
	<p style="text-align: center;">SKILLS CENTER</p> <p style="text-align: center;">STANDARD OPERATING PROCEDURE</p>	<p style="text-align: center;">A BIOFIZZ</p>  <p style="text-align: center;">PRODUCTON</p>
<p style="text-align: center;">PharmGKB</p> <p style="text-align: center;">Module Hours: 2.5</p>	<p style="text-align: center;">Effective Date:02/26/2025</p> <p style="text-align: center;">PRQs: Intro Lab Meeting</p>	<p style="text-align: center;">Revision 1.1 Author: S. Yaladoo</p> <p style="text-align: center;">Checked by Editor: J. Young</p>


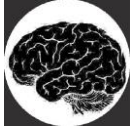
1. Background

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.

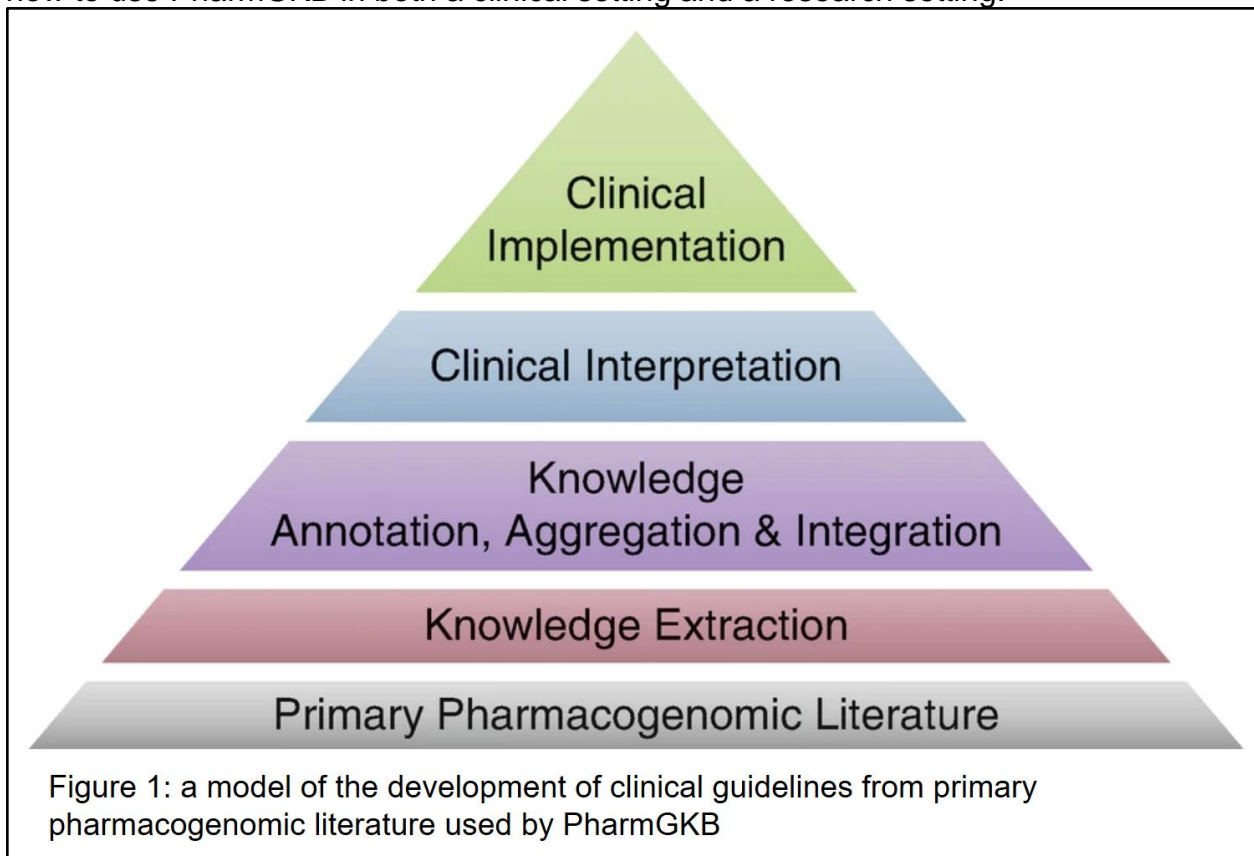
One pharmacogenetics tool is PharmGKB. Developed by Stanford University in 2000 with funding from the U.S. National Institutes of Health (NIH), PharmGKB aggregates pharmacogenetic information from the scientific literature, regulatory agencies such as the U.S. Food and Drug Administration (FDA), and 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

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





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.

