Pharmacogenomic Personality: Being Ultra, Normal, and Poor at the Same Time

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PATIENT INFORMATION
NAME: Patient 10113
ACC #: 10113
DOB: 1/1/1900

SPECIMEN DETAILS
SPECIMEN TYPE:
COLLECTION DATE: 4/1/2019
RECEIVED DATE: 4/1/2019
REPORT DATE: 4/3/2019

ORDERED BY

Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C9	*1/*1	Normal Metabolizer	*2, *3, *4, *5, *6, *11
CYP2C19	*17/*17	Ultra-Rapid Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *17
CYP3A5	*3/*3	Poor Metabolizer	*1D, *2, *3, *3B, *3C, *6, *7, *8, *9
CYP3A4	*1/*1	Normal Metabolizer	*1B, *2, *3, *12, *17, *22
Apolipoprotein E	Indeterminate	Unknown Phenotype	ε2, ε4, (ε3 is reference)
CYP2D6	*4/*4	Poor Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41

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Objectives

Upon completion of this session, participants will be able to:

1. List the categories of pharmacogenes.
2. Relate pharmacogenomics to drug inefficacy and adverse drug events.
3. Differentiate the drug metabolism phenotype and drug transporter phenotype categories.
4. Discuss issues related to pharmacogenetic testing.

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Definitions

Molecular Level

- Pharmacogenomics: The study of variations of DNA and RNA characteristics as related to drug response.[1]
- Pharmacogenetics: The study of variations in DNA sequence as related to drug respose.[1]

Clinical Level

- Pharmacogenomics: The study of many genes, in some cases the entire genome, involved in response to a drug.[2]
- Pharmacogenetics: The study of a gene involved in response to a drug.[2]

[1] E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available at www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073162.pdf. Accessed November 4, 2016.
[2] Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. Reproduced with permission.

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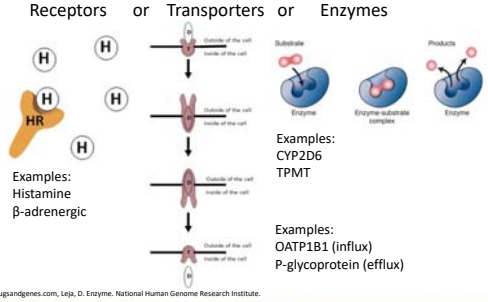
Pharmacogene/Product Categories

Receptors or Transporters or Enzymes



Examples:
Histamine
β-adrenergic

Examples:
CYP2D6
TPMT

Examples:
OATP1B1 (influx)
P-glycoprotein (efflux)

Sources: drugsandgenes.com, Leja, D. Enzyme. National Human Genome Research Institute.

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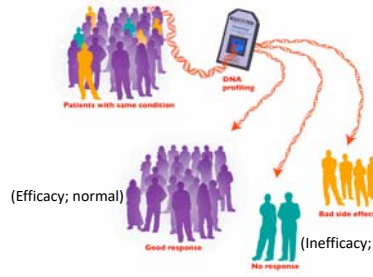
PGx: Drug Efficacy • Adverse Drug Events



NIH, National Human Genome Research Institute. Available at www.genome.gov/27530645/faq-about-pharmacogenomics/. Accessed November 4, 2016.

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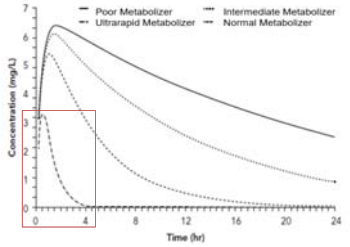
Ineffective Medication



Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. Reproduced with permission.

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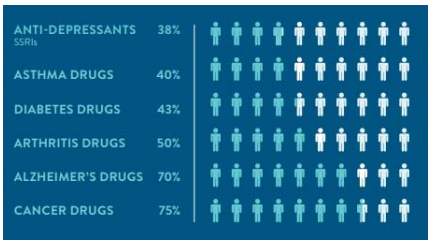
Ineffective Medication



Personalized Medicine Coalition. The Personalized Medicine Report. 2017. Reproduced with permission.
Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol. Med. 7(5), 201–204 (2001).

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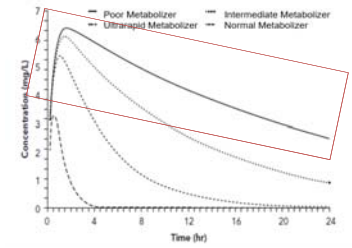
Adverse Drug Events



Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. Reproduced with permission.

