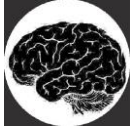|	**SKILLS CENTER** **STANDARD OPERATING PROCEDURE**	**A BIOFIZZ** **PRODUCTON**
PharmGKB **Module Hours: 2.5**	**Effective Date:02/26/2025** **PRQs:** **Intro Lab Meeting**	**Revision 1.1** **Author: S. Yaldoo** **Checked by** **Editor: J. Young**

1. Background

The same drugs can affect different people differently. Therefore, it is important to understand how genetic differences affect drug outcomes and ensure that drug administration is effective without side effects. The study of drug-gene interactions is called pharmacogenetics, and it plays a central role in personalized medicine research.
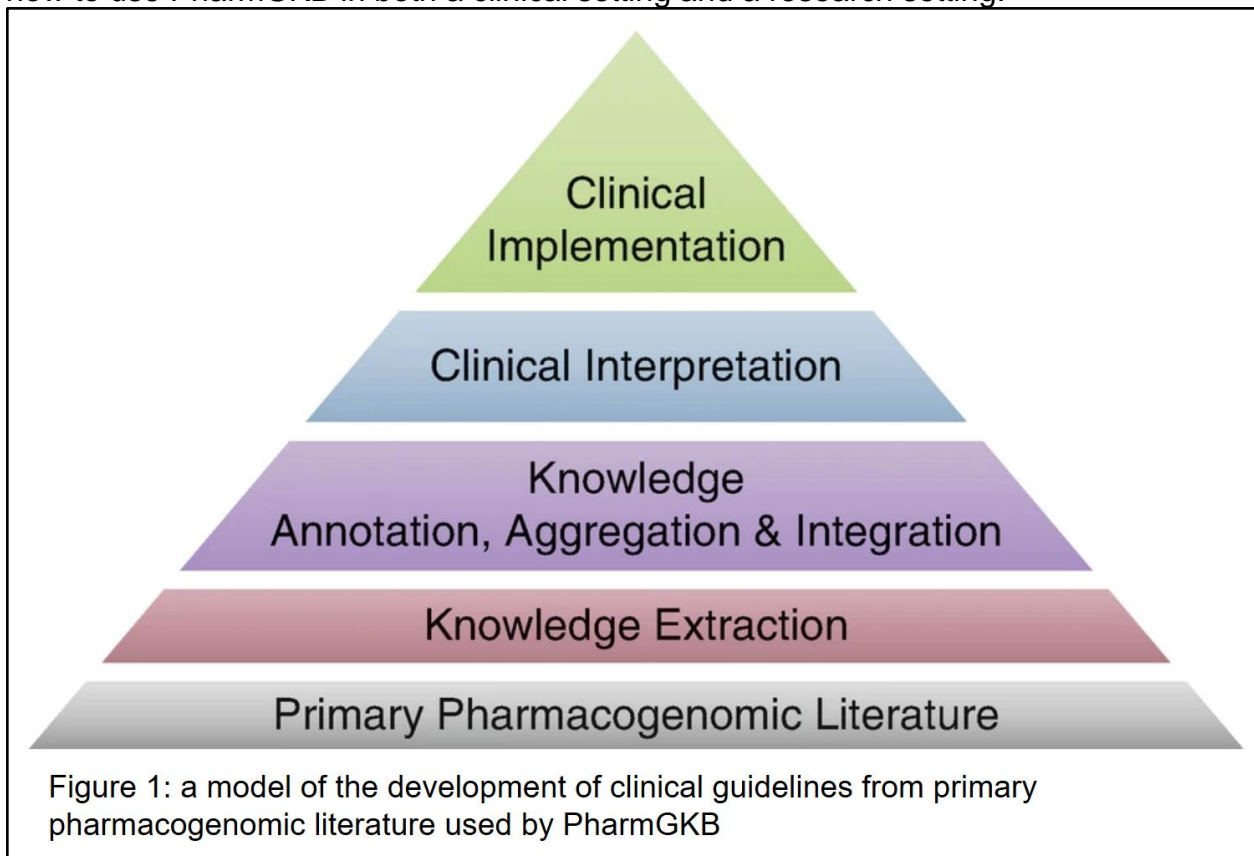
One pharmacogenetics tool is PharmGKB. Developed by Stanford University in 2000 with funding from the U.S. National Institutes of Health (NIH), PharmGKB aggregates pharmacogenetic information from the scientific literature, regulatory agencies such as the U.S. Food and Drug Administration (FDA), and professional organizations like the Clinical Pharmacogenetics Implementation Consortium (CPIC). Some information aggregated includes gene-based drug prescription guidelines, drug mechanisms of action, and the primary and secondary literature from which this information is collected. The site can be used to find pharmacogenetics information by gene or by drug, including guideline recommendations on prescribing drugs by patient genotype.