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- 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](http://www.pharmgkb.org).
- 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

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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

PHARMGKB Publications Blog Downloads Contact Focus Help

Search PharmGKB

Search for a molecule, gene, variant, or combination

Want Personalized PGx Recommendations?
 Try the [GSI \(Genotype Selection Interface\)](#) to access and compare pharmacogenomic prescribing information from CPIC, DPWG, and FDA based on the genotypes you enter.
 Try [DDRx \(DNA-Driven Prescribing\)](#) to access the same prescribing information with a focus on actionability in a mobile-centric web app.

Interested in Pediatric Pharmacogenomics?
 Read about pediatrics on PharmGKB through the [Pediatric Dashboard](#). Turn on the Pediatric Focus (using the Focus menu above) to highlight available pediatric information. See [Pediatric Help](#) for more information.

Clinical Guideline Annotations 207

Drug Label Annotations 1,188



FDA Drug Label Annotations 481

Curated Pathways 255

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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Annotations				
Clinical	 CLINICAL GUIDELINE ANNOTATIONS	207	Research	
	 DRUG LABEL ANNOTATIONS	1,188	 PATHWAYS	255
	 FDA DRUG LABEL ANNOTATIONS	481	 VIPs (Very Important Pharmacogenes)	34
	 CLINICAL ANNOTATIONS	5,179	 VARIANT ANNOTATIONS	28,226
			 ANNOTATED DRUGS	831

Figure 3: the home page of PharmGKB, continued


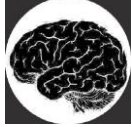
7.4. PharmGKB’s search bar can be used to find pharmacogenetic information. A query for “codeine” will be used as an example. Filters are available to limit search results:

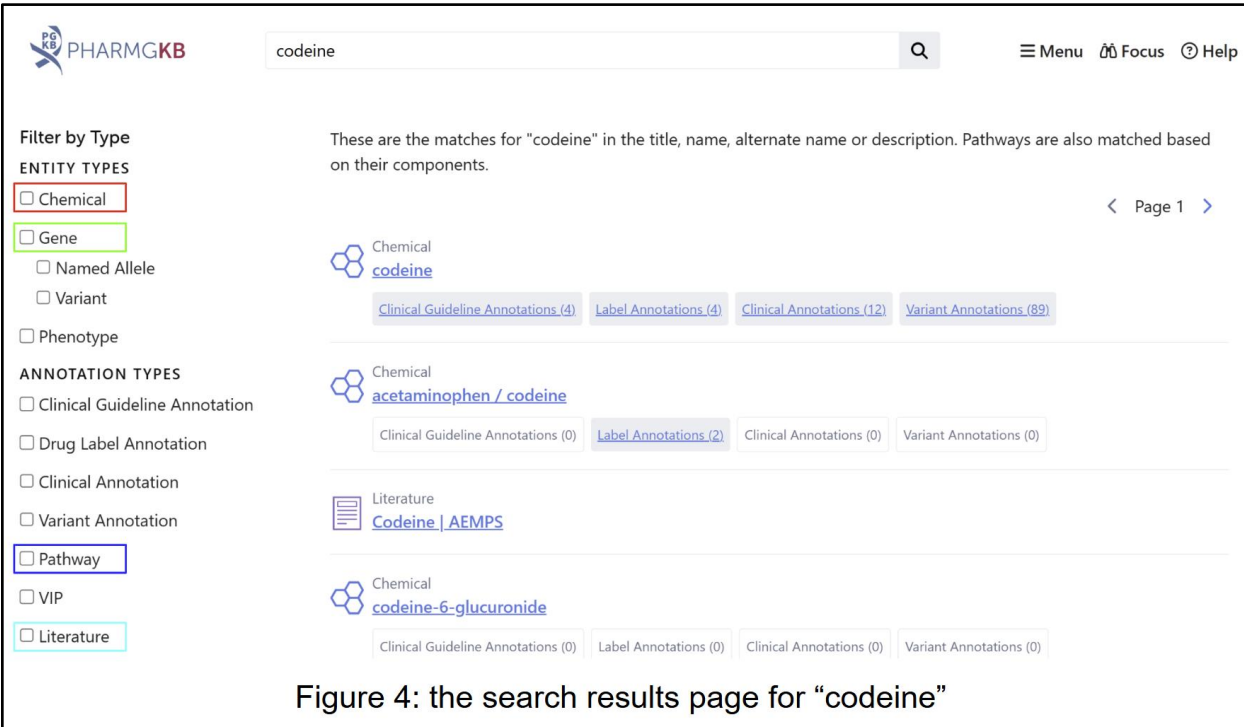
7.4.1. “**Chemical**” filter: this filter limits results to compound pages

