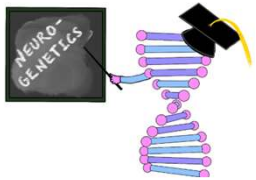
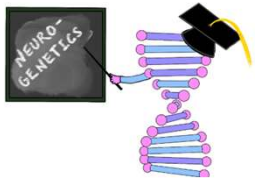
Therapeutics - Pharmacogenomics

MODULE 15



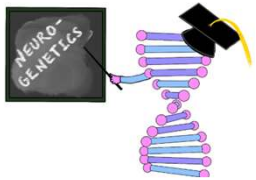
Learning Objectives

- Describe the goals of pharmacogenomics
- Recognize parts of a pharmacogenomic test
- Identify how pharmacogenomics may be useful for neurology patients



Chief Complaint

- 13yo M with a history of juvenile myoclonic epilepsy who is presenting with altered mental status, headache, diplopia, and nausea over the past 1 month.



Differential Diagnosis - Interactive

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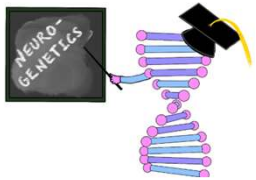
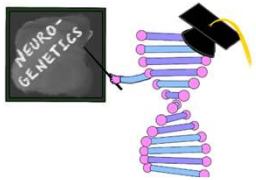


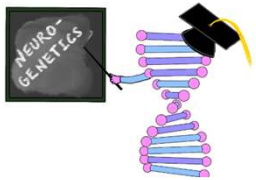
Differential Diagnosis

- Seizures
  - Non-convulsive status epilepticus
- Structural
  - Mass
  - Hemorrhage
- Infectious
- Post-infectious
- Intoxication
- Mitochondrial



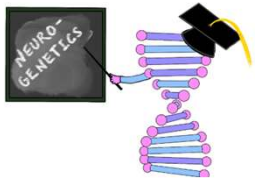
HPI – Epilepsy History

- Absence epilepsy diagnosed at age 9
- First generalized tonic-clonic seizure at age 11. Recently increased in frequency to up to 2 per month prompting multiple medication changes
- Past anti-seizure medications include valproic acid, lamotrigine, zonisamide, levetiracetam, cannabidiol, Modified Atkins Diet
- Current ASMs:
  - ethosuximide (20mg/kg/d) – started at age 9, somewhat effective for absence seizures
  - clobazam 10mg BID (0.4mg/kg/d) – started 6 months ago, initially effective for GTCs. Dose decreased (from 15mg BID) upon starting felbamate.
  - felbamate (25 mg/kg/d) – started 2 months ago, no seizures since starting

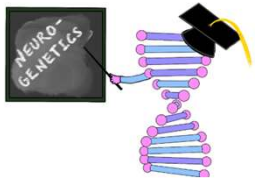


HPI - Continued

- For the past month, the patient complains of daily headache and nausea with diplopia.
- Worsening memory with difficulty concentrating at school. He was a straight-A student but has failed all his exams in the past month.
- Speech is worsening and parents note he often does not make sense.
- His sleep schedule is erratic and will sometimes be awake all night and sleep during the day.
- He has lost 10 lbs due to the nausea and is not eating regularly.
- Family has not noticed any seizures.



Family History



8, autism

10

13

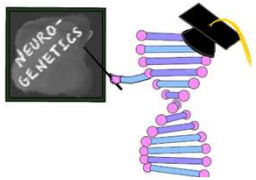
13

8, speech delay

Exam:

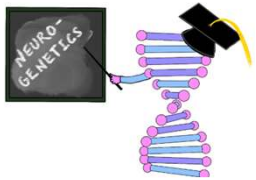
- BP 127/73, P 78, T 36.8
- General exam: normal
- Neuro exam:
  - Awake and alert with tangential and perseverative speech
  - Frequent low-amplitude erratic movements of arms and shoulders
  - Recalled 2/3 objects at 5 minutes, performed serial 7s to 100 with slow responses, unable to add multiple objects
  - Optic discs were flat
  - CN – normal
  - Motor, reflexes, sensation – normal
  - Mild ataxia

- Admitted for further work-up of AMS



Investigations (Non-Genetic)

- EEG – mild background slowing with excessive beta activity. Rare diffuse polyspikes in sleep. No seizures.
- MRI brain with spectroscopy – normal
- Labs: CMP, CRP, Ammonia, Vit B12, Urine organic acids, ceruloplasmin, lactic acid, pyruvic acid, TSH – normal
  - Felbamate level: 36.2 (range 30-60)
  - Autoimmune panel (serum and CSF): normal
  - CSF studies: normal



