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# Genetic Testing for Pharmaceutical Effectiveness

# We will discuss …

How pharmacogenetic testing can improve clinical management and impact health outcomes.

Highlighting the legal implications of submitting to this testing, including the Genetic Information Nondiscrimination Act (GINA).

# Goals

Explain the principles of pharmacogenomics.

Identify utility of pharmacogenetic (PGX) testing to improve clinical management.

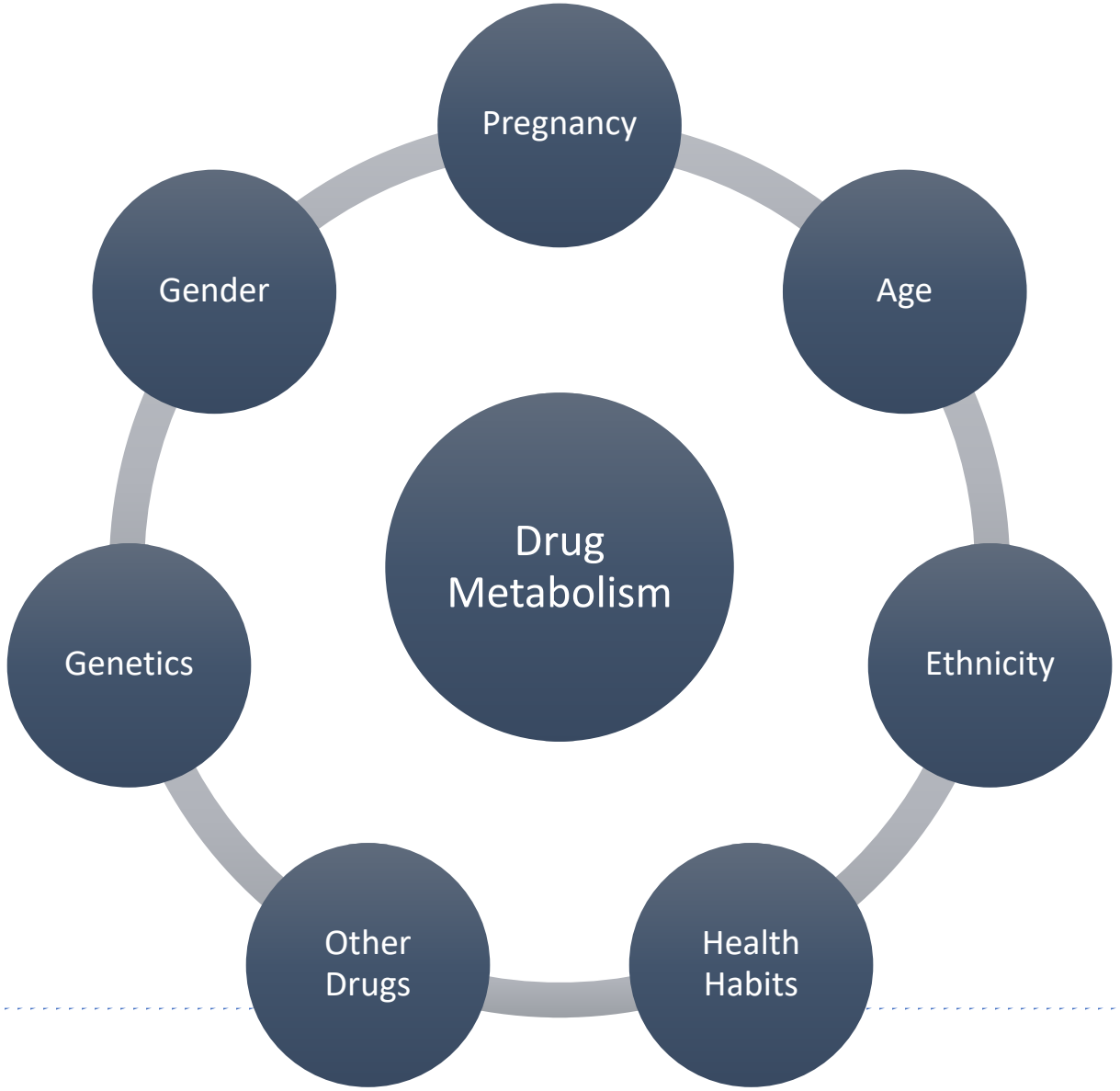
Discuss legal implications to submitting to this testing.

