

ANSWER KEY WITH EXPLANATIONS

FOR CHAPTER 4

Skill Drill Answers

SD 4.1: Transporter-Function Matching

1. **A** — P-gp is an efflux transporter
 2. **B** — OATP1B1 is an uptake transporter
 3. **A** — BCRP is an efflux transporter
 4. **B** — OCT1 is an uptake transporter
 5. **A** — MRP2 is an efflux transporter
 6. **B** — OAT1 is an uptake transporter
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SD 4.2: True/False with Correction

1. **F** — P-gp limits absorption by pumping drugs OUT of enterocytes back into the gut lumen.
 2. **T** — Poor metabolizers have two non-functional alleles.
 3. **F** — Ultrarapid metabolizers should AVOID codeine due to toxicity risk from rapid morphine formation.
 4. **F** — Rifampin INDUCES P-gp, DECREASING digoxin levels.
 5. **T** — The microbiome can metabolize drugs presystemically.
 6. **F** — VKORC1 affects warfarin's target sensitivity, not metabolism. CYP2C9 affects warfarin metabolism.
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SD 4.3: Fill in the Blank

1. **SLC (Solute Carrier)**
2. **ABCB1 (or MDR1)**

3. **poor**
 4. **pharmacogenomics**
 5. **clopidogrel**
 6. **HLA-B*57:01**
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SD 4.4: CYP450 Phenotype Classification

1. **NM** — Two functional alleles = normal metabolizer
 2. **PM** — Two non-functional alleles = poor metabolizer
 3. **IM** — One functional + one non-functional = intermediate
 4. **UM** — Gene duplication = ultrarapid
 5. **IM** — One functional + one non-functional = intermediate
 6. **PM** — Two non-functional alleles = poor metabolizer
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SD 4.5: Category Sorting

1. **I** — Rifampin is a P-gp inducer
 2. **X** — Verapamil is a P-gp inhibitor
 3. **X** — Ketoconazole is a P-gp inhibitor
 4. **I** — St. John's Wort is a P-gp inducer
 5. **X** — Quinidine is a P-gp inhibitor
 6. **I** — Carbamazepine is a P-gp inducer
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SD 4.6: Rapid Recall

1. **P-glycoprotein (P-gp)**
2. **Poor metabolizer**
3. **CYP2D6**
4. **Organic anion transporting polypeptide**
5. **VKORC1**
6. **ABC transporters**

SD 4.7: Complete the Sentence

1. **efflux**
2. **faster**
3. **abacavir**
4. **into**
5. **higher**
6. ***1**

SD 4.8: Genetic Variant Interpretation

1. Patient cannot activate clopidogrel adequately, increasing risk of stent thrombosis and cardiovascular events.
2. Rapid conversion of codeine to morphine may cause respiratory depression, especially in children.
3. Lower warfarin doses needed due to reduced metabolism (CYP2C9 *3) and possibly increased sensitivity.

SD 4.9: Abbreviation Matching

1. **D** — SNP = Single nucleotide polymorphism
2. **C** — BCRP = Breast cancer resistance protein
3. **B** — PM = Poor metabolizer
4. **A** — OATP = Organic anion transporting polypeptide
5. **F** — UM = Ultrarapid metabolizer
6. **E** — MRP = Multidrug resistance protein

SD 4.10: Prodrug Activation Pathways

1. **A** — CYP2D6 converts codeine to morphine
2. **B** — CYP2C19 activates clopidogrel
3. **C** — Bacterial azoreductases cleave sulfasalazine
4. **D** — Esterases activate oseltamivir

SD 4.11: Drug-Gene Pair Matching

1. **C** — Warfarin: CYP2C9 and VKORC1
 2. **A** — Codeine: CYP2D6
 3. **D** — Abacavir: HLA-B*57:01
 4. **B** — Clopidogrel: CYP2C19
 5. **E** — Carbamazepine: HLA-B*15:02
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SD 4.12: Metabolizer Status Dosing

1. **C** — Tramadol also requires CYP2D6; avoid and use alternative.
2. **C** — Poor metabolizers cannot activate clopidogrel; use prasugrel or ticagrelor.
3. **C** — CYP2C9 *3/*3 dramatically reduces warfarin metabolism; substantially lower doses needed.

Case Study Answers

Case 4.1: Warfarin Pharmacogenomic Dosing

Question 1. CYP2C9 metabolizes warfarin, primarily the more potent S-enantiomer. The *3 allele reduces enzyme activity, causing slower warfarin elimination and higher drug levels at standard doses.

Question 2. VKORC1 (Vitamin K epoxide reductase complex 1) is warfarin's target enzyme. Polymorphisms in the VKORC1 promoter affect enzyme expression. The A allele reduces VKORC1 expression, making patients more sensitive to warfarin and requiring lower doses.