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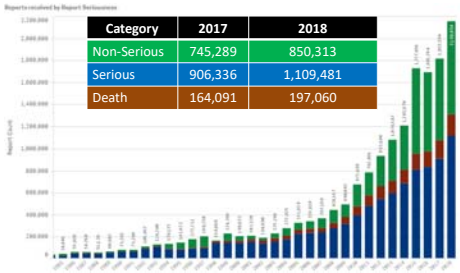
Adverse Drug Events



Category	2017	2018
Non-Serious	745,289	850,313
Serious	906,336	1,109,481
Death	164,091	197,060

Food and Drug Administration. Adverse Event Reporting System. February 21, 2019. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis

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PGx: Drug Efficacy • Adverse Drug Events

Gene	Diplotype	Drug (Standard Dose)	Potential Response	Outcome
CYP2C19	*1/*1 NM	Clopidogrel	Desired antiplatelet effect	Efficacy
	*2/*2 PM	Clopidogrel	Stent thrombosis - death	Inefficacy
CYP2C9	*1/*1 NM	Warfarin	Desired anticoagulation	Efficacy
	*3/*3 PM	Warfarin	Bleeding - death	Adverse Drug Reaction
CYP2D6	*1/*1 NM	Codeine	Desired analgesic effect	Efficacy
	*4/*4 PM	Codeine	Pain	Inefficacy
	*1/*2xN UM	Codeine	Morphine overdose - death	Adverse Drug Reaction

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Driving the Utility of PGx Data

What do you think is the most challenging aspect of the implementation of pharmacogenetics into the clinic?	Response (ASCPT 2010)
1. **Translation of genetic information into clinical action.**	1st
2. Genotype test interpretation (e.g. using genotype information to impute phenotype)	2nd
3. Providing recommendations for selecting the drug/gene pairs to implement	3rd

Adapted from: Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 89(3):64–467,2011.

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Gene	Risk Allele	Drug	Intervention	Guidelines
CYP2C9	*3	celecoxib	(*3/*3) Start dose at 50% of standard dose – decrease risk of cardiovascular and gastrointestinal adverse reactions.	X
*HLA-B*15:02*	positive	carbamazepine	Choose alternative drug – avoid Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis.	CPIC
TPMT	*2	6-mercaptopurine	Lower dose to decrease risk of severe myelosuppression/infection.	CPIC
UGT1A1	*28	irinotecan	Lower dose to decrease risk of neutropenia.	DPWG
*HLA-B*58:01*	positive	allopurinol	Choose alternative drug – avoid serious cutaneous reaction.	CPIC
SLCO1B1	C	simvastatin	Reduce dose to decrease risk of myopathy.	CPIC

CPIC – Clinical Pharmacogenetics Implementation Consortium; DPWG – Dutch Pharmacogenetic Working Group

Adapted from: Chun-Yu Wei CY, Lee MTM, Chen YT. Pharmacogenomics of adverse drug reactions: implementing personalized medicine. Human Molecular Genetics, 2012 R1–R8

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Guidelines

CPIC guideline (n=21); genes (n=20); drugs (44)[1]	DPWG (11 Genes/53 Drugs)[2]
Gene (Number of drugs)-Example	Gene (Number of drugs)-Example
CYP2D6 (n=10)-codeine	*CYP2D6* (n=25)-metoprolol
CYP2C19 (n=9)-citalopram	*CYP2C19*(n=11)-clopidogrel
DPYD (n=3)-fluorouracil	*CYP2C9* (n=7)-phenytoin
IFNL3 (n=3)-peginterferon alfa-2a	*TPMT* (n=3)-mercaptopurine
TPMT (n=3)-thioguanine	*DPD* (n=3)-capecitabine
CYP2C9 (n=2)-warfarin	*VKORC1* (n=2)-acenocoumarol
CFTR (n=1)-ivacaftor	*UGT1A1* (n=1)-irinotecan
CYP3A5 (n=1)-tacrolimus	*HLA-B44* (n=1)-ribavirine
G6PD (n=1)-rasburicase	*HLA-B*5701* (n=1)-abacavir
*HLA-B*57:01* (n=1)-abacavir	*CYP3A5* (n=1)-tacrolimus
*HLA-B*15:02* (n=1)-carbamazepine	*FVL* (n=1)-estrogen containing OCs
*HLA-B*58:01* (n=1)-allopurinol	
SLCO1B1 (n=1)-simvastatin	
UGT1A1 (n=1)-atazanavir	
VKORC1 (n=1)-warfarin	