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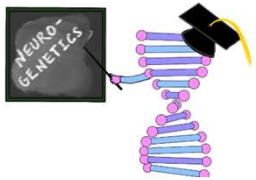
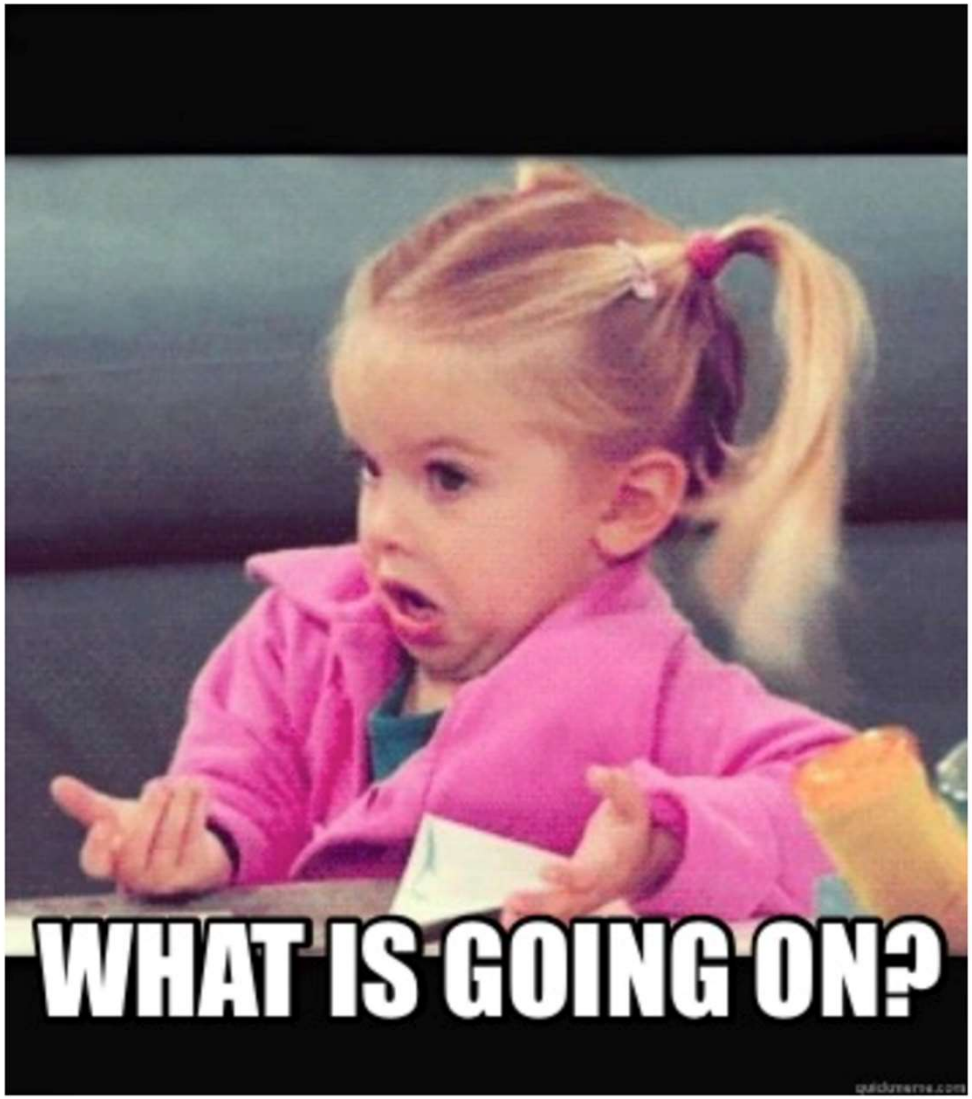
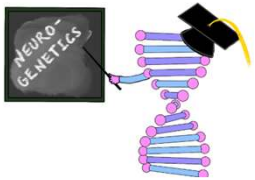
  - Felbamate level: 36.2 (range 30-60)
  - Autoimmune panel (serum and CSF): normal
  - CSF studies: normal
  - Clobazam: 205 (range 30-300)
  - N-desmethylclobazam: >10000 (300-3000)

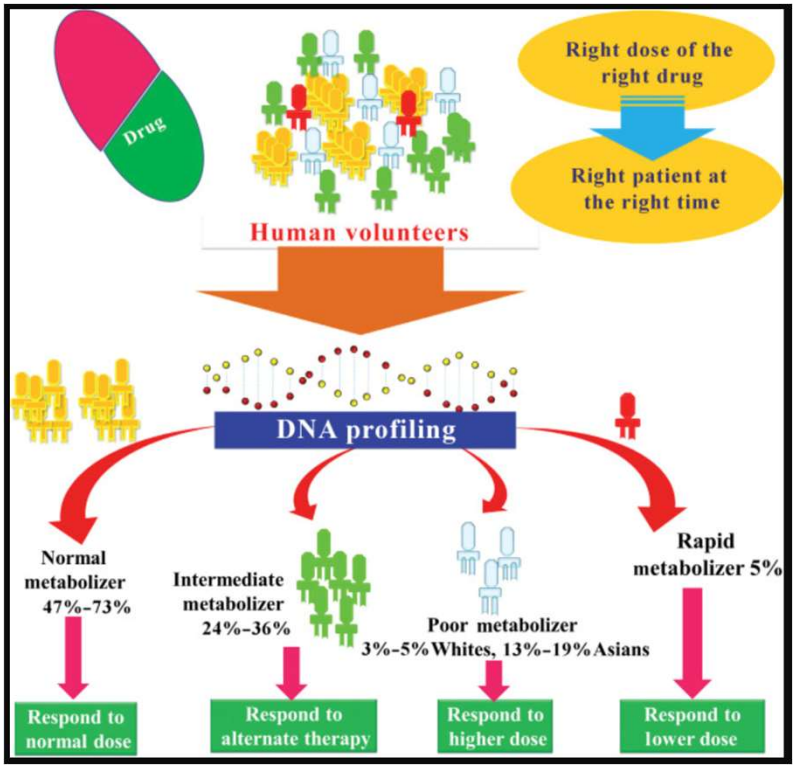


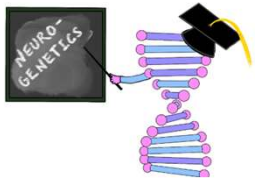

WHAT IS GOING ON?