Question 3. She has both reduced metabolism (CYP2C9 *1/*3) and intermediate sensitivity (VKORC1 G/A). Both factors contribute to needing less warfarin to achieve therapeutic anticoagulation.

Question 4. No. Pharmacogenomic dosing provides a better starting dose but does not predict all factors affecting INR. Diet, drug interactions, illness, and adherence still vary. INR monitoring remains essential for safe warfarin therapy.

Case 4.2: Codeine Non-Response in Poor Metabolizer

Question 1. CYP2D6 converts codeine to morphine, the active analgesic. The *4 allele produces no functional enzyme. With *4/*4, he has no CYP2D6 activity and cannot convert codeine to morphine, so he gets no pain relief.

Question 2. Poor metabolizer (PM).

Question 3. Analgesics that do not require CYP2D6 activation: morphine (already active), oxycodone (less dependent on CYP2D6), hydromorphone, or non-opioid alternatives like NSAIDs or acetaminophen.

Question 4. Ultrarapid metabolizers convert codeine to morphine extremely quickly, producing dangerous morphine levels. This can cause respiratory depression, especially in children or with repeated dosing, and has caused fatalities.

Diagram/Table Exercise Answers

DT 4.1: P-glycoprotein Function

1. Out of the cell (efflux)
2. ATP
3. Blood-brain barrier, intestine, liver, or kidney
4. Digoxin, cyclosporine, tacrolimus, or HIV protease inhibitors

DT 4.2: CYP2D6 Metabolizer Phenotypes

Phenotype	Enzyme Activity	Codeine Response	Dosing Implication
Poor metabolizer	None	No analgesia	Avoid codeine
Intermediate metabolizer	Reduced	Reduced analgesia	Consider alternative or lower dose
Normal metabolizer	Normal	Normal analgesia	Standard dose
Ultrarapid metabolizer	Increased	Toxicity risk	Avoid codeine

DT 4.3: Pharmacogenomic Drug-Gene Pairs

Drug	Gene(s)	Clinical Action for Variant
Warfarin	CYP2C9, VKORC1	Adjust starting dose based on genotype
Clopidogrel	CYP2C19	Use alternative antiplatelet
Abacavir	HLA-B*57:01	Do not prescribe if positive

Drug	Gene(s)	Clinical Action for Variant
Codeine	CYP2D6	Avoid in PM and UM

DT 4.4: Transporter Drug Interactions

Interacting Drug Effect on P-gp Effect on Digoxin Levels

Quinidine	Inhibitor	Increased
Rifampin	Inducer	Decreased
Verapamil	Inhibitor	Increased
St. John's Wort	Inducer	Decreased

Multiple-Choice Question Answers

Question 1. Answer: B

P-glycoprotein is an efflux transporter that pumps substrates out of cells.

Question 2. Answer: D

Poor metabolizer phenotype results from two loss-of-function alleles.

Question 3. Answer: C

CYP2D6 converts codeine to its active metabolite, morphine.

Question 4. Answer: B

Rifampin induces P-gp, increasing digoxin efflux and decreasing levels.

Question 5. Answer: C

HLA-B*57:01 testing is required before abacavir to prevent hypersensitivity.

Question 6. Answer: C

Poor metabolizers cannot activate clopidogrel adequately. Alternative agents like prasugrel or ticagrelor are preferred.

Question 7. Answer: B

OATP1B1 transports statins into hepatocytes. Reduced function variants increase statin plasma levels and myopathy risk.

Question 8. Answer: B

Gut bacteria can metabolize drugs before systemic absorption, affecting bioavailability.

Question 9. Answer: B

Ultrarapid metabolizers produce morphine too quickly from codeine, risking toxicity.

Question 10. Answer: C

VKORC1 is warfarin's target. Polymorphisms alter target enzyme expression and sensitivity.

Question 11. Answer: B

ABC transporters use ATP hydrolysis for active efflux transport.

Question 12. Answer: B

CYP2C9 *3 reduces metabolism; VKORC1 A/A increases sensitivity. Both require lower doses.

Question 13. Answer: B

Quinidine inhibits P-gp, reducing digoxin efflux and causing digoxin toxicity (nausea, visual disturbances).

Question 14. Answer: C

Pharmacogenomic testing is most valuable for drugs with narrow therapeutic indices and established gene-drug associations.

Question 15. Answer: B

Grapefruit juice inhibits both intestinal P-gp and CYP3A4, increasing cyclosporine absorption and decreasing first-pass metabolism.

Question 16. Answer: D

Morphine does not require CYP2D6 activation—it is already active and appropriate for CYP2D6 poor metabolizers.