[1]Clinical Pharmacogenetics Implementation Consortium (CPIC). Available at www.cpicpgx.org/guidelines/. Accessed January 2019.
[2]Royal Dutch Association for the Advancement of Pharmacy Pharmacogenetics Working Group (DPWG). Clin Pharmacol Ther. 89(5):662-273, 2011.

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CPIC Guidelines

Therapeutic Recommendations

Level A: Genetic information **should be used** to change prescribing of affected drug.

Level B: Genetic information **could be used** to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing.

[1]Clinical Pharmacogenetics Implementation Consortium (CPIC). Available at www.cpicpgx.org/genes-drugs/. Accessed January 2019.

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CPIC Guidelines

Strength of Recommendation

Strong recommendation for the statement: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

[1]Clinical Pharmacogenetics Implementation Consortium (CPIC). Available at www.cpicpgx.org/genes-drugs/. Accessed January 2019.

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CPIC Guidelines

Standard Elements of Guidelines

Introduction
Focused Literature Review
Gene
- Background
- Genetic Test Interpretation
- Table 1. Assignment of likely _____ [gene] phenotypes based on genotypes
- Available Genetic Test Options
- Incidental findings
- Other considerations

Drug (s)
Background
- linking genetic variability to variability in drug-related phenotypes
- Dosage Recommendations
- Table 2. Recommended Dosing of ____ [drug/s] by ____ [gene] phenotype
- Strength of recommendations grading system
- Recommendations for Incidental Findings
- Other considerations

Potential Benefits and Risks for the Patient
Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

[1]Clinical Pharmacogenetics Implementation Consortium (CPIC). Available at www.cpicpgx.org/resources/. Accessed January 2019.

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CPIC Guidelines

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes[1]

Likely Phenotype	Genotype	Examples of diplotypes
Ultrarapid metabolizer (UM):	An individual carrying two increased activity alleles (*17)	*17/*17
Rapid metabolizer (RM):	Combinations of normal function and increased function alleles	*1/*17
Normal metabolizer (NM):	An individual carrying two functional (*1) alleles	*1/*1
Intermediate metabolizer (IM):	An individual carrying one functional allele (*1) plus one loss-of function allele (*2–*8) or one loss-of-function allele (*2–*8) plus one increased-activity allele (*17)	*1/*2, *1/*3, *2/*17
Poor metabolizer (PM):	An individual carrying two loss-of-function alleles (*2–*8)	*2/*2, *2/*3, *3/*3

[1]Adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC). Available at www.cpicpgx.org/resources/. Accessed January 2019.

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CPIC Guidelines

Table 2 Antiplatelet recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients[1]

Phenotype	Implications for Clopidogrel	Recommendation	Classification of Recommendation
UM, RM, NM	Normal or increased platelet inhibition; normal or decreased residual platelet aggregation	Clopidogrel: label-recommended dosage and administration	Strong
IM	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
PM	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

[1]Adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC). Available at www.cpicpgx.org/resources/. Accessed January 2019.

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Sample Collection for PGx Testing

	Paternity or Maternity Testing	DNA Forensics	Disease Predisposition	Pharmacogenomics
Utility	Determine biological parent.	Determine identity of crime scene DNA sample.	Determine cause of, or predisposition for, disease or disorder, or if the patient is a carrier for an inherited disease.	Predict optimal drug and/or dose for specific patient.
Sample source	Buccal swab	Varied	Buccal swab, saliva, or blood sample	Buccal swab, saliva, or blood sample
Target	Short tandem repeats (STR)	Short tandem repeats (STR)	Allelic variations linked to disease/disorder	Genes for drug metabolism enzymes, drug transporters, and drug receptors
Rapid testing turnaround required	Infrequently	Infrequently	No	Yes

Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. https://www.manchester.edu/docs/default-source/pharmacogenes-doc/pharmacogenes.pdf

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Adverse Drug Events: Example

Rani J.
- Son Tariq was born April 18, 2005;
  - Episiotomy:
    - Received acetaminophen with codeine;
- 12 days later Tariq died.