NEURO-
GENETICS

Pharmacogenomics

- How a person's genetic sequence affects how they respond to medications.
- Goal of helping to select drugs and doses best suited for each person.



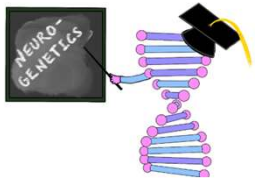


Soni, N. et al., Advances in Pharmaceutical Product Development and Research , 2020

Pharmacogenomic Panels – Vary by Company

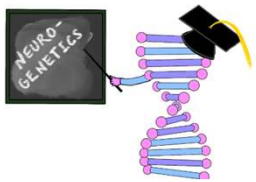
Primary panel
38 genes selected

ABCB1	ABCG2	ADRA2A	ADRB1
ADRB2	ANKK1	COMT	CYP1A2
CYP2B6	CYP2C Cluste	CYP2C19	CYP2C9
CYP2D6	CYP3A4	CYP3A5	CYP4F2
DPYD	DRD2	F2	F5
GRIK4	GRK4	GRK5	HLA-A
HLA-B	HTR2A	HTR2C	IFNL4
MTHFR	NAT2	NUDT15	OPRM1
SLCO1B1	TPMT	UGT1A1	UGT1A4
UGT2B15	VKORC1		



Detects Variants Known to Alter Metabolism

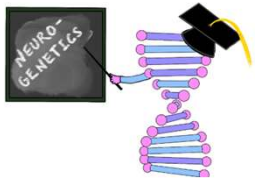
Gene*	Current Nucleotide Change	Legacy Nucleotide Change	Amino Acid Change / Star Allele	dbSNP RS#
ABCB1 (NG_011513.1)	208920T>C	c.3435C>T	p.I1145=	rs1045642
APOE (NG_007084.2)	7903T>C	c.388T>C	p.C130R	rs429358
	8041C>T	c.526C>T	p.R176C	rs7412
COMT (NG_011526.1; LRG_1010)	27009G>A	c.472G>A	p.V158M	rs4680
CYP1A2 (NG_061543.1; LRG_1274)	2035>A	g.-3860G>A	*1C	rs2069514
	5732>A	g.-163C>A	*1F	rs762551
	5166C>T	g.-729C>T	*1K	rs12720461
	9427G>A	g.3533G>A	*7	rs56107638
	6452C>A	g.558C>A	*11	rs72547513
CYP2B6 (NG_007929.1; LRG_1267)	15631>A	c.516G>A	*6	rs3745274
	21011T>C	c.983T>C	*18	rs28399499
CYP2C19 (NG_008384.3; LRG_584)	19154G>A	c.681G>A	*2	rs4244285
	17948G>A	c.636G>A	*3	rs4986893
	1A>G	c.1A>G	*4	rs28399504
	90033C>T	c.1297C>T	*5	rs56337013
	12748G>A	c.395G>A	*6	rs72552267
	19294T>A	g.19294T>A	*7	rs72558186
	12711T>C	c.358T>C	*8	rs41291556
	-806C>T	g.-806C>T	*17	rs12248560



Results

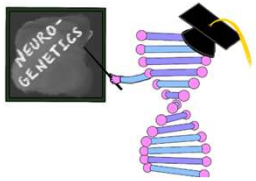
- Panel ordering requires a list of medications and potential considered medications for a personalized report

- Pharmacogenomics (PGx) panel
  - 38 genes
  - PGx interaction report
  - Personalized medicine report

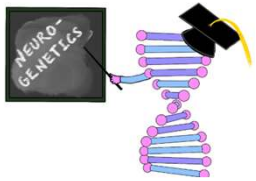


PHARMACOGENOMICS RESULTS

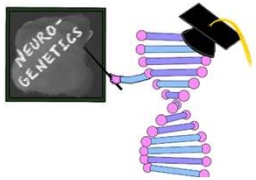
TEST	PHENOTYPE	GENOTYPE
ABCB1 rs2032582	Variant Present	C/C
ABCB1 rs2032583	Variant Present	A/G
ABCG2 rs2231142	Normal Function	G/G
ADRA2A rs1800544	Variant Absent	G/G
ADRB1 rs1801253	Variant Absent	G/G
ADRB2 rs1042713	Variant Absent	G/G
ADRB2 rs1042714	Variant Present	C/C
ANKK1 rs1800497	Variant Absent	G/G
COMT rs4680	Variant Present	A/G
CYP1A2	Hyperinducer	*1F/*1F
CYP2B6	Normal Metabolizer	*1/*1
CYP2C Cluster	Variant Present	A/A



CYP2C19	Poor Metabolizer	*2/*2
CYP2C9	Normal Metabolizer	*1/*1
CYP2D6	Intermediate Metabolizer	*1/*4
CYP3A4	Normal Metabolizer	*1/*1
CYP3A5	Poor Metabolizer	*3/*3
CYP4F2	Intermediate Metabolizer	C/T
DPYD	Normal Metabolizer	*1/*1
DRD2 rs1799978	Variant Absent	T/T
F2	Negative	G/G
F5	Negative	C/C
GRIK4 rs1954787	Variant Absent	T/T
GRK4 rs1024323	Variant Present	C/T
GRK4 rs1801058	Variant Present	C/T
GRK5 rs2230345	Variant Absent	A/A
HLA-A*31:01	Negative	AA/AA