# Precision Medicine (PM)

- Medicine is personal
- We are all different
- PM takes individual variation into account: variation in our genes, environment, lifestyle,
- Some of our differences translate into how we react to drugs as individuals.
  - Why does someone need twice the standard dose to be effective?
  - Why does a drug work for most people but no others?
  - Why do some people have severe side-effects?

http://learn.genetics.utah.edu/content/precision/

# Some Factors Effecting Drug Metabolism



# Case Example

John is a 55-year-old construction worker who injured his back on the job 3 weeks ago resulting in a herniated disc. His symptoms include pain when he walks and when he bends over, numbness and tingling in his lower legs and feet.

Over the counter medications were not sufficient to treat the pain. John was also running the risk of stomach ulcers  due to the amount of Aleve he was ingesting.

His doctor wanted to avoid laminectomy surgery as long as possible due to John's family history blood clots.

His PCP then prescribed Tylenol with codeine to help John experience some relief.

After one week of no relief, John kept increasing the amount he was taking. The PCP then prescribed Oxycodone for three days, but it too had no impact his pain levels.

John was also prescribed Elavil to help combat depressive symptoms with minimal success.

His provider decided to do PGX testing.

# Chronic Pain from Workplace Injuries

- One third of work-related injuries that necessitate days away form work are related to musculoskeletal condition.
- Pain related to these injuries can
  - Resolve when the injury resolves
  - Can last 4-12 weeks
  - Become chronic and can persist over 4 months
- Up to 20% of those that have back pain collect benefits after at least one month following date of injury

Resource: Meshkin, Leis, Svetlana, Anand, and Devila. (2015) International Journal of Biomedical Science

# Opioid Therapy for Chronic Pain

Psychotropic medications are rarely used without opioids among claimants injured in work-related accidents.

Patients with chronic pain are most likely to use opioids and chronic pain can lead to depression.

The amount of opioids prescribed increased with claim duration.

The increasing number of psychotropic medications and the amount of opioids prescribed may put long-term claimants at risk for respiratory depression and death.

Combined use of opioids and psychotropic medication is associated with high workers' compensation cost and prolonged disability.

Resource: Tao, X., Lavin, R. A., Yuspeh, L., Weaver, V. M., & Bernacki, E. J. (2015). *Journal of occupational and environmental medicine.*

# Pennsylvania

In 2017, 170,000 worker's compensation claims

The percentage of injured workers who become long-term users of opioids is among the highest in the nation

Workers who received longer-term prescribing of opioids for work-related lower back injuries had a substantially longer duration of temporary disability.

The average lost time claim for injured workers taking opioids is 900% higher than those who did not.

Resource: PA Guidelines – Safe Prescribing for Workers Compensation (2018)

# Workers' Compensation CDC Data

https://www.cdc.gov/niosh/topics/opioids/data.html

- In 2022, 32% of workers' compensation claims with prescriptions had at least one prescription for opioids.
- Longer-term opioid prescriptions in claims were associated with temporary disabilities that were more than three times longer compared to claims that did not involve any opioid prescriptions.
- Opioid dispensing data from 27 states for 2014-2015 and found that dispensing varied by the following factors:
- **Industry.** Mining (including oil and gas) and Construction had the highest opioid dispensing rates, followed by Agriculture, Forestry, and Fishing and Public Safety.
- **Company size.** Smaller companies had higher opioid dispensing rates than larger companies.
- **Age of the injured worker.** Older workers had higher opioid dispensing rates than younger workers.
- **Type of injury.** Fractures and carpal tunnel syndrome had the highest opioid dispensing rates, followed by neurologic spine pain.
- **County-level factors.**
    - Rural areas had higher opioid dispensing rates than urban areas
    - Areas with low rates of health insurance had higher rates for opioid dispensing than areas with high rates of health insurance.

# What is Pharmacogenomics?

- Field of research that studies how a person's genes affect how he or she responds to medications.
- Part of the field of precision medicine, which aims to treat each patient individually.
- Sometimes called pharmocogenetics

Pharmacogenomics can help providers pick the right treatment option and dose for each patient.

Credit: iStock.

# The Science Behind PGX

# Pharmacogenetic testing

- Blood or saliva sample
- The test looks at DNA for a number of different genes that influence how medications are processed in the liver or at enzymes that influence how the body processes medications.
- A report is generated
- Insurance coverage varies but increasing
- Cost varies depending on types of testing (panel vs singular test). Can range from $33 to $710 (median $175)