Owen Dyer. National Review of Medicine June 15, 2007.

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Adverse Drug Events: Example

- Cause: morphine overdose
- Tariq not receiving morphine
  - Brain/nervous system depression
  - Slow breathing
  - Inactivity/inaction
  - Skin color
  - Poor feeding/failure to thrive

Gene Form	Drug (Std. Dose)	Response	Outcome
*CYP2D6**1/*2xN UM	Codeine	Morphine overdose	Adverse Drug Reaction - Death

http://babygooroo.com/2007/06/is-codeine-safe-for-breastfeeding-mothers-and-infants/

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CPIC: *CYP2D6*-Codeine

Table 1 Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (CYP2D6) diplotypes

Likely phenotype[a]	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN
Extensive metabolizer (~77–92% of patients)	1.0–2.0[b]	An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10
Intermediate metabolizer (~2–11% of patients)	0.5[b]	An individual carrying one reduced-function and one nonfunctional allele	*4/*10, *5/*41
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]

KR Crews KR, A Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clin Pharmacol Ther. 95(4):376-382.

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Case: Metoprolol/Fluoxetine-*CYP2D6*

Samuel is a 64 year old male with heart failure. He is receiving metoprolol succinate 100 mg once daily. Samuel is now started on fluoxetine for treatment of depression. Two days after starting on the fluoxetine, the patient is seen at the emergency room, having suffered a fractured arm after getting "dizzy" and falling. As part of his discharged process, the pharmacist is asked to provide medication counseling.

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Case: Metoprolol/Fluoxetine-*CYP2D6*

Pharmacist recommends genetic testing

- Samuel states as an "old techie", he had provided a direct-to-consumer company (DTC) his saliva for DNA analysis. Samuel gets the results from his smart phone, telling the pharmacist that he is a CYP2D6 *4/*10 individual, "Whatever that means!"

CYP2D6 *4/*10

Specify a genotype for specific annotations

Pick alleles for CYP2D6

*4 / *10

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

CYP2D6 Genotype to Phenotype table (current vs new)

Activity Score	Likely phenotype	CURRENT CPIC activity score definition	CURRENT DPWG activity score definition	PROPOSED NEW standardized activity score definition	With no gaps PM=0	Examples of CYP2D6 diplotypes for new system
	CYP2D6 ultrarapid metabolizer	>2	>2.5	>2.25	>2.25	*1/*1xN, *1/*2xN, *2/*2xN, *2x2/*9
	CYP2D6 normal metabolizer	1-2	1.5-2.5	1.25 1.5 2.0 2.25	1.25 ≤ x ≤ 2.25	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2, *1/*10, *2x2/*10
0.5	CYP2D6 intermediate metabolizer	0.5	0.5-1	0.25 0.5 0.75 1	0 < x < 1.25	*4/*10, *4/*41, *1/*5, *10*10, *41/*41
	CYP2D6 poor metabolizer	0	0	0	0	*3/*4, *4/*4, *5/*5, *5/*6

PharmGKB. https://www.pharmgkb.org/guidelineAnnotation/PA166104995. Accessed March 22, 2019. CPIC https://cpicpgx.org/wp-content/uploads/2019/03/Final-Consensus-CYP2D6-genotype-to-phenotype-table_-final_Mar2019.pdf. Accessed March 22, 2019.

Case: Metoprolol/Fluoxetine-*CYP2D6*

Pharmacist recommends genetic testing

- Samuel states as an "old techie", he had provided a direct-to-consumer company (DTC) his saliva for DNA analysis. Samuel gets the results from his smart phone, telling the pharmacist that he is a CYP2D6 *4/*10 individual, "Whatever that means!"

Genotype	Phenotype	Consequences	Recommendation
*4/*10	IM		

What are the consequences of the *CYP2D6*4/*10* genotype/IM phenotype in a patient taking metoprolol?

- Decreased metabolism (CL) of metoprolol
  - Increased exposure to metoprolol
  - Higher AUC, Longer t½

Drug-Gene (metoprolol/CYP2D6) Interaction Influence

Genotype	Phenotype	Consequences	Recommendation
*4/*10	IM	↓ metabolism (CL) ↑ AUC ↑ t½	Still to come…

The administration of a drug to an individual who carries at least one variant form of a gene or multiple copies of a gene that codes for the enzyme that metabolizes the drug.