NEUROLOGY	
brivaracetam (Briviact)	CYP2C19 Poor Metabolizer[1, 2]
carbamazepine (Equetro, Tegretol)	HLA-A*31:01 Negative[1, 2] HLA-B*15:02 Negative[1, 2]
clobazam (Onfi, Sympazan)	CYP2C19 Poor Metabolizer[1]
donepezil (Adlarity, Aricept)	CYP2D6 Intermediate Metabolizer[1]
fosphenytoin (Cerebyx)	HLA-B*15:02 Negative[1, 2] CYP2C9 Normal Metabolizer[1, 2]
modafinil (Provigil)	CYP2D6 Intermediate Metabolizer[1]
oxcarbazepine (Oxtellar XR, Trileptal)	HLA-B*15:02 Negative[1, 2]
phenytoin (Dilantin, Phenytek)	HLA-B*15:02 Negative[1, 2] CYP2C9 Normal Metabolizer[1, 2]
pimozide (Orap)	CYP2D6 Intermediate Metabolizer[1, 2]
tetrabenazine (Xenazine)	CYP2D6 Intermediate Metabolizer[1]



CHILD NEUROLOGY SOCIETY

Also includes sections for:

- Behavioral Health
- Cardiology
- Endocrinology
- Gastroenterology
- Urology
- Hematology/Oncology
- Infectious Disease
- “Other”

CHILD NEUROLOGY SOCIETY

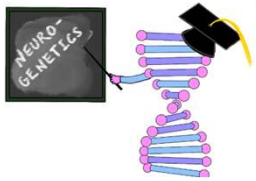
MEDICATION MANAGEMENT

CUMULATIVE DRUG-DRUG AND DRUG-GENE INTERACTIONS

IMPACT	MEDICATION	CAUSE	EFFECTS & MANAGEMENT
MODERATE	**clobazam**	• CYP2C19 Poor Metabolizer • felbamate	• Clobazam active metabolite levels may increase by >200%. • Increased risk of constipation, suicidality, fever, sedation and sialorrhea. • Monitor for adverse effects and adjust dose accordingly. • Initiate clobazam dose at 5 mg daily and slowly titrate according to weight in CYP2C19 Poor Metabolizer patients.

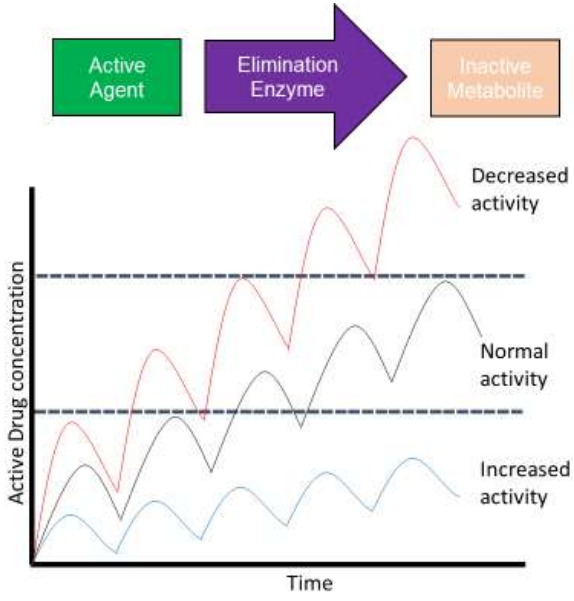
DRUG-DRUG INTERACTIONS

IMPACT	MEDICATION	CAUSE	EFFECTS & MANAGEMENT
MODERATE	**Nayzilam**	• clobazam	• Nayzilam active metabolite levels may increase by >200%. • Increased risk of agitation, respiratory depression, bradycardia, sedation, vomiting and nausea. • Decrease Nayzilam dose and monitor for adverse effects with coadministration of clobazam.



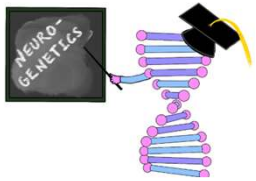
What is Pharmacogenomics (PGx)