# Drug Metabolism

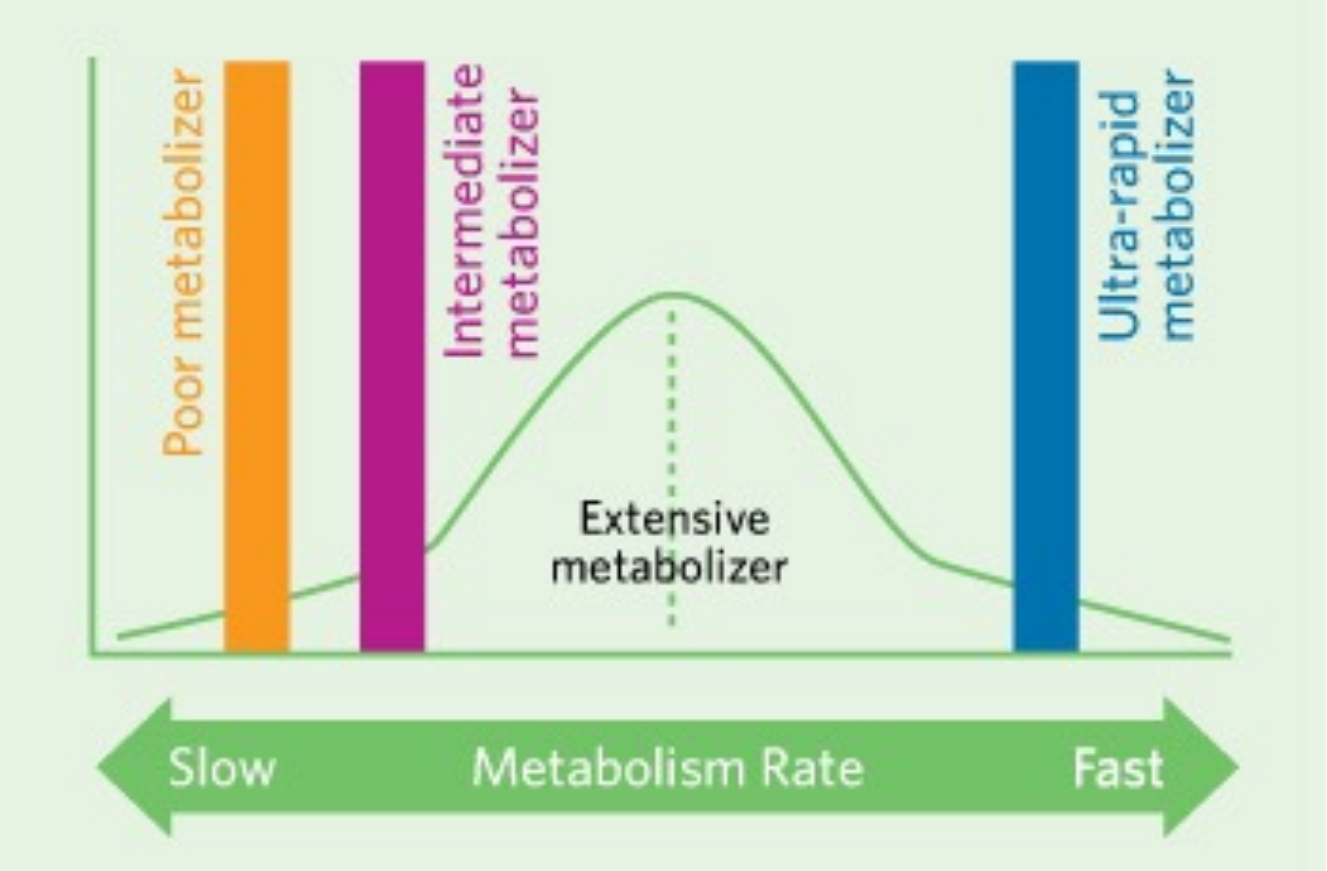
**Cytochrome P450 (CYP)**

- Superfamily of well-known drug-metabolizing enzymes
- 57 CYP genes are known in humans
- CYP1, 2 & 3 families are mainly responsible for metabolism of 80% of clinical drugs
- Drug inserts can contain PGx information, recommended or required testing language.

# Population Types

CYP alleles can result in absent, decreased, or increased enzyme activity thus affecting rate at which many drugs are metabolized

- Poor Metabolizer (PM)
- Intermediate Metabolizer (IM)
- Extensive Metabolizer (EM)
- Ultra-Rapid Metabolizer (UM)




https://adhdrollercoaster.org/wp-content/uploads/2015/06/drug_metabolism_chart.jpg

## ULTRARAPID METABOLIZER

Breaks down medications rapidly. May not get enough medication at normal doses.

## EXTENSIVE (NORMAL) METABOLIZER

Breaks down medications normally. Has normal amounts of medication at normal doses.



