Innovative Approaches Working Group
Universal Team-Based Learning Activity
Exercise 4
Polygenic Disease Testing and Pharmacogenomics

Objectives: By the end of the session, you will be able to:

1. Describe utility of genetic/genomic testing in polygenic diseases.
2. Interpret genetic/genomic testing in the context of patient history
3. Describe benefits and limitations of pharmacogenomic testing
4. Use online tools to interpret the clinical significance of genomic data
5. *Possible objective: Describe the process of microarray analysis (in a lecture component)*

Case Presentation
Part 1:

The woman with *(disease)* from Exercises #1 and #2 has two older brothers, one of whom suffers from *(a different illness related to your specialty that is polygenic)*. The second brother, at age 38, has been healthy but is concerned that he is at high risk for *(same illness as brother)* , given what happened to his brother and the fact that their father is also affected *by (a similar or same illness as brother related to your specialty).*

Because of this concern, as well as the fact that his sister has been diagnosed with *(disease from exercise #1)* , the second brother (who will be referred to as the "patient" in this Exercise) is interested in genotyping to determine his disease risk.

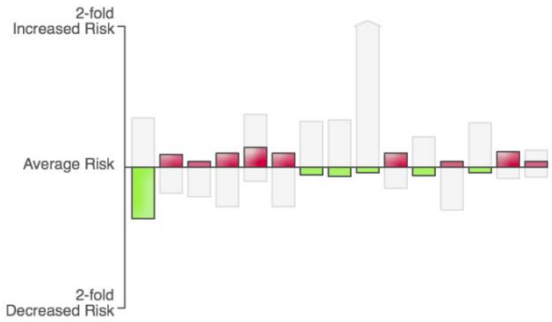
1. **Using http://www.snpedia.com/ (*Can also consider use of http://www.ncbi.nlm.nih.gov/snp)***

    a. **List 3 SNPs that are associated with *(brother's disease)*. For each SNP, what are the low risk and high risk alleles? Is the frequency of the at-risk allele similar in different ethnic groups?**

    b. **For one of the above SNPs, list a PubMed reference that supports the association of the SNP with the disease. Describe the study methods and the strength of the evidence.**

    The idea is to get the learner thinking about genome-wide association studies (GWAS) and whether they are useful in determining individual patient risk.

2. **To try and learn more about his disease risk, the patient signs up for direct-to-consumer genotyping. The company tests for 15 genetic markers (SNPs) related to *(brother's disease)* and the graph below is provided by the company to illustrate the predicted effects on risk of (compared to the average person of European ancestry) from each of the SNPs:**



The chart shows the approximate effects of the selected person's genotype at the 15 reported markers. Higher, red bars indicate increased risk from the average, while lower, green bars indicate decreased risk from the average. The light gray bars show the maximum possible effects for the possible genotypes at the marker.

When you add up the predicted effects on risk, you find that the patient's risk (based solely on the 15 SNPs) is only slightly higher than that of an average Caucasian man of the same age.

3. **Given the patient's family history, are you reassured by this genetic risk assessment? How certain are you that the 15 SNPs capture the true inherited predisposition for *(brother's disease)*? Why?**

4. **Would this genetic risk assessment be relevant if the patient were not Caucasian but rather of a different ethnicity? Why or why not?**

5. **Should the patient be treated any differently than the typical 38-year-old man in regard to risk for *(brother's disease)*? Why or why not?**

Case Presentation
Part 2:

The following year, at age 39, the patient develops *(similar illness as brother and father)* . *(can also enter additional information regarding presentation (e.g., symptoms)).*

The patient is initially prescribed *(drug in which there is some pharmacogenomic data)* at standard dosing. However, the patient tells the medical team that he has had his "genome sequenced," and that he remembers that there was information about *(prescribed drug)* in the report.

6. **Using https://www.pharmgkb.org, what gene(s) are associated with the efficacy of the prescribed drug? How do these gene(s) affect treatment?**

7. **Below are the patient's genotypes at the best characterized sites of variants in *(a gene the learner would have figured out from question #1)*. The "reference base" is the DNA base found in that position in the vast majority of people's chromosomes. The "variant base" represents a**

mutation that possibly alters the function of the protein product. Of note, the normal version of the gene (i.e., a version without any variant bases) is called the *1 allele.

Example of data to be presented:

Allele Name	Nucleotide/ Amino Acid Change	Reference Base	Variant Base	Patient Genotype
*2	191g>a/P27G	G	A	G/A
*3	17948g>a/W212X	G	A	G/G
*4	1a>g/M1V	A	G	A/A

8. **Using the allele names described above, what is his genotype? Using https://www.pharmgkb.org, what is the predicted pharmacologic effect of the patient's genotype? What are the possible clinical consequences for the patient, assuming he takes the standard dosing of (*prescribed drug*)?**

9. **Using https://www.pharmgkb.org and PubMed:**

   a. **Should you adjust the patient's dosing based on the pharmacogenomic testing? Explain your reasoning in the context of the existing literature.**

   b. **Should genotyping for the *(gene under discussion)* be prospectively performed in all patients before they are prescribed *(drug under discussion)*? Explain your reasoning in the context of the existing literature.**

   c. **Would your answer to "b" change based on the frequency of altered (i.e., reduced or increased) function alleles in the population? Explain why or why not.**