**Question: What is the most important message to parents of children with epilepsy regarding genetic testing?**

**Answer:** While every situation and family is different, it is important for parents to be aware of the testing options, understand the pros and cons of getting genetic testing, and have realistic expectations for what information genetic testing may provide. Connecting families with resources and communities that can help them on their journey and answer questions can be beneficial.

**Question: How do you deal with VUS in clinical practice?**

**Answer:** It's mostly dependent on the VUS and the gene:

- Does it fit the phenotype?
- Test parents if available, but make sure you know their phenotype to help with interpretation. This can still be difficult because so many genes associated with epilepsy can have a variable phenotype and reduced penetrance. If doing an exome/genome, try as hard as possible to do a trio on the front end so parental information is already included in the analysis
- Are there other relatives to test that would be informative? For example – an affected cousin.
- Look for any publications regarding the VUS (often there aren't any).
- Are there additional labs (biochemical, methylation, etc…) or imaging that can be ordered to help with interpretation?
- Check population databases but remember the caveats
- There are some online tools to help with VUS interpretation – these all have limitations but can be helpful because they show you how they arrived at the classification
- There will be a new variant classification guideline coming out "soon" that is supposed to provide even more of a spectrum – such as "VUS leaning likely path" "VUS leaning likely benign", etc…
- Genematcher is an excellent resource to connect physicians/providers who have patients with VUS in candidate genes – this is not really for VUS in known disease-causing genes, but rather to try to help with increasing the identification of disease-causing genes.

**Question: Do we need to repeat WES/WGS in few years or just reanalyze the data from the old test?**

**Answer:** We usually just do a reanalysis because many labs offer one free reanalysis. We try to wait 2-3 years between reanalyses. There are some caveats – for example, a WES that was run many years ago may have used older technology so it could be recommended to actually run a new WES/WGS – I recommend calling the lab to ask if the WES was done prior to 2016-2018. If it is a lab that doesn't offer free re-analysis and you did an exome, you could consider trying WGS if insurance will cover. There are limited insurance companies that will cover genome and they often have strict criteria.

**Question: Thoughts on using the term inconclusive vs. negative as the testing outcome on reports with a VUS? Thoughts on finding community/support as a consideration for reclassifying a VUS?**

**Answer**: I do not personally like when a laboratory classifies a result as "negative" when there is a VUS because it implies that nothing potentially related was identified. It's tough to answer the community/support question – many times family members will actually ask about specific variants, so it is possible that someone could go to an online group and ask "has anyone had this variant reported before?" The difficulty is if one other person says yes, we won't have that individual's medical history so it may be hard to get enough information to help with reclassification.

**Question: What education is needed for child neurologists to be able order, interpret and provide the counseling needed for WES and GS?**

**Answer**: I find it most helpful when residents/fellows get exposure to genetics during their training so they can take it into their practice. For already practicing physicians, CME programs listed below, but also connecting with a local geneticist/genetic counselor would be my recommendation. Because many genetics clinics are so busy, often they are happy to try to help other providers become comfortable with ordering testing themselves and interpreting results. Some facilities will have a specific genetic counselor who is affiliated with their clinic who can be the one to help facilitate, and I think this is becoming more common in epilepsy.

- The Jackson Laboratory Genetic Testing in Pediatric Neurology (CME)
- NIH Healthcare Provider Genomics Education Resources
- AES Genetic Testing and Epilepsy CME

**Question: Does tissue sampling in patients with grey matter heterotopia yield a increased chance of finding a genetic component or is peripheral preferred?**

**Answer:** I have found a couple publications regarding subcortical band heterotopia and somatic mutations being identified, particularly in DCX. But there are very few. We haven't ourselves done this thus far. There aren't really clinical guidelines around genetic testing in affected tissue for these conditions, so often the genetic testing is done because someone is already undergoing surgery for their clinical care.

**Question: For Dalila Lewis - I was wondering if your patient with a VUS in the LAMC3 gene had just one or two variants identified. As this condition is expected to follow an autosomal recessive inheritance pattern, one variant.**

**Answer:** I did not have the final genetics report but I believe a compound heterozygous variant was identified.

**Question: For young adults (say age 20-30s) with seizures with unusually aggressive progression, leading to surgical evaluation within a year of diagnosis, how should i be thinking about testing for channelopathies, etc? Any resources on comparing medical vs surgical outcomes?**

**Answer:** It is not possible to compare medical vs surgical outcomes without knowing what the cause of this progression.

I would think more broadly and not just about channelopathy. In fact, there are a few metabolic diseases that can have a rapid progression after a few years of well controlled epilepsy. The other possible causes include mitochondrial diseases and finally, if there is myoclonus and ataxia or tremor, I would consider a progressive myoclonic epilepsy (PME).

In terms of genetic testing, if there's a clinical suggestion of PME, I would go for a PME panel that includes evaluation of the dodecamer repeat of CSTB gene.

Otherwise, I would do a whole exome sequencing. Finally, if the clinical picture is appropriate, I would consider mitochondrial diseases (other then MERRF, which should be tested on the PME panel).

If all those above are negative, I would consider either a genome or if difficult to order, I would do a chromosome microarray.