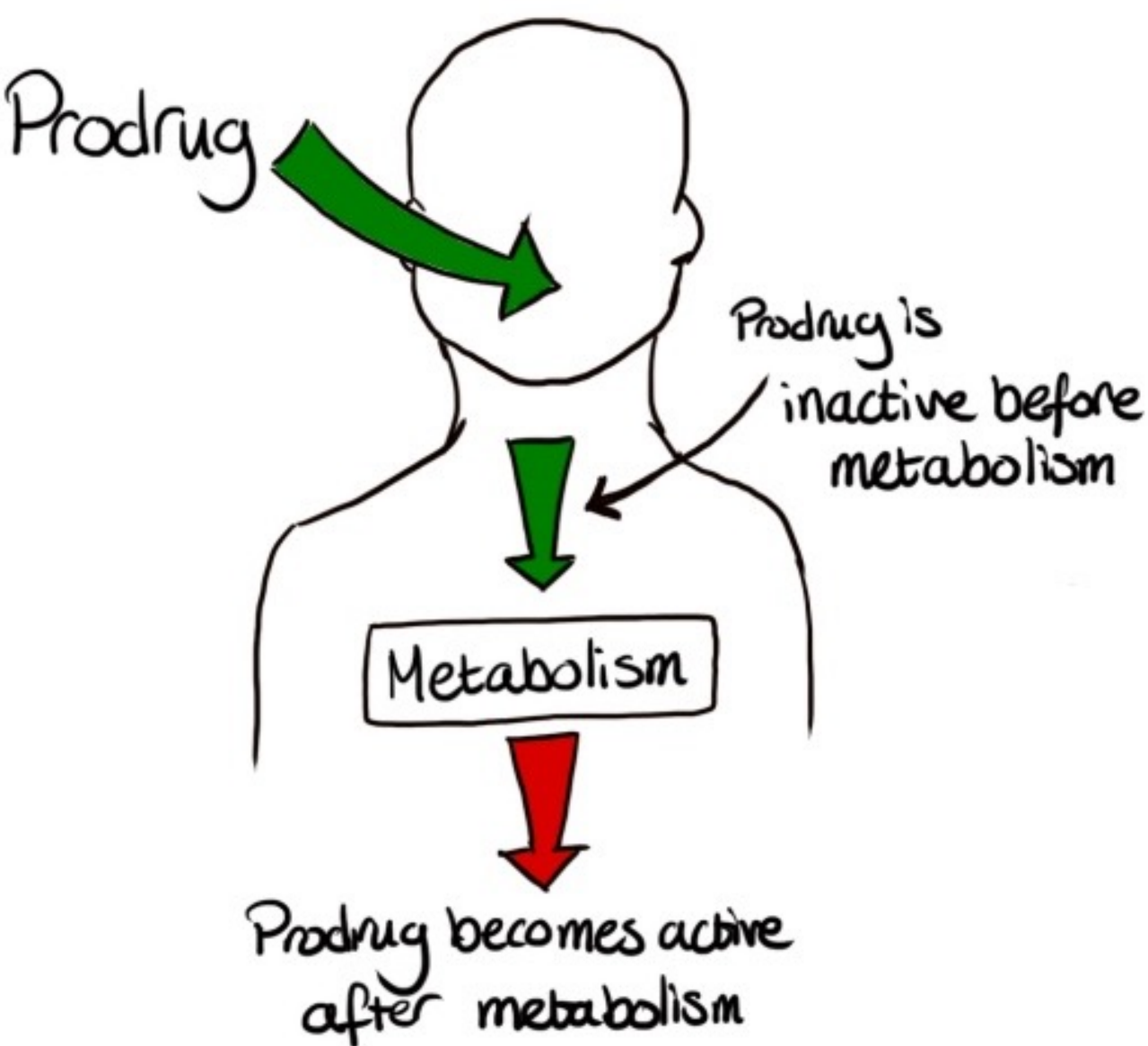
## INTERMEDIATE METABOLIZER

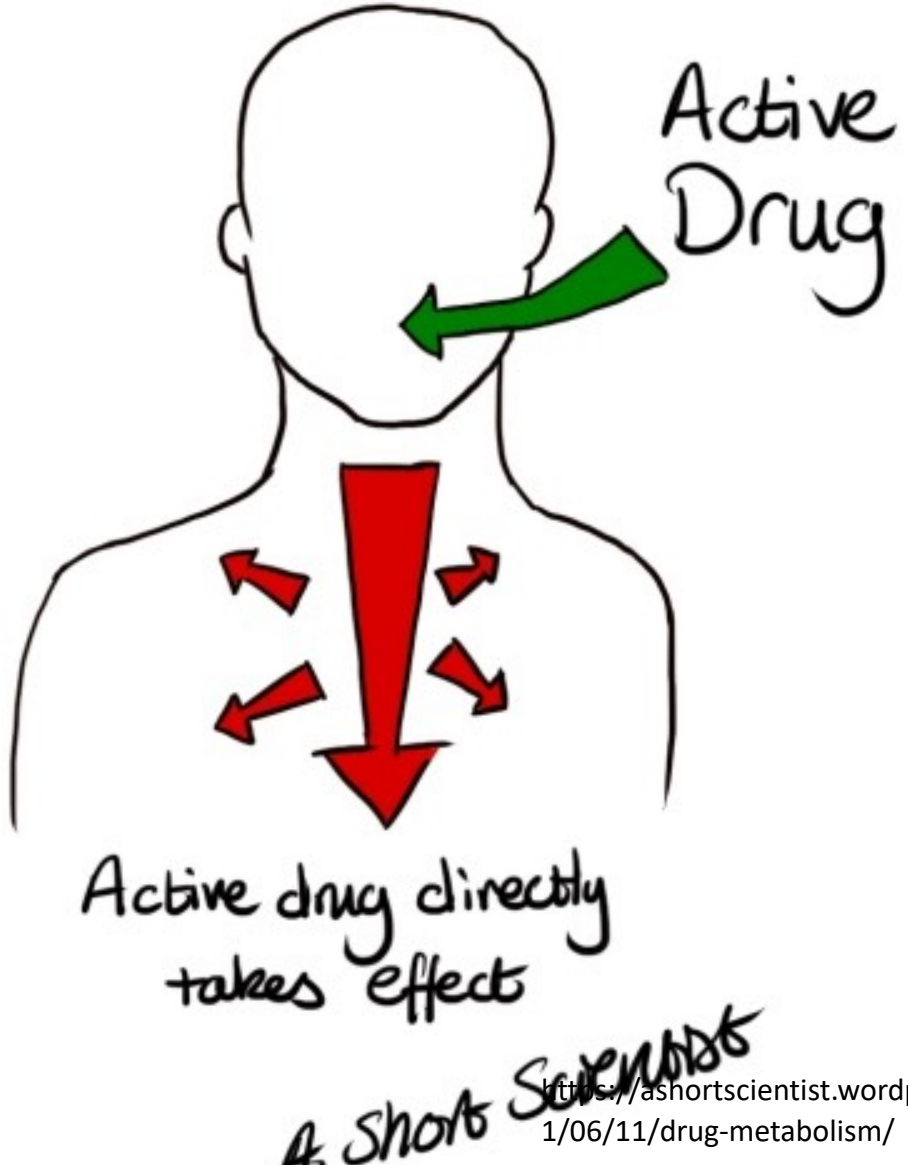
Breaks down medications slowly. May have too much medication at normal doses.

## POOR METABOLIZER

Breaks down medications very slowly. May experience side effects at normal doses.

https://genesight.com/blog/patient/how-to-minimize-antidepressant-side-effects/




https://ashortscientist.wordpress.com/2021/06/11/drug-metabolism/

selfhacked.com

| | Poor (Slow) Metabolizer | Intermediate Metabolizer | Normal (Extensive) Metabolizer | Ultra-rapid (Rapid, Fast) Metabolizer |
|---|---|---|---|---|
| **When the drug itself is active** | Much less of the drug is decomposed (deactivated). Reacts more and to lower doses. More prone to adverse effects. | Less of the drug is decomposed (deactivated). Reacts more and to lower doses. Prone to adverse effects. | Usual doses are effective. | Much more of the drug is decomposed (deactivated). The drug is less efficient and higher doses are necessary. Alternative drugs may be required. |
| **When the CYP converts the drug into the active form** | Much less of the drug is converted to its active form. The drug is less efficient and higher doses are necessary. Alternative drugs may be required. | Less of the drug is converted to its active form. The drug is less efficient and higher doses are necessary. | Usual doses are effective. | Much more of the drug is converted to its active form. Reacts more and to lower doses. More prone to adverse effects. |

https://selfhacked.com/blog/cyp-enzymes-interact-supplements-related-genes/

# Sample Report

**PATIENT:** Gene Omics2

| | | | | | |
|---|---|---|---|---|---|
| **DOB:** | 1/1/1935 | **SPECIMEN TYPE:** | Buccal Swab | **RECEIVED DATE:** | 12/30/2016 |
| **GENDER:** | Male | **COLLECTION DATE:** | 1/18/2017 | **REPORT GENERATED:** | 10/19/2017 |
| **ETHNICITY:** | | **ACCESSION #:** | P1777777 | **FACILITY/CLINIC:** | PGX HOUSE ACCOUNT |
| | | **ICD-10:** | None Specified | **ORDERING PHYSICIAN:** | |