Pharmacokinetic drug-gene interactions

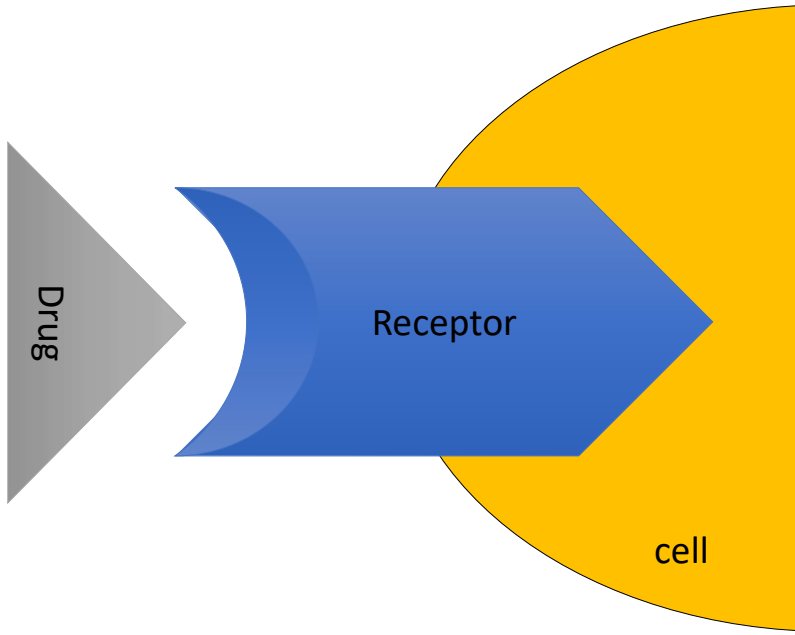


Drug concentrations above the therapeutic window may increase risk of toxicity

Drug concentrations below the therapeutic window may increase risk of inefficacy

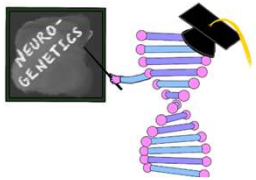


Pharmacodynamic drug-gene interactions



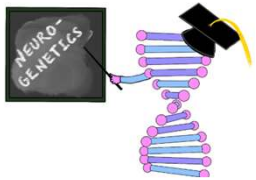
Pharmacogenomic Testing

- Most commercially available PGx tests are targeted variant assays
  - Single gene tests or PGx panel test using next-gen sequencing, real-time PCR, and microarray
- Some ES/GS tests are returning PGx as incidental findings- coverage may not be optimal so confirmatory testing may be needed
- Should not be used in patients with a history of allogeneic bone marrow transplant or liver transplant



Pharmacogenomic Test Reports

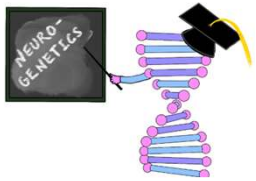
- Star allele nomenclature
  - Summarizes all genetic variant(s) occurring on a single allele/gene copy
  - Designation is used to assign functional activity of the downstream protein
  - *1 ALWAYS means no variants detected and inferred normal activity (wild-type)
  - Any other star allele number will be unique to each gene respectively
  - Pharmacogene Variant Consortium (PharmVar) sets allele definitions
- Some genes may still be reported as rsID, nucleotide position, or amino acid substitution



Pharmacogenomic Testing Results

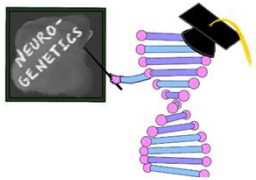
- 99% of individuals carry at least one PGx variant
  - Whether that variant is applicable to the medication of interest will be variable based on functional impact of the variant and overall patient phenotype

Example Standardized PGx Phenotype Terms		
	Phenotype	**Genotypes that confer this phenotype**
Drug metabolizing enzymes (i.e. CYP450s, UGT1A1)	Ultra-rapid metabolizer	Two increased function alleles or > 2 normal function alleles
	Rapid metabolizer	One normal and one increased function allele
	Normal metabolizer	Two normal function alleles
	Intermediate metabolizer	One normal and one decreased or poor function allele
	Poor metabolizer	Combination of decreased or poor function alleles
HLA	Positive	Heterozygous or homozygous for evaluated variant
	Negative	Wild-type



PGx Evidence and Resources

- Clinical Pharmacogenetic Implementation Consortium
- All resources freely available at cpicpgx.org
- NIH funded multidisciplinary, international consortium of pharmacogenetic experts
- Develop evidence-based guidelines on HOW to apply pharmacogenetic results into patient care
- DO NOT provide recommendations on when to obtain testing



<u>Existing CPIC guidelines for ASM</u>

- Carbamazepine
  - HLA-B*15:02
  - HLA-A*31:01
- Oxcarbazepine
  - HLA-B*15:02
- Phenytoin
  - HLA-B*15:02
  - CYP2C9

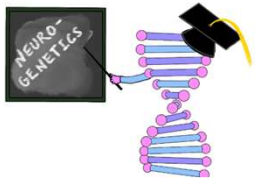
CPIC Guidelines

- Summarizes gene and medication and describes evidence of gene-drug interaction
- Provides recommendation for modifying therapy based on the genotype
  - Table 1: Defines how to assign phenotype with example diplotypes

Table 1 Assignment of *HLA-B* and *HLA-A* genotypes

Genotype	Definition	Examples of diplotypes
*HLA-B*15:02* negative	Homozygous for an allele other than *HLA-B*15:02*	$*X^a/*X^a$
*HLA-B*15:02* positive	Heterozygous or homozygous variant	$*15:02/*X^a$, $*15:02/*15:02$
*HLA-A*31:01* negative	Homozygous for an allele other than *HLA-A*31:01*	$*Y^b/*Y^b$
*HLA-A*31:01* positive	Heterozygous or homozygous variant	$*31:01/*Y^b$, $*31:01/*31:01$

[a]Where *X = any *HLA-B* allele other than *HLA-B*15:02*. [b]Where *Y = any *HLA-A* allele other than *HLA-A*31:01*.

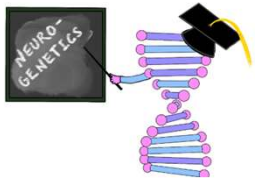


CPIC Guidelines Continued

- Summarizes gene and medication and describes evidence of gene-drug interaction
- Provides recommendation for modifying therapy based on the genotype
  - Table 2: Provides drug therapy recommendations by **genotype**

Table 2 Recommendations for carbamazepine therapy based on *HLA-B* and *HLA-A* genotypes

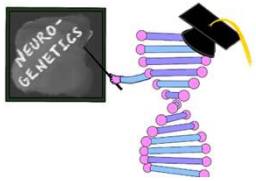
Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative and *HLA-A*31:01* negative	Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	Use carbamazepine per standard dosing guidelines.[b]	Strong	N/A
*HLA-B*15:02* negative and *HLA-A*31:01* positive	Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	If patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent.