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

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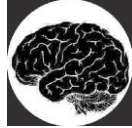


The screenshot shows the PharmGKB search interface. The search bar contains 'codeine'. The left sidebar has filters for 'Filter by Type' (ENTITY TYPES: Chemical, Gene, Phenotype) and 'ANNOTATION TYPES' (Clinical Guideline Annotation, Drug Label Annotation, Clinical Annotation, Variant Annotation, Pathway, VIP, Literature). The main content area shows search results for 'codeine' with the following entries:

- Chemical codeine**: Clinical Guideline Annotations (4), Label Annotations (4), Clinical Annotations (12), Variant Annotations (89)
- Chemical acetaminophen / codeine**: Clinical Guideline Annotations (0), Label Annotations (2), Clinical Annotations (0), Variant Annotations (0)
- Literature Codeine | AEMPS**
- Chemical codeine-6-glucuronide**: Clinical Guideline Annotations (0), Label Annotations (0), Clinical Annotations (0), Variant Annotations (0)

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.

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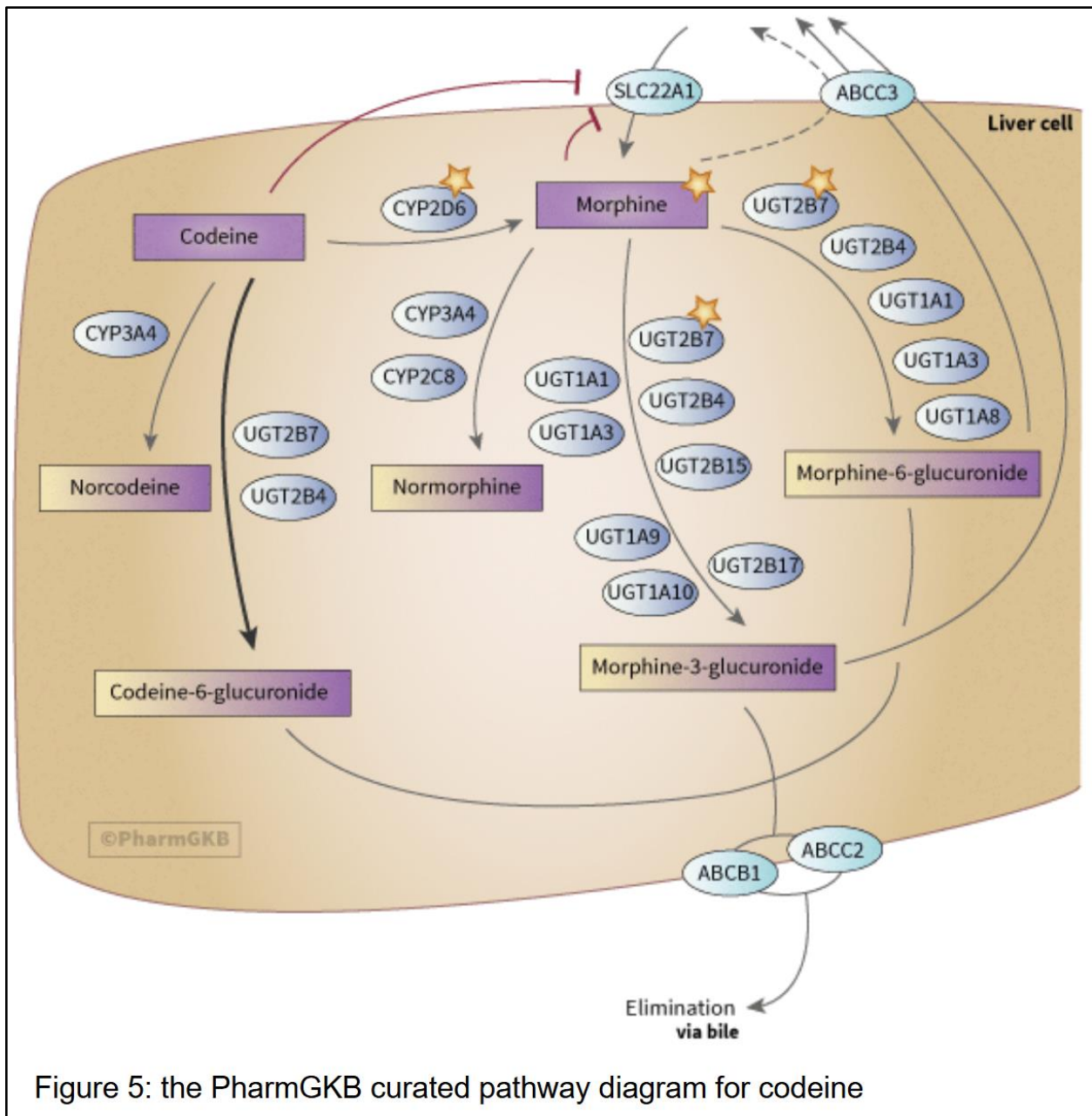