## TEST DETAILS SUMMARY

| GENE | GENOTYPE | PHENOTYPE |
|---|---|---|
| CYP2C9 | *1/*1 | Normal Metabolizer |
| CYP2C19 | *1/*17 | Rapid Metabolizer |
| CYP3A5 | *3/*3 | Poor Metabolizer |
| CYP3A4 | *1/*1 | Normal Metabolizer |
| VKORC1 | -1639G>A G/G | Low Warfarin Sensitivity |
| Apolipoprotein E | ε3/ε4 | Altered APOE function |
| CYP2D6 | *1/*4 XN | Ultra-Rapid or Normal Metabolizer |
| CYP2B6 | *1/*1 | Normal Metabolizer |
| CYP1A2 | *1A/*1F | Normal Metabolizer - Higher Inducibility |
| SLCO1B1 | 521T>C T/T | Normal Function |
| COMT | Val158Met G/G | High/Normal COMT Activity |
| OPRM1 | A118G A/G | Altered OPRM1 Function |
| UGT2B15 | *1/*2 | Intermediate Metabolizer |
| MTHFR | 1298A>C AA<br>677C>T CC | No Increased Risk of Hyperhomocysteinemia |
| MTHFR | 677C>T CC | Normal MTHFR Activity |
| Factor II<br>Factor V Leiden | 20210G>A GG<br>1691G>A GG | No Increased Risk of Thrombosis |

# Current Patient Medications

Allegra, Lisinopril, Loratadine, Omeprazole, Warfarin, Ibuprofen, Zoloft, Adderall, Prilosec

**Omeprazole**
*Prilosec*

**Insufficient Response to Omeprazole (CYP2C19: Rapid Metabolizer)** — ACTIONABLE

- Helicobacter pylori eradication: increase dose by 100-200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 100-200%.

**Prilosec**
*Omeprazole*

**Insufficient Response to Omeprazole (CYP2C19: Rapid Metabolizer)** — ACTIONABLE

- Helicobacter pylori eradication: increase dose by 100-200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 100-200%.

**Zoloft**
*Sertraline*

**Possible Reduced Response to Sertraline (CYP2C19: Rapid Metabolizer)** — INFORMATIVE

Sertraline can be prescribed at standard label-recommended dosage and administration. If patient does not respond to recommended maintenance dosing, consider an alternative medication.

**Adderall**
*Amphetamine*

**Good Response to Amphetamine salts (COMT: High/Normal COMT Activity)** — INFORMATIVE

The patient's genotype result predicts a higher likelihood of response to amphetamine stimulants. Amphetamines should be administered at the lowest effective dose, and dosage should be individually adjusted.

**Ibuprofen**
*Advil, Motrin*

**Normal Sensitivity to Ibuprofen (CYP2C9: Normal Metabolizer)** — INFORMATIVE

Individuals with a normal CYP2C9 activity (i.e normal metabolizers) can be prescribed ibuprofen according to standard label recommended-dosage and administration.

**Warfarin**
*Coumadin*

**Less than normal Sensitivity to Warfarin (CYP2C9 *1/*1 VKORC1 -1639G>A G/G)** — ACTIONABLE

Initiation Therapy: a dose increase may be required. Consider using the following warfarin dose range as provided in the FDA-approved label: **5-7 mg/day.** OR consider using a personalized dose calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 4-5 days.

**Medications outside the scope of the report:** Allegra, Lisinopril, Loratadine

A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.

Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.

The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

**ACTIONABLE** — Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA. EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.

**INFORMATIVE** — There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

| | | | | |
|---|---|---|---|---|
| **Pain** | **Fibromyalgia Agents** | Milnacipran (Savella) | | |
| | **Muscle Relaxants** | Cyclobenzaprine (Flexeril, Amrix)<br>Metaxalone (Skelaxin)<br>Methocarbamol (Robaxin) | Carisoprodol (Soma)<br>Tizanidine (Zanaflex) | |
| | **NSAIDs** | Celecoxib (Celebrex)<br>Diclofenac (Voltaren)<br>Flurbiprofen (Ansaid)<br>Ibuprofen (Advil, Motrin)<br>Indomethacin (Indocin)<br>Ketoprofen (Orudis)<br>Ketorolac (Toradol)<br>Meloxicam (Mobic)<br>Nabumetone (Relafen)<br>Naproxen (Aleve)<br>Piroxicam (Feldene)<br>Sulindac (Clinoril) | | |
| | **Opioids** | Alfentanil (Alfenta)<br>Buprenorphine (Butrans, Buprenex)<br>Hydromorphone (Dilaudid, Exalgo)<br>Levorphanol (Levo Dromoran)<br>Meperidine (Demerol)<br>Methadone (Dolophine)<br>Oxymorphone (Opana, Numorphan)<br>Sufentanil (Sufenta)<br>Tapentadol (Nucynta) | Dihydrocodeine (Synalgos-DC)<br>Fentanyl (Actiq)<br>Hydrocodone (Vicodin)<br>Morphine (MS Contin)<br>Oxycodone (Percocet, Oxycontin) | Codeine (Codeine; Fioricet with Codeine)<br>Tramadol (Ultram) |