2. Purpose

The purpose of this module is to train students on the use of the PharmGKB tool and familiarize students with basic pharmacogenetic concepts. Students should understand

how to use PharmGKB in both a clinical setting and a research setting.

Figure 1: a model of the development of clinical guidelines from primary pharmacogenomic literature used by PharmGKB

3. Scope

3.1. This procedure applies to qualified skills center users.

4. Responsibility

4.1. It is the responsibility of the user to understand and perform the procedure described in this document.

4.2. It is the responsibility of the user to fully document any deviations from the written procedure.
4.3. It is the responsibility of the user to become trained on and display mastery of the procedure.

5. Definitions

5.1. Alleles: one of the potentially many DNA sequences for a copy of a gene.
5.2. Drug-gene interactions: a difference in a drug's effect on different genotypes
5.3. Gene variants: same as an allele
5.4. Genotypes: a set of alleles of a gene carried by an individual or population of cells
5.5. Personalized medicine: the practice of considering patient characteristics to optimize therapeutic efficacy
5.6. Pharmacogenetics: the study of drug-gene interactions
5.7. Pharmacogenomics: typically used interchangeably with pharmacogenetics
5.8. Star allele notation: a notation using *N to denote alleles of a gene, where N is a number. Genotypes are sometimes denoted as *NxM/*O, where *N and *O are alleles, and M represents the copy number of the *N gene.

6. Materials/Equipment

6.1. PharmGKB: www.pharmgkb.org

7. Procedures

7.1. Go to the PharmGKB website.
7.2. At the top of the home page, the following will be found:
    7.2.1. Search bar
    7.2.2. Clinical guidelines: a collection of all entries for information from professional organization guidelines

7.2.3. Drug label annotations: a collection of all entries for information from regulatory agencies

7.2.4. Curated pathways: a collection of all entries for the biochemical mechanisms of drugs

Figure 2: the home page of PharmGKB

7.3. Further down the home page, the following will be found

7.3.1. Very important pharmacogenes: a collection of entries on genes considered to have great pharmacological importance

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Figure 3: the home page of PharmGKB, continued
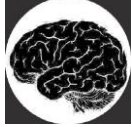
7.4. PharmGKB's search bar can be used to find pharmacogenetic information. A query for "codeine" will be used as an example. Filters are available to limit search results:

7.4.1. "Chemical" filter: this filter limits results to compound pages

7.4.2. "Gene" filter: this filter limits results to gene pages

7.4.3. "Pathway" filter: this filter limits results to curated pathways

7.4.4. "Literature" filter: this filter limits results to literature entries, including primary scientific literature and secondary literature guidelines