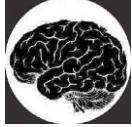


Figure 5: the PharmGKB curated pathway diagram for codeine

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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

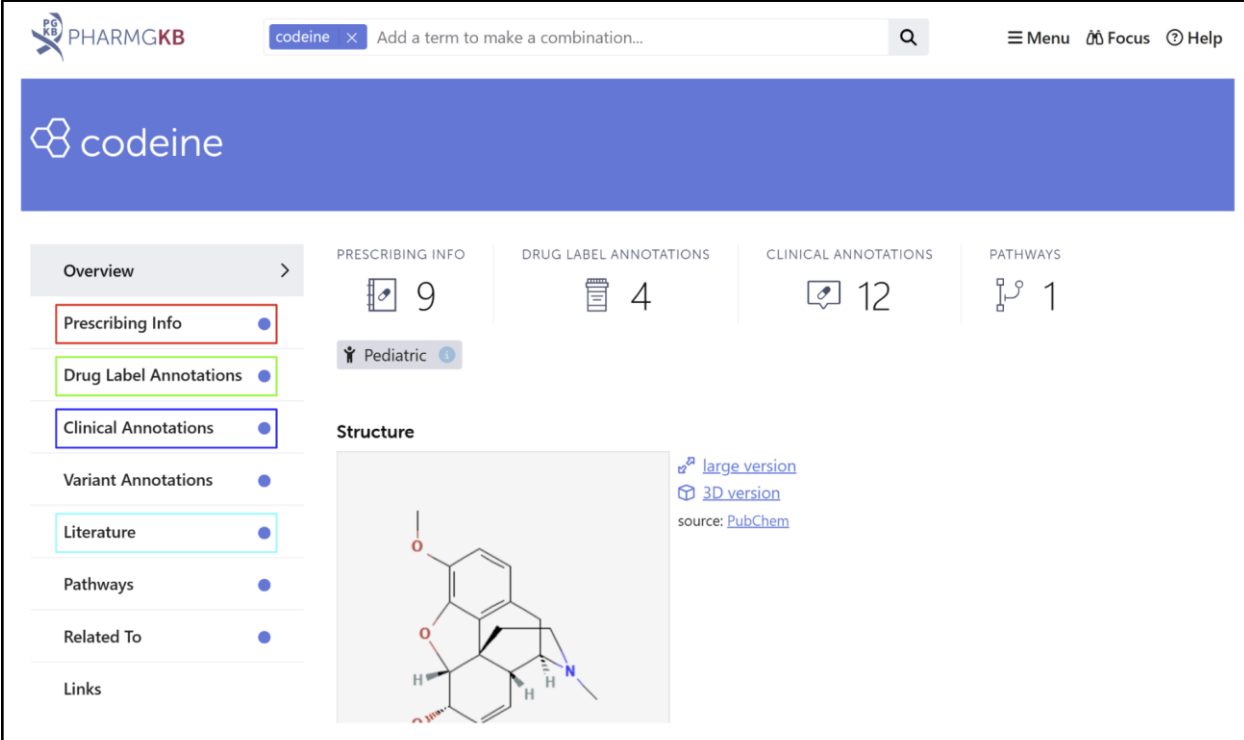




Figure 6: the PharmGKB entry for codeine

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

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- 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

