ANSWERS TO SUMMARY QUESTIONS

Introduce your patient to the class!  *Who is he? What is his story?* *(see the referral form)*	Jeff is a 46 y.o. male of Scottish descent who was initially diagnosed with Cirrhosis & Diabetes due to alcoholism An initial trip to the hospital emergency room with blurry vision, dizziness, and confusion caused the attending physician to his measure blood sugar levels. With a blood glucose value of 617, they diagnosed him with Diabetic Ketoacidosis. They also noticed that he had significant ascites fluid in his abdomen, splenomegaly (an enlarged spleen), and that his liver enzymes were elevated. He appeared to be in kidney and liver failure. After a few convulsions, which were attributed to DTs, the staff diagnosed him with Cirrhosis of the liver due to chronic alcoholism and subsequent adult-onset Diabetes (despite denials of alcoholism from Jeff and friends and relatives). After a week in the hospital, he was told to radically change his diet, abstain from alcohol and was prescribed insulin. But his health did not significantly improve and a few months later, while visiting an ex-girlfriend's father (a retired pathologist and a fellow diabetic), while looking through a physician's desk reference manual - he read an entry on "hemochromatosis" which was cross-referenced with diabetes (as a cause for) and cirrhosis (as a cause for). Returning home, he demanded his physician order another blood test and a genetic test (that he had found mentioned in the manual). In addition to his own health, getting a proper diagnosis was of particular importance to him, because of the genetic nature of the disorder, and its potential implications for his brother and twin sister.
What was the preliminary diagnosis and the rationale for it? *(see the referral form)*	Assuming his claims of limited drinking is correct, then evidence of liver damage, sugar dysregulation, spleen, and eye problems along with his western european ancestry - suggest testing for Hemochromatosis.
What did the genetic test find and how does this relate to the preliminary diagnosis? *(see the genetic test result form)*	Two genetic pathogenic variants in his HFE gene causing homozygous protein residue changes from Cysteine to Tyrosine at amino acid residue 282.
What is the implicated/affected gene and what is its normal function? *(NCBI's Gene database should help!)*	The HFE (homeostatic iron regulator) gene regulates iron absorption by impacting the interaction of the transferrin receptor with iron-transport protein transferrin.
Where in the gene and gene product is the patient's genetic variant located? *(Where in the gene? In what part of the mRNA? Where in the protein? In what functional part of the protein?)*	The gene is on chromosome 6p22.2. The variant is in the HFE Gene: NG_008720.2:g.10633G>A and is encoded in the HFE Protein: NP_000401.1:p.Cys282Tyr It is in the middle of the protein at a residue involved in a disulfide bridge.
What is the molecular impact of the genetic variant on the gene product? *(What do you think the variant ended up doing to the protein structurally?)*	In changing the Cysteine to a Tyrosine, you lose the ability of the residue to participate in a disulfide bridge which is a structural stabilize for the protein. So the protein unfolds and is targeted for degradation by the cell's "unfolded protein response".
What *do you think might be* the functional impact of the variant on the gene product and in the patient? *(What impact do you think the variant had on the function of the protein? How might this relate to the patient's symptoms?)*	If there isn't functional HFE protein (because it got degraded), then it cannot serve as a competitive inhibitor to prevent excess ferro-transferrin from binding to the transferrin receptor. Thus, an unending stream of iron is "dumped" into the cell, causing an increase in reactive iron ions causing indiscriminate damage to the cell. Transferrin receptor is on lots of tissues including the liver, kidney, spleen, adrenal gland, and other organs which happen to coincide with Jeff's symptoms.