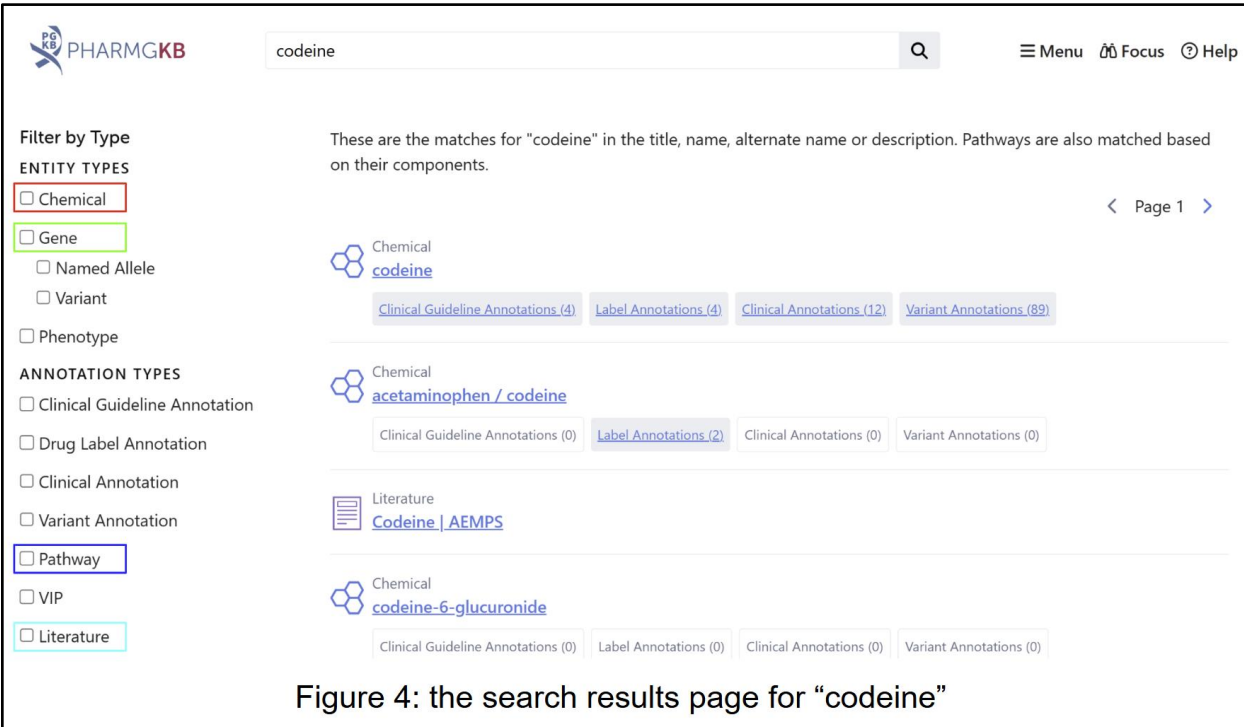|	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ PRODUCTON
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Figure 4: the search results page for "codeine"

7.5. In a drug pathways entry, a diagram of the biochemical pathway affected by the drug is presented. This is followed by a textual description of the drug's biochemical mechanism.

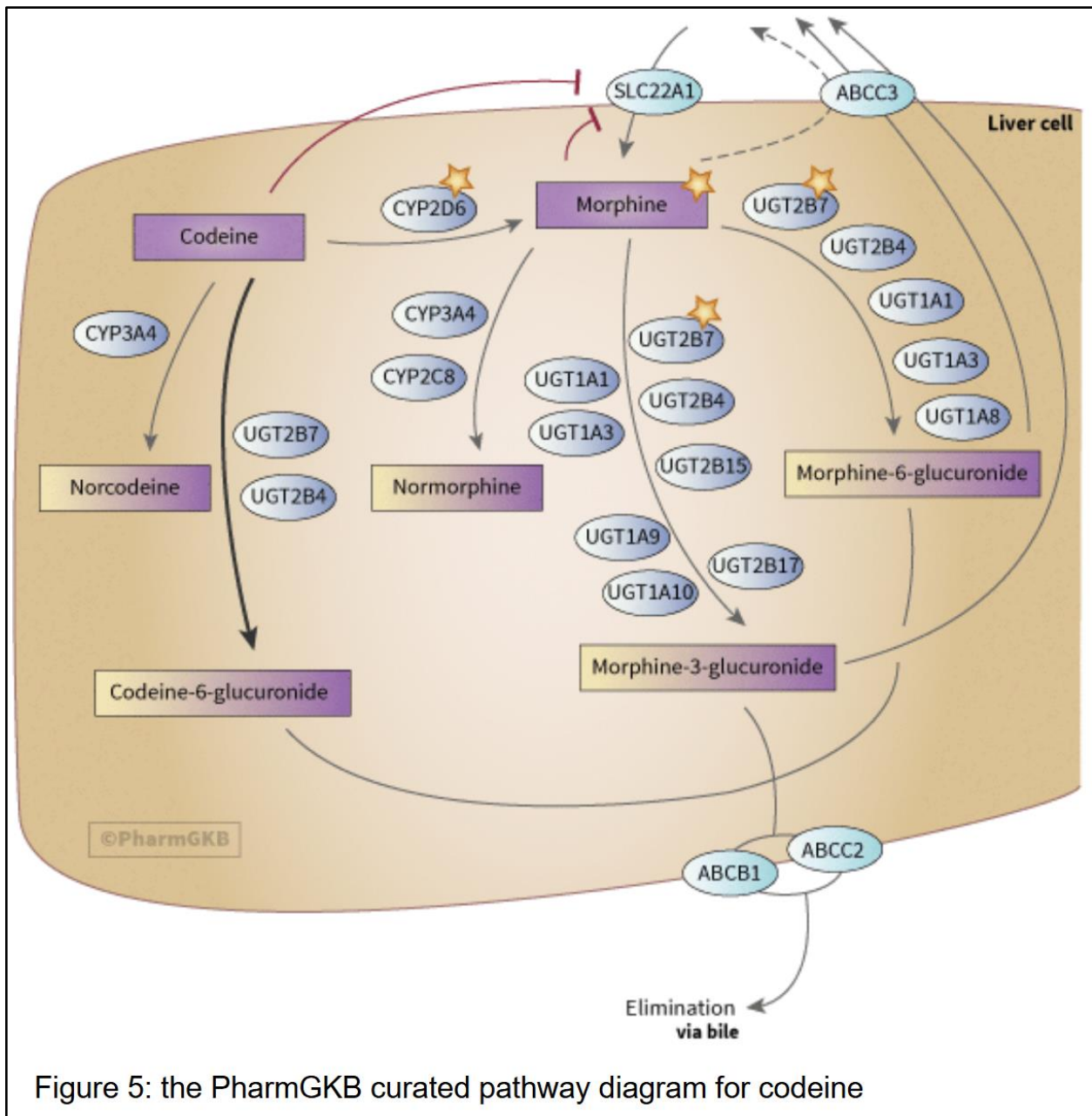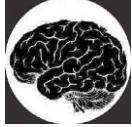| ![CU Buffalo logo]	**SKILLS CENTER** **STANDARD OPERATING PROCEDURE**	**A BIOFIZZ** ![brain logo] **PRODUCTON**
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Figure 5: the PharmGKB curated pathway diagram for codeine