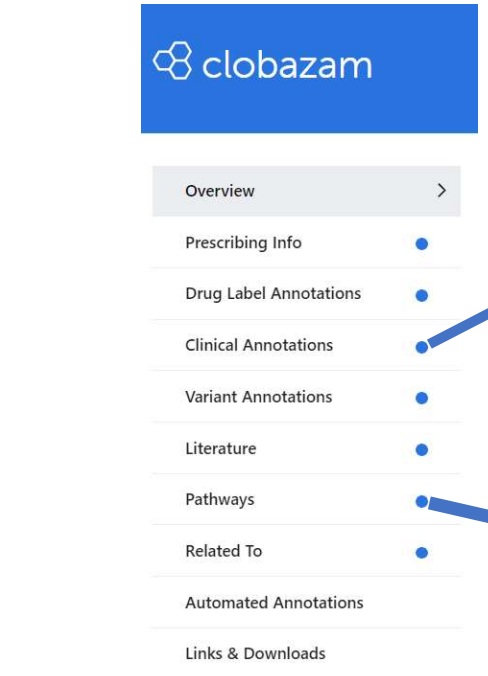
Food and Drug Administration

- Drug labeling may have required pharmacogenomic considerations (any type)
  - Carbamazepine BBW
  - Oxcarbazepine and phenytoin – Warnings and Precautions
  - Clobazam - Dosing
- Table of Pharmacogenetic Associations:
  - Drug-gene associations for alerted drug metabolism and response

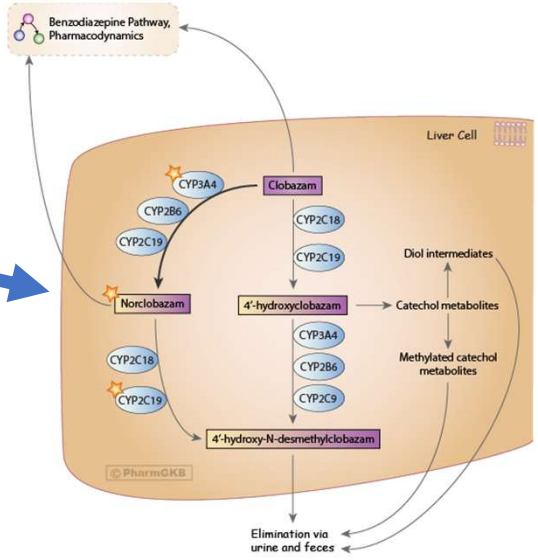
	Drug	Gene
Actionable	Carbamazepine	HLA-B*15:02
	Clobazam	CYP2C19
	(Fos)phenytoin	HLA-B*15:02 and CYP2C9
Safety	Carbamazepine	HLA-A*31:01
	Oxcarbazepine	HLA-B*15:02

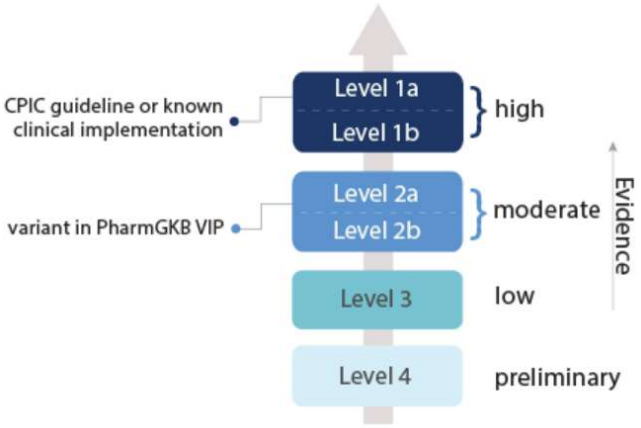


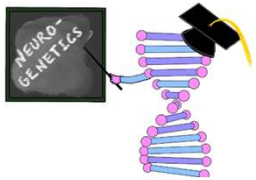
Pharmacogenomics Knowledgebase (PharmGKB.org)



	LEVEL	VARIANT	GENE	DRUGS	PHENOTYPE CATEGORIES	PHENOTYPE
Details	Level 3	CYP2C19*1, CYP2C19*2, CYP2C19*3	CYP2C19	clobazam	Efficacy	Epilepsy
Details	Level 3	CYP2C19*1, CYP2C19*2, CYP2C19*3	CYP2C19	clobazam	Dosage	Epilepsy
Details	Level 3	CYP2C19*1, CYP2C19*2, CYP2C19*3	CYP2C19	clobazam	Metabolism/PK	Epilepsy







PGx Testing Recommendations for ASM

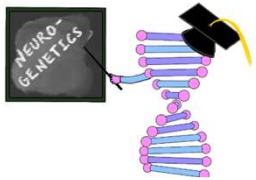
Pre-emptive testing: carbamazepine

- FDA drug label

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

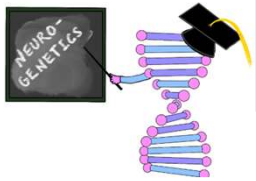
SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS, LABORATORY TESTS**).



