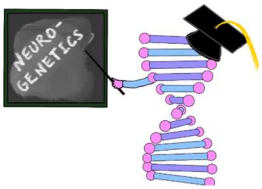


Teaching Guide

Module 15: Pharmacogenomics

Slide 1: Title.

Slide 2: Text on slide.

Slide 3: Present the chief complaint.

Slide 4: Interactive slide – **list potential etiologies for the chief complaint**. This can be broad and include genetic and non-genetic etiologies.

Slide 5: Potential etiologies on the differential. This list is not expansive.

Slide 6-7: Text on slides. Expand on the chief complaint with a more thorough history.

Slide 8: Pedigree – **only notable for a paternal great grandmother with epilepsy (questionable).** Several cousins with potential learning problems, ASD.

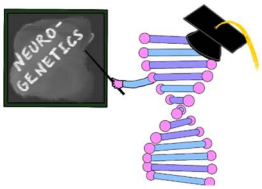
Slide 9: Text on slide.

Slide 10: Review the text on slide. Moderator should ask the participants if there are any other labs they would request.

Slide 11: Reveal that the **N-desmethylclobazam level is excessively high,** despite recent dose decrease and clobazam level in normal range.

Slide 12: Moderator should prove if participants have any background information that may explain these lab findings. Patient has been stable on clobazam for 6 months, dose was decreased with felbamate start. *Why is N-desmethylclobazam level still so high?*
Any other work-up?

Slide 13: Introduce the field of pharmacogenomics. Text on slide. This field is newly emerging and may become more prominent in **creating "personalized medicine" for patients**. Note that there is direct-to-consumer marketing and some patients have sought out this testing on their own, paid out of pocket, and present the results to their physicians.



Slide 14: Sample of the genes found on one commercial pharmacogenomic panel. Current panels vary in number of genes assessed from 20-38. These genes include:

1. Genes/proteins that metabolize medications:
    a. cytochrome P450 family (CYP)
    b. drug transporters
    c. Other enzymes that metabolize drugs like uridine diphosphate glucuronosyltransferase (UDP-glucuronosyltransferase), which transforms fat-soluble molecules into water-soluble ones for secretion.
2. immune system genes that can be associated with adverse effects from medication (e.g., HLA-B and carbamazepine)
3. others that can affect receptor sensitivity (e.g., GRK5, a G-protein coupled receptor).

Slide 15: **Pharmacogenomic panels probe for specific nucleotide changes** that are known to play a role in variable drug metabolism or response. This slide shows a subset of potential gene changes that are reported. If there is a single variant to report, they may be reported as "presence or absence" of the variant. If there are multiple variants that may affect metabolism, they are classified as "star alleles". This will be discussed further later in the lecture.

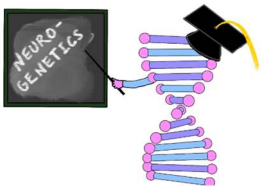
Slide 16: A pharmacogenomic panel was ordered for our patient. Of note – to order a panel, the lab requests a list of current medications and a list of potential medications for consideration. This allows them to create a "personalized medicine report" and can help guide treatment.

Slide 17-18: Our patient's results. Multiple variants are present which will be further evaluated in the remainder of the report. **The patient also has several CYP variants associated with a "hyperinducer" phenotype and "poor metabolizer".**

Slide 19: The report then provides interpretation for various medications that may be affected by the pharmacogenomic profile. <u>As a CYP2C19 poor metabolizer, they recommend caution with clobazam.</u>

Slide 20: The personalized profile also gives more specific recommendations based on the patient's current medication list.

Slide 21: *What is pharmacogenomics?* It allows us to better assess pharmacokinetic and pharmacodynamic drug-gene interactions to improve individual patient safety, limit side-effects and inform medication choices. [Reminder: Pharmacokinetics encompasses how the drug moves in the body (absorption, distribution, time to peak, metabolism/chemical modification, excretion) and pharmacodynamics are the drug's molecular/biochemical/physiological effects. Also remember that for a given drug, there can be active and inactive metabolites.]



