Key for Bi188 Midterm

1. A) Just one possible outline: (Illustration not attached)

i) Whole genome or exome sequencing: obtain samples from tumors (if available) and normal breast tissue, sequence total DNA and look for mutations common between breast cancer patients. Common mutations that either does not occur or has less copies in non-patients are potential candidates for the TS gene of interest, and can be further filtered using other techniques.

ii) ChIP against known histone modifications (H3K27me3 as indicator of "dormancy", for example), again from tumors as well as normal breast tissue across individuals. Patients' part of genome "silenced" by histone modification can include important tumor suppressors, in which case the downregulation will not be apparent in whole genome sequencing.

B) (One possible explanation) As in the case of Rb, they might both have one copy of tumor suppressor gene lost. Amy probably lost the other copy through mutation and hence had breast cancer; Kate did not. Whether Kate has a high risk in the immediate future will depend on where the tumor suppressor is functionally important; if it is only important in early development, Kate might have to close to normal chance of acquiring breast cancer, while if the TS is necessary at all ages, Kate will indeed has a very high chance of developing breast cancer.

C) Mr. Smith is unlikely to carry the mutation, as mutation of the only copy means that it'll be likely for Mr. Smith to have early-onset breast cancer.

2. A) [Please adapt from CNV section of lecture]

B) Some possible explanations, extrapolate from:

i) DNA-FISH (high copy number will result in widespread fluorescent signal, visible under microscope)

ii) Direct DNA sequencing (site of CNV will have a lot more mapped reads compared to other unique regions)

3A) 1.25 per each of two answers. Some example answers: point mutation that would create or affect an enhancer or delete a repressor near the proto-oncogene; gene duplication event; mutation in the coding sequence that would affect its activity (binds more readily, changed binding sequence)

3B) 2.5 points. A complete answer will contain the a description of the experiment, the experimental material as well as the control used, several expected results, and what a the results would look like if your hypothesis is correct.

3C) 1.25 points for location of mutation: either in a cell-type-specific enhancer that regulates which isoform is expressed or a mutation that affects mRNA splicing, or even a deletion that has gotten rid of that exon (less likely since everything else looks normal)

1.25 points for molecular mechanism (point mutation, translocation affecting regulatory apparatus, deletion where that exon is gone, etc.)

3D) 2.5 points; variable answers. Example: the mutation causes a different (longer) 3' end of the c-Myc mRNA. This might make the mRNA more stable than normal, causing there to be more c-Myc transcription factors in the tumor than in healthy cells. The extra c-Myc factors will cause their target genes to be upregulated.

4A) 0.5: What is it? chromosomes "shatter." They can recombine with each other, become small plasmids, and parts of chromosomes can be lost.

0.5: how contribute to tumor development? Can lose tumor suppressors, gain multiple copies of oncogenes, cause all sorts of genes to gain and lose regulatory sequences, etc.

4B) 2.0 Compare the two populations of tumor cells in terms of RNA-Seq or SNV's. If they are from the same sub-clone, you expect only a few mutations to be different between them.

4C) 3.0 TP53 mutations drive many lung cancer tumors, but not all. The MD friend should know not to expect all of the patients with lung cancer to respond to the same treatment, since they can have different driving mutations. More tumor/normal pairs might show you which mutations are most common in lung cancer, but they will also probably show you many more driving mutations.

4D) 1.0: Why are they symptoms different even if all mutations happen in same locus: CTFR encodes a transport channel. However, there are many options for CTFR phenotypes between having no channel and having normal amounts of the channel. Some patients may have mutations that merely decrease the number of the channels in the cell membrane, giving them lighter symptoms. Other patients may have a dominant negative phenotype, where the mutation negatively affects the healthy channels (as can be the case when the working channel is made of more than one gene product).

1.0: How should the physician treat: look for how the receptor is affected by analyzing genome and/or exome and/or the channel activity itself (by artificially expressing it). Use the treatment customized for what's actually wrong, rather than using all of them.

4E) 1.0: positive result tells you that either you or her other parent has the disease allele. If her other parent has no disease alleles, then your daughter being positive means you're positive.

1.0: negative result doesn't tell you anything.