PGx Recommendations for ASM

- CPIC guideline recommendations

Medication	Phenotype	Therapeutic impact	Recommendation
Carbamazepine	HLA-A*31:01 positive	↑ risk of severe cutaneous adverse reactions	Avoid carbamazepine
Carbamazepine	HLA-B*15:02 positive	↑ risk for Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN)	Avoid carbamazepine
Oxcarbazepine	HLA-B*15:02 positive	↑ risk for SJS/TEN	Avoid oxcarbazepine
(Fos)phenytoin	HLA-B*15:02 positive	↑ risk for SJS/TEN	Avoid (fos)phenytoin
(Fos)phenytoin	CYP2C9 Intermediate metabolizer (AS=1)	↓ metabolism, ↑ concentrations will ↑ probability of toxicities	Use typical loading dose. ↓ maintenance dose ~25% and adjust with TDM
(Fos)phenytoin	CYP2C9 Poor metabolizer	↓ metabolism, ↑ concentrations will ↑ probability of toxicities	Use typical loading dose. ↓ maintenance dose ~50% and adjust with TDM

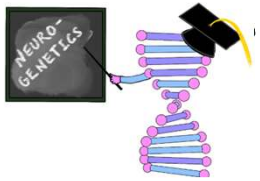


PGx Recommendations for ASM

- Clobazam
  - FDA (2019) drug label-
    - Usual dosing:

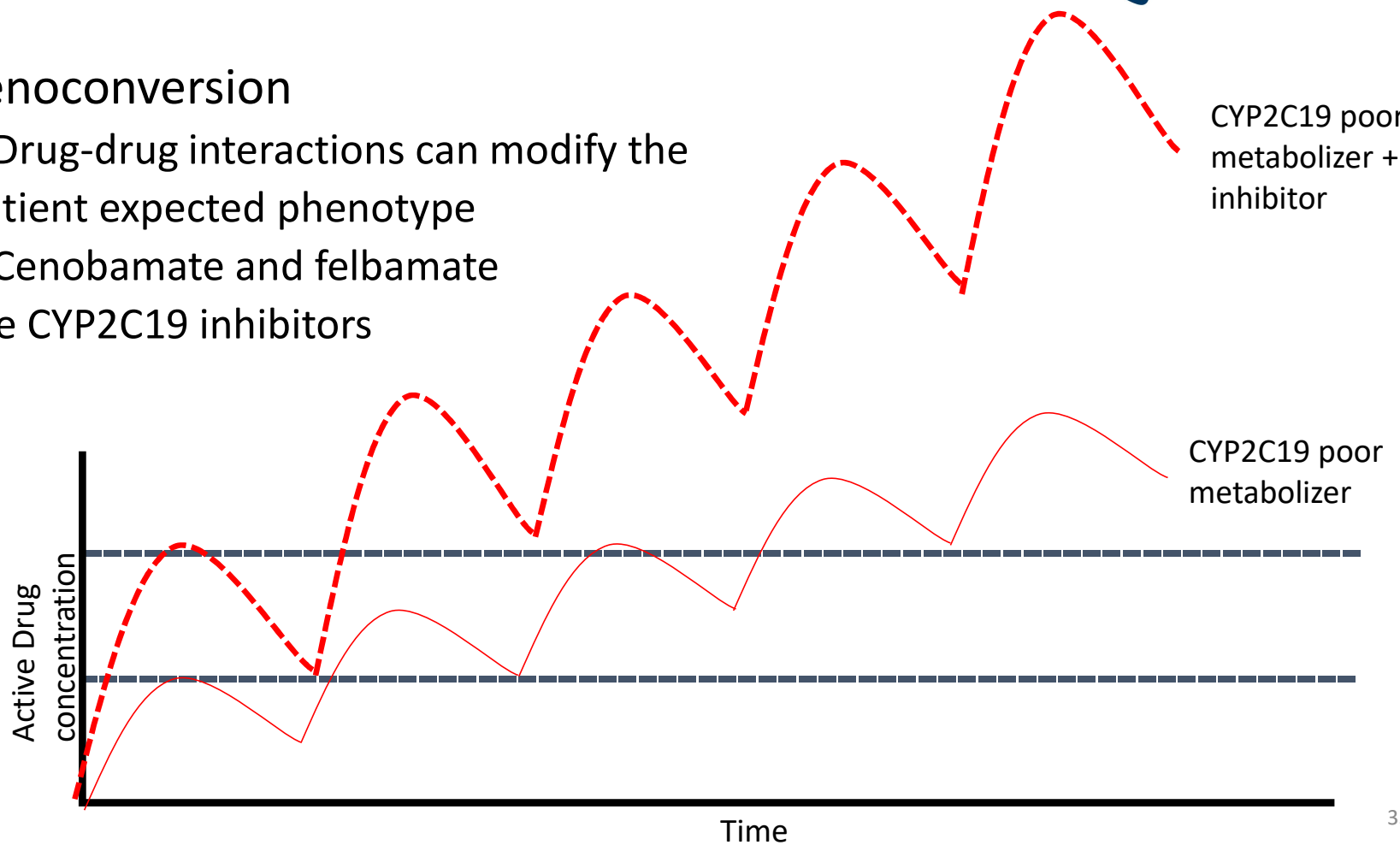
Total daily doses	<=30kg weight	>30 kg weight
Starting dose	5 mg	10 mg
Day 7	10 mg	20 mg
Day 14	20 mg	40 mg

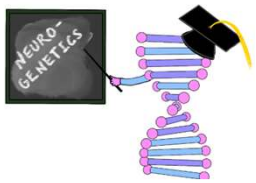
  - Actionable for CYP2C19 poor metabolizers
    - Start at 5 mg/day and titrate slowly according to weight to half the max recommended dose
    - Max dose (20 or 40 mg) may be considered on day 21 based on clinical response
  - PharmGKB: Level 3 (Low level evidence)
  - CPIC Level: B/C



Non-PGx Considerations

- Phenoconversion
  - Drug-drug interactions can modify the patient expected phenotype
  - Cenobamate and felbamate are CYP2C19 inhibitors





Clinical Implications of PGx

Table 1. *CYP1A2, CYP2C9, CYP2C19, EPHX1*, and *ABCB1* genotypes, phenotypes, and frequencies.