Slide 22: Text on slide. **Single gene testing can be used if there is a specific concern** (i.e. – HLA typing prior to initiation of carbamazepine.) Allogenic BMT or liver transplant would mean that the patient's leukocytes sequenced may not match the genotype of the relevant cells (e.g. hepatocytes that carry out the metabolism.

Slide 23: **The star allele nomenclature was developed to simplify and standardize notation of gene-level haplotypes (**combinations of all genetic variants on a single allele of a gene), instead of writing out each individual genetic variant, sort of a shorthand. 1* is the reference haplotype. This was initially (and still is mostly) used for the cytochrome P450 genes, and now their star allele nomenclature is also used for other gene families: UDP-glucuronosyltransferase (UGT) and N-acetyltransferase (NAT). More info here: https://ascpt.onlinelibrary.wiley.com/doi/full/10.1038/sj.clpt.6100284.
The PharmVar website is here: https://www.pharmvar.org/

Slide 24: Text on slide.

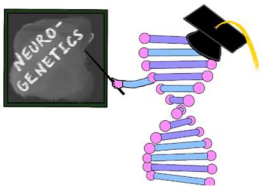
Slide 25: There is a consortium to help establish guidelines in pharmacogenomic testing. At this point, few guidelines exist for how to include pharmacogenomics in anti-seizure medication management outside of HLA typing. ASM = anti-seizure medications.

The primary guideline resource used in the US is the CPIC guidelines.
CPIC is an NIH funded consortia of experts who write clinical guidelines for how to apply pgx results in clinical medication decisions. CPIC **DOES NOT** make recommendations for when to obtain pgx testing, all guidelines are written with the assumption that the genetic information is available.

Slide 26: **CPIC (Clinical Pharmacogenetic Implementation Consortium) guidelines** follow a consistent structure wherein they provide a summary of the gene and drug and then review the evidence for the drug-gene interaction and finally provide clinical recommendations about how to manage therapy based on the patient phenotype.

Slide 27: Tables within the guideline are always consistent- **the first table reviews the genotype assignment for the gene/diplotype while table 2 provides the drug therapy recommendations by each genotype**. Diplotype is the combination of the two haplotypes that a patient has.

Slide 28: Text on slide. Note that FDA recommendations for clobazam dosing were recent. BBW = black-box warning.



Slide 29: The PharmGKB.org website is an excellent resource to get more information about how pharmacogenomics may influence various drugs.

Slide 30: For ASMs, **current FDA labeling only recommends HLA screening for at-risk patient populations (those from Asian ancestry)** prior to starting carbamazepine due to the risk of Stevens Johnson syndrome.

Slide 31: CPIC guidelines have recommendations for carbamazepine, oxcarbazepine, and fosphenytoin. AS=1 means activity score =1, where AS=2 is 2 functional alleles and AS=0 is no function for metabolism. TDM = therapeutic drug monitoring.

Slide 32: **The FDA has recently issued "actionable" guidelines for clobazam dosing based on CYP2C19 testing,** suggesting a lower dose for patients who are poor metabolizers. This has moderate evidence in PharmGKB.

Slide 33: There are also non-pharmacogenomic considerations to consider, which likely led to the presentation of our patient. In addition to being a poor metabolizer, felbamate is a CYP2C19 inhibitor, which compounded the elevated level of the clobazam active metabolite.

Slide 34: There have been limited studies on pharmacogenomics in anti-seizure medications to date. A recent pilot study of 21 patients performed saliva testing on 5 common genes involved in ASM metabolism and found a significant number of patients with at least 1 potentially impactful variant.

Slide 35: In reviewing the patient histories, the authors found clinical implications of **pharmacogenomic testing that may have influenced treatment plans**. This suggests that pharmacogenomic testing may have a greater role in ASM selection in the future.

Slide 36: Text on slide to review patient follow-up**. It is notable that it took months for the clobazam metabolite level to become undetectable given the slow metabolism**.

Slide 37: Text on slide.

Slide 38: Suggested reading.

Slide 39: Acknowledgements.