Introduction to Pharmacogenomics

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Executive Summary

Pharmacogenomics (PGx) is the study of how a person's genes affect their body's response to medications, primarily focused on liver metabolism, transport, and excretion. This is important because 90% of drugs are metabolized in the liver and kidneys. Mutations in the patient's genome may impact the dose a patient needs and the patient's response to drug therapy. For example, a patient that metabolizes a drug more rapidly than the general population may require a higher-than-normal dose.

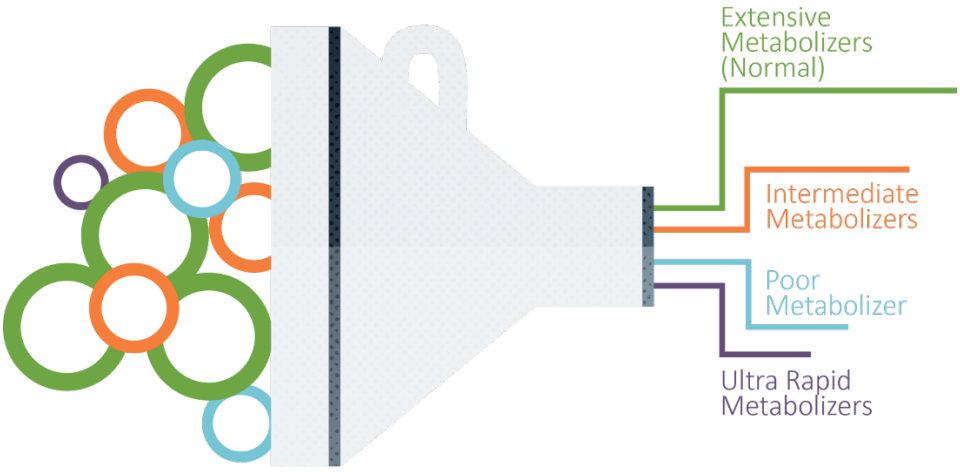
Abbreviations	
CPIC	Clinical Pharmacogenetics Implementation Consortium
FDA	Federal Drug Administration
PGx	Pharmacogenomics

How does pharmacogenomics testing work?

Enzyme function is often estimated based on an activity score. Activity scores are based on mutations present in a gene that tell whether that gene has normal function, increased function, decreased function or no function at all.

Example Activity Score for enzyme CYP2D6

Allele 1: *1 Activity Score = 1 (Normal Function)
Allele 2: *1 Activity Score = 1 (Normal Function)
Total Activity Score (sum the score for each allele) = 2 (Normal Metabolizer)



Factors outside of genetics can also cause a change in enzyme function. As a result, the activity scores based on gene mutations are adjusted based on drug interactions (enzyme inducers or inhibitors), environmental factors (smoking), liver dysfunction, and other comorbid health conditions to give a final result. This process is called phenoconversion.

Phenoconversion Example for enzyme CYP2D6

Allele 1: *1 Activity Score = 1 (Normal Function)
Allele 2: *1 Activity Score = 1 (Normal Function)
Total Activity Score (sum the score for each allele) = 2 (Normal Metabolizer)
Patient is taking bupropion which is a strong inhibitor of CYP2D6
Phenoconverted Activity Score = 2 (Total Activity Score) * 0 (adjustment for bupropion) = 0 (Poor Metabolizer)

Guidelines published by the CPIC provide recommendations that help clinicians understand how to optimize drug therapy with available genetic test results.

Table 1: Common Medications with FDA/CPIC Guidance

Gene	Medication(s)
CYP2B6	efavirenz
CYP2C9	celecoxib, ibuprofen, meloxicam, piroxicam, fluvastatin, warfarin
CYP2C19	citalopram, escitalopram, sertraline, amitriptyline, clomipramine, doxepin, imipramine, clobazam, carisoprodol, clopidogrel, omeprazole, lansoprazole, pantoprazole, dexlansoprazole, voriconazole
CYP2D6	fluvoxamine, paroxetine, vortioxetine, amitriptyline, clomipramine, doxepin, imipramine, desipramine, nortriptyline, perphenazine, thioridazine, aripiprazole, brexpiprazole, clozapine, iloperidone, amphetamine, dextroamphetamine, lisdexamfetamine, methamphetamine, atomoxetine, codeine, tramadol, hydrocodone, metoprolol, ondansetron, tamoxifen, fluoxetine, risperidone, venlafaxine
CYP3A5	tacrolimus
DPYD	fluorouracil, capecitabine
NUDT15	azathioprine, mercaptopurine, thioguanine
SLCO1B1	atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin
TPMT	azathioprine, mercaptopurine, thioguanine
UGT1A1	irinotecan
VKORC1	warfarin

Table 2: Codeine Therapy Recommendations Based on CYP2D6 Phenotype

Phenotype	Activity Score	Implications	Recommendations
CYP2D6 ultrarapid metabolizer	> 2.25	Increased formation of morphine leading to higher risk of toxicity	Avoid codeine use because of potential for serious toxicity. If opioid use is warranted, consider a non-tramadol opioid.
CYP2D6 normal metabolizer	1.25 ≤ x ≤ 2.25	Expected morphine formation	Use codeine label recommended age-specific or weight-specific dosing.
CYP2D6 intermediate metabolizer	0 < x < 1.25	Reduced morphine formation	Use codeine label recommended age-specific or weight-specific dosing. If no response and opioid use is warranted, consider a non-tramadol opioid.
CYP2D6 poor metabolizer	0	Greatly reduce morphine formation leading to diminished analgesia.	Avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid.
CYP2D6	N/A	N/A	No recommendation

CPIC Guidance for Codeine

More research is being done every day to better define genetic effects on medication outcomes. Additionally, increased understanding is needed for phenoconversion, pharmacodynamics, epigenetics and microbiome impact on drug metabolism. PGx is a valuable piece of the clinical picture, but it does not provide the only definitive information to guide medication selection or decide if a medication has a high likelihood of therapeutic success. When utilized in addition to other clinical factors, PGx can lead to more informed decisions and better outcomes.

Who may benefit from PGx and when should we consider testing?

Psychiatry: failed a medication, adverse effects, premature discontinuation, depression, anxiety, ADHD medication selection
Cardiovascular: clopidogrel usage, recurrent strokes or TIAs
Pain: chronic or acute pain issues, poor experience with prior surgery's pain medications, adverse effects, non-response
Lipids: struggling with statin selection and adverse effects
Transplant: tacrolimus dosing modifications, pain and other indications with full panel
Polypharmacy: 5-10+ medications +/- multiple chronic conditions, the more conditions and medications used to treat the conditions the higher the likelihood of drug and genetic interactions

Obtaining Avera's PGx Panel (GeneFolio®)

Order: Orderable in MEDITECH under the mnemonic "PharmGeno" or "GeneFolio."
Structured Laboratory Results: Laboratory Module → Miscellaneous tab → genotype/phenotype results + comments for reports.
Pharmacist Report: Reports entitled "Pharmacogenomics Report" signed by a pharmacist.
Lab-linked report: Laboratory Module → Scanned Lab Reports "pharmacogenomics..."
Avera Chart: Patient-viewable reports in Documents → Reports. Patients can print the full color report.
Clinical Decision Support Alerts: Populated automatically when trying to prescribe if there is an affected phenotype + medication of interest for the drug-gene pairs deployed in MEDITECH.
Re-consultation Order in MEDITECH

References

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