Learning for Life Week 4 Summary

Topic: Transforming Cardiology Using Genetics

Speakers: Elizabeth McNally and Robert Gregory Webster

An impressive session on Wednesday where we heard about the power of collaboration between the basic science behind genetic analysis of disease and its impact on actual patients and families who have cardiac conditions. Beth McNally is the director of Northwestern's Center for Genetic Medicine and began the presentation by explaining the work that is being done in identifying the genes that are responsible for many diseases. This session focused on cardiac diseases, specifically cardiomyopathies (disease of the heart muscle) and cardiac arrhythmias (abnormal heart rhythms) that can lead to sudden cardiac death, but the center also does work on genetic variations identified with cancers, neurological disease and muscular dystrophy.

Beth explained that an individual human has about twenty thousand genes. Their center tests up to 100 specific genes that have been associated with cardiac disease. While mapping an individual's genome has become much less costly and easy to perform, it is not always straightforward to identify which genetic variants are associated with disease. Based on current data bases of individuals who have shared their genome via blood samples, researchers can identify genetic variations that range from high frequency variants which generally are ancestral traits (what you would get from ancestry.com) and do not cause disease, to rare frequency variants which are associated with disease. The challenge is in the majority of variants called "variants of uncertain significance". It is not clear if these mutations in genes cause diseases. More sequencing of individuals' genomes will allow for better classification of these variants of uncertain significance. She told us that an NIH sponsored project called "All of Us" (https://allofus.nih.gov/) is attempting to map the genome of one million or more people in the United States.

Finding a genetic mutation or variant does not necessarily mean that an individual will develop a disease Researchers and clinicians use family trees which can identify inheritance patterns to help isolate the genes associated with certain conditions. However, even if that variant may result in a disease in one individual, there are variations in how the gene is expressed in others. The presence of co-existing mutations or environmental factors influence how a genetic mutation may be expressed.

Greg then used actual patient cases to describe how he applies the principles outlined above to populations of people- specifically, patients and families affected by sudden cardiac death- a condition that occurs when a life-threatening arrhythmia occurs in an otherwise healthy person. He has developed a national network involving coroners in 15 US states who send his team blood samples of patients along with any clinical evidence (like pathological slides and family histories) who have died of sudden cardiac death from a presumed arrhythmia. He can then look for known genetic mutations associated with cardiac death in these patients. He described a "molecular autopsy conference" where clinicians look at whole genome sequencing, the patient's pathology slides and family history to understand the details of the patient's death and most importantly, to then work with the family members to identify any others affected individuals. Treating those individuals carrying the same gene with certain

medications or in some cases with an implantable defibrillator can prevent a similar fate for family members.

Take home points:

1. A human genome can be mapped for as little as $1,000.00 when just a few years ago, the cost was in the millions
2. Mapping of thousands of genomes has allowed medicine to identify genes that are associated with certain conditions, but the significance of many genes is yet to be ascertained.
3. Clinicians and researchers use family inheritance information to help associated genetic variations with disease.
4. Sudden cardiac death is associated with a number of specific genetic variations/mutations. Identifying patients who have these mutations allows for interventions which can save their lives.
5. LEARN CPR!!