# Psychiatry

- One in five U.S. adults live with a mental illness (57.8 million in 2021)
- 30%–50% of patients with major depressive disorder (MDD) do not respond to the first antidepressant prescribed
- There are 25,000 emergency visits per year due to antidepressant-induced adverse events
- Workers Compensation Costs
  - Average medical cost for claims with opioids alone was $28,563 with a closure rate of 89.1%;
  - Average cost of a combination of benzodiazepines and opioids was $53,366 with a closure rate of 75.8%;
  - The combination of antidepressants and opioids resulted in average medical costs of $64,507 with a 64.8% closure rate;
  - The average cost of claims with antidepressants, benzodiazepines, and opioids was $93,667 with a closure rate of 58.3%.

***PGx test results and recommendations can provide greater symptom improvement, higher response rates, and individuals were more likely to reach remission than those who received treatment as usual.***

# Health Outcomes

- Avoids trial and error prescribing
- Reduces cost of multiple prescriptions & improves adherence
  - PGx saved pharmacy cost $2774.53 for psychiatric population while improving adherence (Winner, et al., 2015)
- Minimizes lost days of work
- Reduces potential effects of Adverse Drug Events (ADE's)
  - $ 30.1 billion annually (Sultana, Cultroneo, Trifiro, 2013)
- Minimizes death due to overdose
- Medicare and other plans now cover testing, some without co-pay or deductibles

# GENETIC INFORMATION NONDISCRIMINATION ACT ("GINA")

42 U.S.C. 2000ff

Effective since November 21, 2009

# Overview of GINA

**GINA prohibits and regulates the acquisition and use of genetic information by health insurance providers and employers:**

- Title I: Regulates Health Insurance Providers
- Title II: Regulates Employers

Congress recognized that genetic testing allows for early detection of illness and to reduce likelihood of contracting disorders, but also **"gives rise to the potential misuse of genetic information to discriminate in health insurance and employment."**

- Genetic conditions/disorders are associated with race, ethnic groups, and gender
- Groups may be stigmatized or discriminated against

# Application of GINA

**Protects:** Applicants for employment, employees, and former employees

| | | |
|---|---|---|
| Private Employers (15 or more employees) | Many state and federal government employees | Employees hired through employment agencies |

# GINA Employment Prohibitions

- Discrimination based on genetic information of any employee or a family member of that employee
  - Refusal to hire or refer for employment;
  - Discharge;
- Limiting, segregating, or classifying employees in any way that would deprive or tend to deprive any employee of employment opportunities or otherwise adversely affect the status of the employee as an employee
- To cause or attempt to cause another covered entity or its agent to discriminate
- Retaliating against employees for opposing any unlawful act or practice under GINA

# GINA Employment Prohibitions (continued)

- Requesting, requiring, or purchasing genetic information with respect to an employee or a family member of that employee, including
  - Conducting an Internet search on an individual in a way that is likely to result in a covered entity obtaining genetic information
  - Actively listening to third-party conversations
  - Searching an individual's personal effects for the purpose of obtaining genetic information
  - Making requests for information about an individual's current health status in a way that is likely to result in a covered entity obtaining genetic information

# Relevant Definitions

- **Genetic Information**
  - 1) genetic tests,
    - Genetic tests include analysis of human DNA, RNA, chromosomes, proteins or metabolites, that detects genotypes, mutations or chromosomal changes
  - 2) genetic tests of family members and
  - 3) manifestation of a disease or disorder in family members

  - **Does not include** information about sex, age, or a *manifested* (as opposed to a possible future) disease, disorder, or pathological condition that has or may have a genetic basis.
    - Examples of nongenetic tests include HIV tests, cholesterol tests, or drug/alcohol tests

# Relevant Definitions

**Family** – Defined as a dependent of the employee or up to a fourth degree relative

- **First-degree relatives: parents, siblings, and children.**
- **Second-degree relatives:** grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings.
- **Third-degree relatives:** great-grandparents, great grandchildren, great uncles/aunts, and first cousins.
- **Fourth-degree relatives:** great-great-grandparents, great-great-grandchildren, and first cousins once-removed (i.e., the children of the individual's first cousins).