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7.6. In a chemical entry, a variety of pharmacogenetic information could be found. These are organized into tabs including:

    7.6.1. Prescribing Info: information relevant to the clinical use of a drug

    7.6.2. Drug Label Annotations: information from regulatory agencies. May replicate information in the "prescribing info" section

    7.6.3. Clinical Annotations: information of individual gene allele's pharmacogenetic implications for a drug

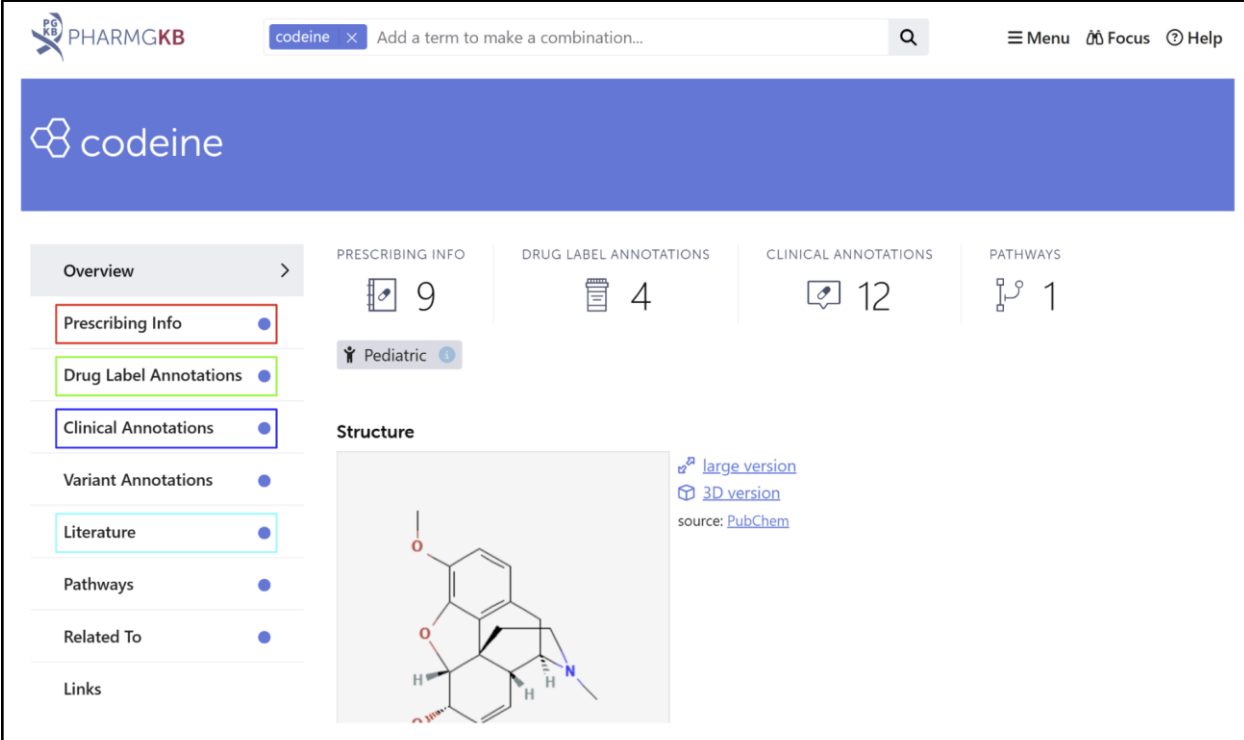   7.6.4. resources on a drug's pharmacogenetics