Gene	Genotype	Phenotype	Frequency
CYP1A2	*1/*1F	EM	15/21 (71.4%)
	*1F/*1F	FM	6/21 (28.6%)
CYP2C9	*1/*1	EM	11/21 (52.4%)
	*1/*2	IM	5/21 (23.8%)
	*1/*3		4/21 (19%)
	*2/*3	PM	1/21 (4.8%)
CYP2C19	*1/*1	EM	10/21 (47.6%)
	*1/*17		3/21 (14.3%)
	*1/*17	FM	1/21 (4.8%)
	*1/*2	IM	6/21 (28.5%)
	*2/*2	PM	1/21 (4.8%)
EPHX1	337T>C (CC)	↓ efficacy CBZ	6/21 (28.5%)
ABCB1	3489+80C>T (CC)	Drug-resistant	6/21 (28.5%)
	3489+80C>T (CT or TT)	Drug-sensitive	7/21 (33.3%)

Legend: EM= extensive metabolizer (standard); FM= fast metabolizer; IM= intermediate metabolizer; PM= poor metabolizer.

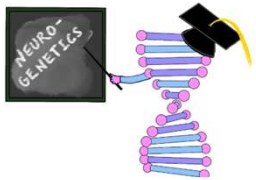


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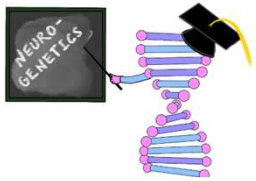
Table 3. Clinical implications and importance of pharmacogenetic testing according to each patient's characteristics

Patient code	Gender	Age (y)	Diagnosis	Comorbidities	Failed treatments	Current treatment	Genetic variants (phenotypes)	Clinical implications
#1	M	18	FNLE	None	CLB, CBZ	OXC, LCM, PER, LEV	CYP2C9 *1/*2 (IM) CYP2D6 *41/*41 (IM)	Increased risk of AEs with LCM
#2	M	14	FNLE	ID	CLB, PER	TPM, CBZ	CYP1A2 *1F/*1F (FM) CYP2C9 *1/*2 (IM) ABCB1 3489+80CC	CBZ is the optimal choice
#3	F	14	EE	ID, psychosis	VGB, NZP, VPA, CLB, TPM, ACTH	ACZ, LTG, ZNS, PER	CYP2C19 *1/*2 (IM)	CLB could have been avoided
#4	F	5	EE	ID	CLB, GVG, LTG, TPM	VPA, RFM, ACZ, NZP	CYP2C9 *1/*2 (IM) CYP2C19 *1/*2 (IM)	CLB could have been avoided
#5	F	9	GGE	ID	ACTH	LTG, VPA	EPHX1 337 CC	CBZ should be avoided
#6	F	7	FNLE	None	PB, LEV, CCS	VPA, TPM, CLB	CYP2C19 *2/*2 (PM) EPHX1 337 CC	Increased risk of AEs with CLB; CBZ should be avoided
#7	M	19	EE	ASD, ID	LEV, ETS, ZNS, FBM, LTG, TPM, PB, CBZ, VGB	VPA, CLB, RFM	CYP1A2 *1F/*1F (FM) ABCB1 3489+80CC	Pharmacoresistance could have been predicted
#8	F	30	EE	ID	VPA, ZNS, TPM, CLB, ETS, LTG, FBM, PHT	LEV, OXC, CNZ	CYP1A2 *1F/*1F (FM) CYP2D6 *2/*4 (IM) ABCB1 3489+80CC	Pharmacoresistance could have been predicted
#9	M	6	GGE	ASD, ID	VPA, ETS	None	CYP2C9 *1/*3 (IM) ABCB1 3489+80CC	VPA could have been avoided
#10	F	8	GGE	None	VPA, CNZ	ETS, LCM	-	None



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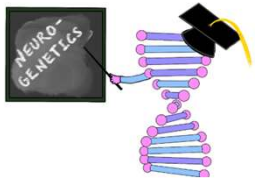
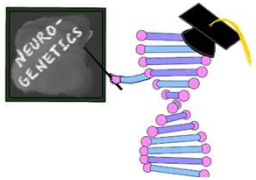
Patient Follow-Up

- Clobazam was stopped
- N-desmethylclobazam levels decreased over 3 months until undetectable
- Mental status improved slowly over this time
- Remains clinically seizure-free on felbamate and ethosuximide



Take Home Points

- Pharmacogenomic testing is becoming an increasingly useful tool in neurology
- May be particularly useful in patients who have not responded as expected to medication regimens
- Drugs such as carbamazepine, oxcarbazepine, and phenytoin may have safety implications that can be delineated with pharmacogenomic testing
- Other drugs may have dosing implications specific for patients
- More information at cpicpgx.org



Suggested Reading

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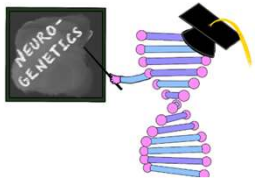

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Committee members:
- Daniel Calame (Baylor)
- Divakar Mithal (Northwestern)
- Christa Habela (Hopkins)
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