Overview

Prescribing Info ● >

Drug Label Annotations ●

Clinical Annotations ●

Variant Annotations ●

Literature ●

Pathways ●

Related To ●

Links

Clinical Guideline Annotations


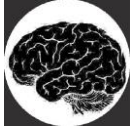
PharmGKB annotates PGx-based drug dosing guidelines published by [multiple sources](#). Annotations present a brief summary of the genotype-based dosing recommendations, including selected excerpts from the guidelines, and links to the source publications/documents. [Tags](#) indicate if the guideline provides dosing information, states that a drug is either indicated or contraindicated, or gives other guidance based on genotype/metabolizer phenotype. See the [legend](#) for more information.

We welcome any information regarding published PGx dosing guidelines - please [contact us](#).

	SOURCE ⇅	GENES ⇅	TITLE ⇅
Details	CPIC	CYP2D6	Annotation of CPIC Guideline for codeine and CYP2D6
Details	CPIC	COMT, OPRM1	Annotation of CPIC Guideline for alfentanil, buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, levomethadone, morphine, naltrexone, remifentanil, sufentanil, tramadol and COMT, OPRM1 No recommendation
Details	CPNDS	CYP2D6	Annotation of CPNDS Guideline for codeine and CYP2D6
Details	DPWG	CYP2D6	Annotation of DPWG Guideline for codeine and CYP2D6

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**

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Annotation of CPIC Guideline for codeine and CYP2D6

Alternate Drug ⓘ
Other Guidance ⓘ
Pediatric ⓘ

Summary

Alternate non-tramadol analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers. A label recommended age- or weight-specific dose of codeine is warranted for CYP2D6 normal and intermediate metabolizers.

Specify a genotype for specific annotations

Pick alleles for CYP2D6

-- ▾ -- ▾

Alleles not present in the above pull-down menus have no guideline recommendation.

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


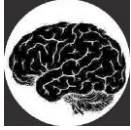
	<p align="center">SKILLS CENTER</p> <p align="center">STANDARD OPERATING PROCEDURE</p>	<p align="center">A BIOFIZZ</p>  <p align="center">PRODUCTON</p>
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Table 1: Codeine therapy recommendations based on CYP2D6 phenotype

Adapted from Tables 1 and 2 of the guideline.



PHENOTYPE ^a	ACTIVITY SCORE RANGE	ACTIVITY SCORE ^b	EXAMPLES OF CYP2D6 DIPLYPES ^b	IMPLICATIONS	RECOMMENDATIONS	CLASSIFICATION 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

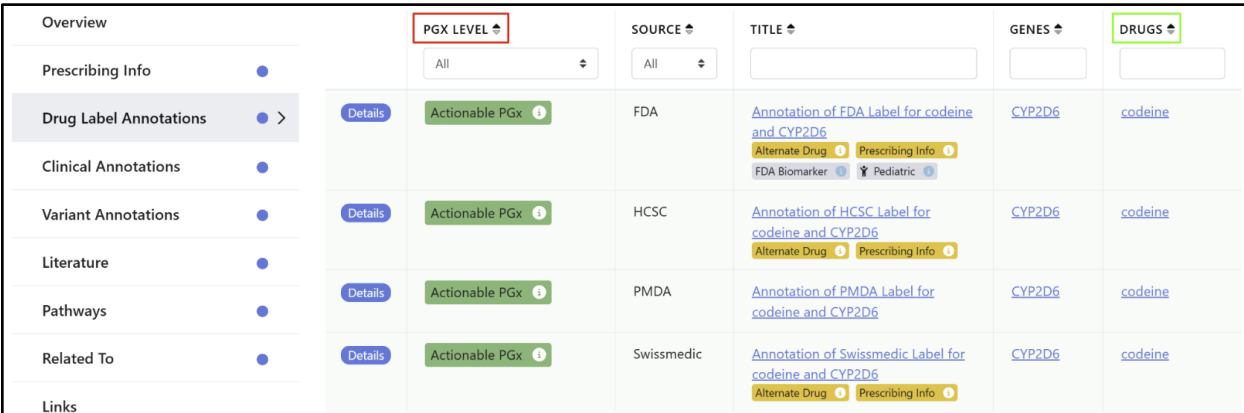
Figure 9: clinical guideline table for codeine and CYP2D6

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.

