Case Background: A 71-year-old man is admitted to the emergency room complaining of severe abdominal pain. He describes persistent, dark urination, tingling in his toes and feet, nausea that has been more noticeable over the past 4 months, and appears slightly jaundiced. Two years prior, his primary care physician had diagnosed him with type-2 diabetes after running a routine blood test. His glucose level was 129 mg/dL (normal is less than 100 mg/dL) and his glycosylated hemoglobin was 6.2%. He was sent home to follow up with an endocrinologist.

Clinical Findings: An ultrasound of his abdomen reveals a small mass on his liver, as well as several other small masses throughout the small intestine and abdominal cavity. One mass from his liver is biopsied and found to be a glucagonoma, or a tumor that causes the hormone glucagon to be secreted, which increases blood glucose levels and can lead to diabetes. Upon further testing, it is determined that he has been living with undiagnosed pancreatic cancer, which has now advanced to stage four. Doctors suspect that there is a mutation somewhere in the MAPK pathway.

Physicians first prescribe him an insulin antagonist, which binds to tyrosine kinase receptors and inhibits other growth factors from binding. Yet, the cancerous cells continue to proliferate and more tumors form. Next, he is prescribed Mekinist (Trametinib), which inhibits the MEK protein that is involved in the signal cascade of the MAPK pathway. His symptoms subside for three months, until he is hospitalized again. Unfortunately, he is unable to return to baseline health after hospitalization and is placed in a rehab facility.

Analysis
1. This man was examined by medical professionals prior to his diagnosis, yet was not diagnosed with pancreatic cancer until it had progressed to stage IV. Why is this?
2. What does his lack of response to the insulin antagonist indicate about the location/nature of the mutation within the pathway?
3. What does his response to the Mekinist reveal about the location of the mutation within the pathway? Why does his response last only three months?
4. Upon further genetic testing, a mutation is found in the Ras protein (a G-protein) within the MAPK pathway. What are some possible effects of this mutation, given the case background?
5. Sadly, this man died nine months after his initial hospitalization. What, if anything, could have been done differently in this case to prolong his life?

References:
4. Hruban, R., Genetics of Pancreatic Cancer - The Discoveries. Hopkins Pancreas