Figure 6: the PharmGKB entry for codeine

7.7. The **Prescribing Info** tab provides an overview of a drug's clinical pharmacogenetic considerations

    7.7.1. A clinical guideline table is often available summarizing guidelines from professional organizations

7.7.1.1.1. The professional organization that issued each clinical guideline is listed in the Source column

7.7.1.1.2. Gene pages associated with each clinical guideline is available in the Genes column

7.7.1.1.3. ***No recommendation*** appears in the Title column of clinical guideline entries that makes no recommendations

7.7.1.1.4. Clicking on the **Details** button or the Title column link will open the clinical guideline annotation with more information

Figure 7: Prescribing Info page clinical guidelines table, codeine

7.8. A clinical guideline page summarizes a published guideline

7.8.1. The **Summary** section appears at the top of the annotation

7.8.2. Recommendations for a genotype can be viewed using the **genotype picker**

Figure 8: clinical guideline annotation summary and genotype picker for codeine and CYP2D6

7.8.3. Additional details and a link to the original guideline can be found below the summary.

7.8.3.1.1. All CPIC guideline annotations feature a video summary.

7.8.3.1.2. Tables are often available to summarize guideline recommendations, but differences may exist in content and organization
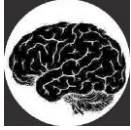
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Table 1: Codeine therapy recommendations based on CYP2D6 phenotype

Adapted from Tables 1 and 2 of the guideline.

ⓘ Scroll for more

PHENOTYPE[a]	ACTIVITY SCORE RANGE	ACTIVITY SCORE[b]	EXAMPLES OF CYP2D6 DIPLOTYPES[b]	IMPLICATIONS	RECOMMENDATIONS	CLASSIFICAT RECOMMEN
CYP2D6 ultrarapid metabolizer	>2.25	>2.25	*1/*1xN, *1/*2xN, *2/*2xN[c]	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.	Strong
CYP2D6 normal metabolizer	1.25 <= x <= 2.25	1.25 1.5 1.75 2.0 2.25	*1/*10 *1/*41, *1/*9 *10/*41x3 *1/*1, *1/*2 *2x2/*10	Expected morphine formation	Use codeine label recommended age- or weight-specific dosing	Strong
CYP2D6 intermediate	0 < x < 1.25	0.25 0.5 0.75	*4/*10 *4/*41, *10/*10 *10/*41	Reduced morphine	Use codeine label recommended age- or weight-specific dosing. If no response and opioid	Moderate
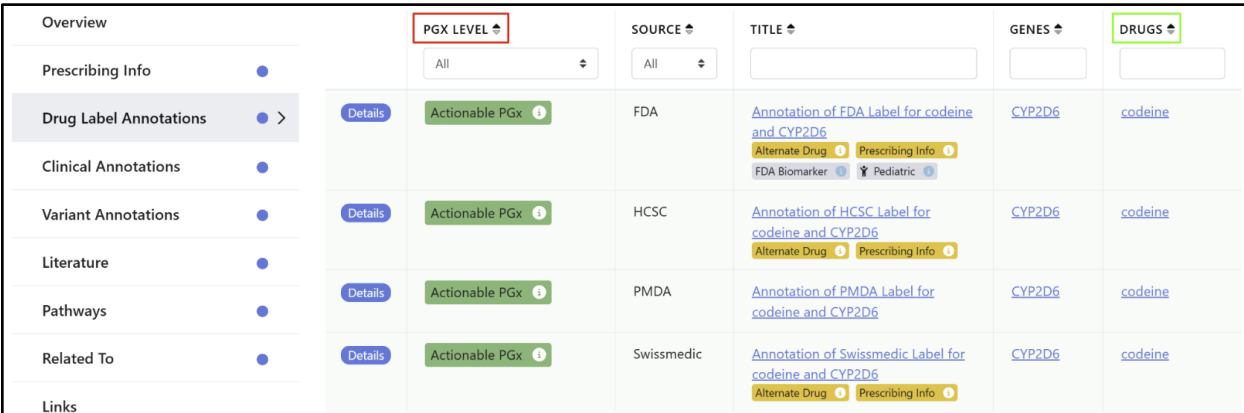
Figure 9: clinical guideline table for codeine and CYP2D6