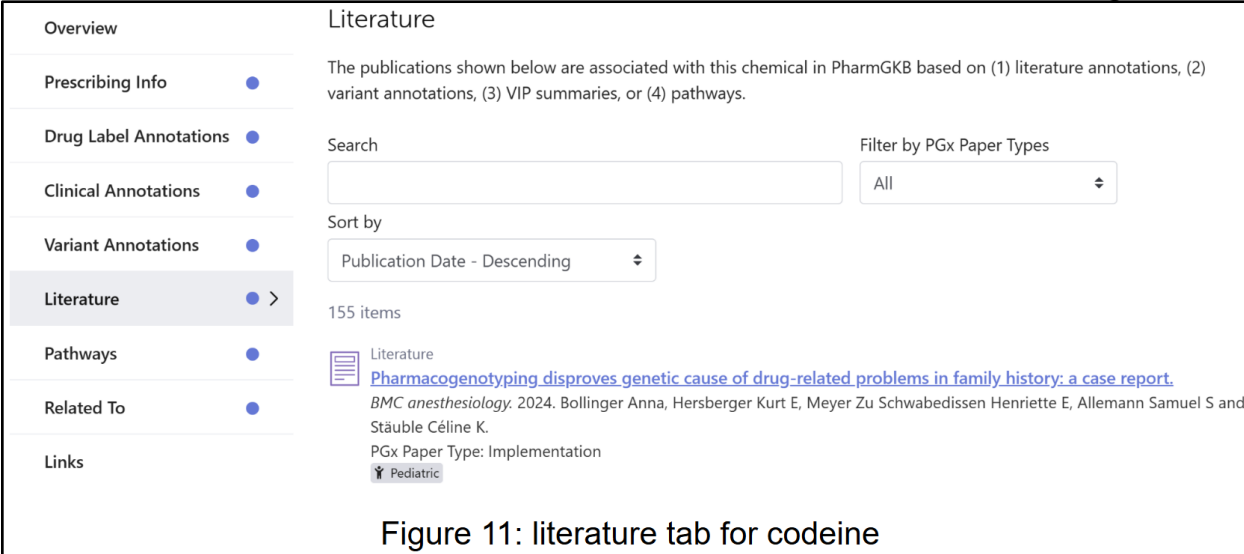
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The screenshot shows a table of drug label annotations for codeine. The table has columns for PGX LEVEL, SOURCE, TITLE, GENES, and DRUGS. The PGX LEVEL column is highlighted with a red box, and the DRUGS column is highlighted with a green box. The table contains four rows of annotations from FDA, HCSC, PMDA, and Swissmedic, all related to CYP2D6 and codeine. Each row includes a 'Details' link and a green 'Actionable PGx' badge. The table also features a left sidebar with navigation options like Prescribing Info, Drug Label Annotations, Clinical Annotations, Variant Annotations, Literature, Pathways, Related To, and Links.

Figure 10: drug label annotations table for codeine

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





The screenshot shows the literature tab for codeine. The left sidebar has the 'Literature' tab selected. The main content area shows a search bar, a filter by PGx Paper Types dropdown (set to 'All'), and a sort by dropdown (set to 'Publication Date - Descending'). Below the search results, it indicates '155 items' and shows a list of literature entries. The first entry is a paper from BMC anesthesiology (2024) by Bollinger Anna, Hersberger Kurt E, Meyer Zu Schwabedissen Henriette E, Allemann Samuel S and Stäubli Céline K. The PGx Paper Type is 'Implementation' and it is marked as 'Pediatric'.

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.


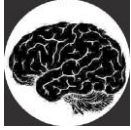
Hall, Kristopher R., and Tamer E. Fandy. “Pharmacogenomics and Pharmacoepigenomics: Impact on Therapeutic Strategies.” *Genomics-Driven Healthcare*, Adis, Singapore, 2018, pp. 227–38. *link.springer.com*, https://doi.org/10.1007/978-981-10-7506-3_12.

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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.

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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.