>
<td>Medical notes documenting the following, when applicable:</td>
</tr>
<tr>
<td>0175U</td>
<td>• Diagnosis</td>
</tr>
<tr>
<td>0345U</td>
<td>• History of illness, including treatments tried and failed</td>
</tr>
<tr>
<td>81418</td>
<td>• Genes included in the panel</td>
</tr>
<tr>
<td>81479</td>
<td>• Name of lab performing test and name of test, if available</td>
</tr>
<tr>
<td></td>
<td>• Physician treatment plan based on results of genetic testing</td>
</tr>
</tbody>
</table>

*For code descriptions, refer to the Applicable Codes section.

Prior authorization process outsourced to Avalon

No documentation requirements listed in the PGx testing

NARROW coverage policy of one gene:one drug
HUNA HEALTH SERVICES
THE HUNA HEALTH VALUE

• A comprehensive medication review including all medications, Rx and OTC from all providers, and lifestyle factors that can affect enzymatic pathways

• A COMPREHENSIVE PGx panel including ~100 medications ($250)

• A pharmacist driven genomic action plan for current and future medication use and comprehensive medication report for future use

• Updates on pharmacogenomics evidence

• Proactive vs. reactive use of PGx
Physician Partnership Opps

Insured patients – flexible to work with providers to establish billing network and team-based care approach
• Pharmacist must bill and order under CPA

Narrow panels, but possible implementation

Reactive vs. proactive approach

Grant opportunities possible with partnership
BARRIERS TO STANDARDIZATION

• Lack of or Narrow Scope of Reimbursement
  • Between 15% and 20% of both privately and publicly insured individuals experience coverage disruptions or change plans each year*

• Pharmacists cannot bill independently for services in the state of Hawai‘i

• Technology has outpaced education

• Lack of electronic medical record infrastructure

• No pharmacogenomics labs on island

*JAMA Netw Open. 2022;5(2):e220320
HOT TAKES

• There is a possibility that the standard of care looks different in Hawai’i than anywhere else in the US

• Personalized prescribing is no longer ‘the future’

• Consumers are more educated than ever before
  • 23&Me testing, nutrigenomics, etc

• Pharmacists are playing a key role in PGx management and implementation across the country – team-based care models needed
“IF IT’S NOT SAFE, IT’S NOT CARE”

Dr. Tedros Adhanom Ghebreyesus
World Health Organization Director-General
2023 Global Ministerial Summit on Patient Safety
QUESTIONS?

THANK YOU!

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