7.9. The **Drug Label Annotations** tab summarizes guidelines from regulatory agencies

7.9.1. The PGx level column indicates the significance of the drug-gene interaction described by a drug label. From strongest to weakest, they are Testing Required , Testing Recommended , Actionable PGx , Informative PGx , and No Clinical PGx . Criteria Not Met indicates that a drug label provides no pharmacogenetic information. More details can be found here.

7.9.2. The Drugs column lists the specific drug types affected by a drug guideline recommendation. This is important for entries covering multiple drugs.

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Figure 10: drug label annotations table for codeine

7.10. The **Literature** tab summarizes some literature associated with a drug.

Figure 11: literature tab for codeine

8. Troubleshooting

8.1. What if I don't see any entries for a drug?

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8.1.1. Your drug may not be sufficiently researched. In this case, you may need to choose another drug.

8.1.2. If you do not see expected tabs, you are likely looking at a different entry type than expected. For example, a "chemicals" annotation contains the "Prescribing Info" tab, but a "pathways" annotation does not.

9. References

"Clinical Guideline Annotation Legend." *PharmGKB*, https://www.pharmgkb.org/page/clinicalGuidelineLegend. Accessed 13 Jan. 2025.

"Drug Label Information and Legend." *PharmGKB*, https://www.pharmgkb.org/page/drugLabelLegend. Accessed 12 Jan. 2025.
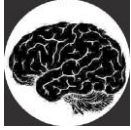
Hall, Kristopher R., and Tamer E. Fandy. "Pharmacogenomics and Pharmacoepigenomics: Impact on Therapeutic Strategies." *Genomics-Driven Healthcare*, Adis, Singapore, 2018, pp. 227–38. *link.springer.com*, https://doi.org/10.1007/978-981-10-7506-3_12.

"I Am a Researcher." *PharmGKB*, https://www.pharmgkb.org/page/iAmAResearcher. Accessed 13 Jan. 2025.

"PharmGKB History." *PharmGKB*, https://www.pharmgkb.org/page/history. Accessed 13 Jan. 2025.

Thorn, Caroline F., et al. "PharmGKB: The Pharmacogenomics Knowledge Base." *Methods in Molecular Biology (Clifton, N.J.)*, vol. 1015, 2013, pp. 311–20. *PubMed Central*, https://doi.org/10.1007/978-1-62703-435-7_20.

Walkthrough of the PharmGKB Website. Directed by PharmGKB, 2022. *YouTube*, https://www.youtube.com/watch?v=Yuja_6JRsFw.

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10. Module Methods Task (MMT)

10.1. Briefly describe the function of the CYP2D6 gene.

10.2. Determine the star allele nomenclature for a gene in a person with one copy of the *1 allele and three copies of the *12 allele.

10.3. Choose a drug for tasks 10.4–10.10 below. Make sure enough information exists to answer the questions below. You may not choose codeine.

10.4. Briefly describe the mechanism of action for this drug.

10.5. Describe **one** pharmacogenetic guideline recommendation for this drug (not including "no guideline" recommendations).

10.6. Describe one genotype listed in this guideline.

10.7. Explain the clinical significance of this guideline.

10.8. How is this guideline supported or refuted by primary literature evidence? Cite any papers considered.

10.9. Identify a future research direction for your chosen drug.

10.10. Explain why this future research direction could be meaningful.