An Asian couple comes to your office for testing. They had met at a support group for families who lost a member to cystic fibrosis. Each has a sibling who died of cystic fibrosis. However, the siblings' DNA is not available for testing. As a first step, you order the "ACOG 25 mutation panel". Both test negative.

1. What is the likelihood of each of them being a carrier, prior to testing. (Clue: they are both unaffected, cystic fibrosis is an autosomal recessive condition – what are their possible genotypes?)
2. What is the likelihood of being a carrier following testing, if the sensitivity of the ACOG mutation panel for detection of mutations among Asians is 30%?
3. What is the likelihood of their having an affected child? (Clue: use independent probabilities – remember them from college?).
4. What further recourse could you suggest?
5. If this were a Caucasian Couple, how would your answers differ?

A parent brings an eight year-old child to you to screen for primary pulmonary hypertension. A sister of the child died in her late 20s following a lung transplant. You obtain a detailed family history, and find out that there is no other history of pulmonary hypertension in the family. You "Google" primary pulmonary hypertension, look up "Online Mendelian Inheritance in Man" and see that approximately 25% of apparently sporadic cases of primary pulmonary hypertension appear to harbor mutations in a gene called "Bone Morphogenetic Protein-2 (BMPR-2). You look up Gene-Tests.org and find a lab performing sequencing of the entire coding region of the gene. Comment on the following questions:

1. Under what circumstances do you think you can ethically perform genetic testing on an asymptomatic minor?
    a. Think of some possible harm that can occur as a result of genetic testing
    b. What does performing a genetic test on a minor do to his/her ability to refuse to know when old enough?
    c. Can you think of a situation when you would NOT delay genetic testing until adulthood?
    d. What further information would you try to find out about primary pulmonary hypertension, prior to performing genetic testing on this child?
    e. You hear about a new drug in the pipeline, which specifically targets the functional defect caused by mutations in BMPR2 – how would that affect your decision to test?
2. How would you interpret a positive or a negative test result?
    a. What types of mutations, do you think direct sequencing will miss?
    b. Your literature search tells you that only 50% of families with clear linkage to this locus have mutations detectable by direct sequencing. What are possible explanations for this?
    c. The result shows one missense mutation – what further information would you need to interpret this.
    d. Results show a truncating mutation which clearly affects protein function – what would you inform the parent about the child's chances of developing
    e. The result shows two mutations. Does this mean that the patient is homozygous for mutations in BMPR2? What could you do to answer this question? (Bonus: Can you think of a danger in pursuing this approach? – clue – what happens if you find only one mutation? Or none?).

A five year old uninsured boy has a neck mass. Unable to obtain a timely schedule for open biopsy, the physician treating the patient performs a fine needle aspiration of the mass; some of the aspirate is sent for gene rearrangement analysis while most of it is sent for cytological examinaton.

The PCR results show clonal immunoglobulin heavy chain gene rearrangement and cytology shows an almost acellular specimen.

In view of the cytologic result – how would interpret the results of the PCR?

What, about PCR testing for clonality, do you think, could explain this result?

Microsatellite instability (microsatellite instability) is a feature of cancers associated with mutations or loss of expression of mismatch repair genes. There are at least four genes involved. MLH1, MSH2, MSH6 and PMS1 Loss of function may be associated with, either an inherited mutation in one of these genes (a familial condition known as Hereditary non Polyposis Colon Cancer or HNPCC), or "epigenetic" silencing (loss of expression, usually associated with promoter methylation, most often of MLH1). Although all tumors with MSI have a slightly better response to chemotherapy, this difference is not enough to be significant.

1. If there is no *clinical* difference between tumors with or without MSI, given the above information, could you think of a possible reason for testing for this change in tumors. (Clue: what do you think is the age distribution of inherited and sporadic cancer, and for whom would this be important?).
2. You have a have a person with a family history of colon cancer, most getting cancer at 55-65 years. How would this affect your screening strategy for the family?
3. You find out that genetic testing for mutations of the four genes involved costs $10,000. How would this compare with surveillance?
4. You look up the literature and find out that mutations in these genes are most often associated with loss of expression of the protein in the tumor? Could you use this information to optimize testing for the patient/family?
5. You look further read the literature, and find out that HNPCC associated cancers tend to be right-sided, that not all "index" cases are young, and that most MSI positive cancers which are NOT associated with an inherited mutation are associated with loss of expression of MLH1, and also with a mutation of a gene called "BRAF" - mainly with the so-called "V600E" mutation. You also find out that up to 2% of all apparently sporadic cancers are associated with inherited mutations in one of the mismatch repair genes? How would this affect your management of cases of colon cancer?