# Exceptions to Seeking Genetic Information Under GINA

- Inadvertent requests for such information
  - **<u>When seeking medical information</u>, receipt is not generally inadvertent unless the provider is directed not provide such information or the request was not "likely to result in a covered entity obtaining genetic information."**
- Related to health or genetic services offered by the employer (such as a wellness program)
  - Requires prior *<u>voluntary</u>* written authorization;
  - With only the employee and the healthcare professional or genetic counselor receiving the results; and
  - With the genetic information only being available for the purposes of that service and not disclosed to the employer unless under aggregate terms that do not disclose the identity of employees
- Complying with certification provisions under Family Medical Leave Act certifications or other medical leave laws

# Exceptions Pertaining to Seeking Genetic Information Under GINA (continued)

- Where an employer purchases documents commercially or publicly available that include family medical history
  - Excluding a variety of sources, such as medical databases, court records, research databases, or sources accessed with the intent of obtaining such information or where such information would likely be contained
- For genetic monitoring of the biological effects of toxic substances in the workplace, provided:
  - Employee receives written notice of the monitoring;
  - Prior voluntary written authorization or a legal requirement;
  - Employee is informed of the monitoring results
  - The monitoring complies with state and federal regulations; and
  - The employer only receives the results in aggregate terms that do not disclose the identity of employees
- Conducting DNA analysis for law enforcement purposes as a forensic laboratory or for human remains identification, but only for purposes of quality control or sample contamination

# Confidentiality of Genetic Information

**Genetic information possessed must be kept confidential**

- **Such information must be maintained:**
  - On separate forms;
  - In medical files separate from personnel files; and
  - Be treated as confidential medical record of the employee or member.
- **Can only be disclosed under certain circumstances:**
  - To the employee or family member, upon written request
  - To an occupational or other health researcher if the research complies with federal regulations
  - In response to a court order, limited to the information authorized and with knowledge of the employee
  - As relevant to government officials investigating compliance with GINA
  - To the extent made in compliance with the certification provisions of the Family and Medical Leave Act or other medical leave laws
  - To a government public health agency regarding the manifestation of a disease or disorder in family members of an individual that concerns a contagious disease that presents and immediate hazard of death or life-threatening illness, with notice to the employee

# GINA Enforcement

- Administrative Exhaustion Requirement
  - An aggrieved employee must exhaust their administrative remedies by filing a charge with the EEOC within 180 days of the adverse action
- Remedies
  - There is a right to a private cause of action
  - Same remedies as a Title VII violation
    - ✓ Compensatory Damages (limited by number of employees)
    - ✓ Punitive Damages
    - ✓ Attorneys' fees and costs
    - ✓ Injunctive relief, including reinstatement and hiring, back pay, and other equitable remedies

# Workers' Compensation Considerations

- An employer or its agent (including physicians) **MAY NOT**:
  - Preemptively attempt to screen workers for those likely to expose them to later workers' compensation claims;
    - Such as: Screening firefighters or coal-miners for a predisposition to lung cancer, individuals with excitable jobs for heart-related diseases, manual laborers for degenerative diseases, etc.
  - Request genetic information to preemptively defend against later possible claims.
- GINA explicitly states it does not "limit or expand the protections, rights, or obligations of employees or employers under applicable workers' compensation laws," but this must be closely followed:
  - Carefully follow the rights that are provided under workers' compensation laws, as there is limited other guidance in this area
  - Limited litigation in this realm
    - Use caution in requesting relevant documentation and consider using carve-outs for family information
    - Be careful as to how workers' compensation files, which may contain this information, are stored

# Relevant Cases

- *See Bronsdon v. City of Naples*, No. 2:13-cv-778-FtM-29CM, 2014 U.S. Dist. LEXIS 70502 (M.D. Fla. May 22, 2014)
  - Court found a plausible GINA claim when defendant considered family genetic information obtained without consent in denying WC benefits, despite that actual utilization of the evidence at the hearing was legal under Florida Workers' Compensation law.
- *See Lowe v. Atlas Logistics Grp. Retail Servs. Atlanta, LLC*, 102 F. Supp. 3d 1360, 1361 (N.D. Ga. 2015)
  - Judgment was entered against Atlas Logistics for DNA testing two employees, despite that the testing had a purported legitimate purpose and no basis in genetic discrimination.