CYP2D6: UM 1-2%, NM 77-92%, **IM 1-13%**, PM 5-10%

What are the consequences of the addition of fluoxetine in a patient taking metoprolol?

- Decreased metabolism (CL) of metoprolol
  - Increased exposure to metoprolol
  - Higher AUC, Longer t½

Drug-Drug Interaction Influence

Drug	Interacting Drug	Consequences	Recommendation
Metoprolol	Fluoxetine	↓ metabolism CL ↑ AUC ↑ t½	Still to come...

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What are the consequences of the *CYP2D6*4/*10* genotype/IM phenotype **and** the addition of fluoxetine in a patient taking metoprolol?

Decreased metabolism (CL) of metoprolol
Increased exposure to metoprolol
Higher AUC, Longer t½

Drug	Interacting Drug	Consequences	Recommendation
Metoprolol	Fluoxetine	↓↓ metabolism CL ↑↑ AUC ↑↑ t½	Still to come...

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Drug-Drug-Gene Interaction

The addition of an inhibitor or inducer of a drug metabolizing enzyme in an individual receiving a drug metabolized by a variant form of that enzyme.

- Drug-gene interaction: metoprolol/*CYP2D6*
- Drug-drug interaction: metoprolol/fluoxetine

- Drug-drug-gene interaction = phenoconversion - Δ to PM

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DPWG: *CYP2D6*-Metoprolol

Drug	n	Phenotype	EL	CR	Interaction	Recommendation	
Metoprolol	1,966	PM	4	C	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 75% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)	95–110
		IM	4	B	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 50% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)	96–100,102, 107,108, 110–115
		UM	4	D	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE Other indications: select alternative drug (e.g., atenolol, bisoprolol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE	98, 100–103

EL = Evidence level; CR = Clinical relevance
4 = Published controlled study of "good quality"; 0 = Data "on file"; - = not reported
C = Clinical effect (long standing, not permanent); B = Clinical effect (short lived) ; D = Clinical effect (long standing permanent)

Royal Dutch Association for the Advancement of Pharmacy Pharmacogenetics Working Group (DPWG). Clin Pharmacol Ther. 89(5):662-273, 2011.

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DPWG: *CYP2D6*-Metoprolol

Drug	n	Phenotype	EL	CR	Interaction	Recommendation	
Metoprolol	1,966	PM	4	C	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 75% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)	95–110
		IM	4	B	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 50% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)	96–100,102, 107,108, 110–115
		UM	4	D	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE Other indications: select alternative drug (e.g., atenolol, bisoprolol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE	98, 100–103

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Royal Dutch Association for the Advancement of Pharmacy Pharmacogenetics Working Group (DPWG). Clin Pharmacol Ther. 89(5):662-273, 2011.

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"Work through cases"

Epilepsy Therapy

JL is a 16-year-old Asian male, who is 5'7", 147 lbs. JL suffered a general onset seizure of unknown origin and has been diagnosed with epilepsy. JL has been prescribed phenytoin and you are asked to design an appropriate dosing regimen and monitor JL's progress. JL is otherwise healthy. Pharmacogenetic (PGx) testing was performed and the results report is available. What is your recommendation for JL?

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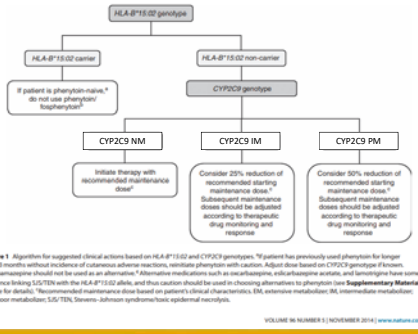

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Conclusions

In clinical therapeutics, the application of pharmacogenomics has utility:

- as a component of clinical information (data) for use in designing an efficacious drug regimen.
- as a component of clinical information (data) for use in designing a drug regimen that minimizes or avoids the risk of an adverse drug reaction.

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Conclusions

The utility of pharmacogenomics is supported:

- guidelines for many drug-gene interactions
  - CPIC
  - DPWG
  - CPNDS/Others **PharmGKB**
- mechanistic understanding relating gene variants to gene product activity to pharmacokinetics and pharmacodynamics.
  - similar to utilizing information related to drug-drug interactions

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Questions?

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