PROBING QUESTION
2. What is CF and how is it inherited? (LO 1)

Dr. Carver explains that, by using the Hardy Weinberg equilibrium, she can calculate the odds that Greg and Michelle have for their child to develop cystic fibrosis or CF. She tells them that they have an risk of 1 in 2500 for having a child with CF based on their ethnic background alone. Dr. Carver then estimates that Michelle's risk for having a child with CF would increase to 1 in 400, given she has a first cousin with CF. Even though the couple is confused, Michelle has blood drawn for screening of mutations in the CF gene.

PROBING QUESTION
3. What is an *a priori* risk? How did Dr. Carver develop these risk estimations? Will the Hardy-Weinberg equilibrium be of any help in developing risk figures? What is a punnet square and how does it help in risk calculations? (LO 2, 3)

Michelle returns to Dr. Carver's office for a follow-up visit and to learn about her screening results. The CF testing demonstrates that she is a carrier of the ΔF508 CFTR mutation.

PROBING QUESTIONS
4. What is the gene for CF? What does CDTR mean? What is the æF508 mutation? (LO 1, 7)

The couple is nervous at first. Dr. Carver explains that the risk that their child has for developing CF depends initially on Greg's population risk of being a carrier of a CFTR mutation, but this risk is modified either up or down depending upon whether a mutation is also discovered in Greg. Their risk is now 1 in 100 for having a child with cystic fibrosis. Greg decides to undergo the screening test, and they are much relieved when they learn that Greg's screening test is negative for CFTR mutations.

PROBING QUESTIONS
5. How likely is it that Greg or Michelle is a carrier of a CF mutation before and after testing? (LO 2)
6. What does is mean when a screening test comes back positive or negative? (LO 4)

Greg and Michelle's son, Brian, was born at term without any difficulties. His birthweight, length, and head circumference was normal. His Ohio Newborn Screen is normal, but he born two months prior to the implementation of immunoreactive trypsinogen test now required of all babies born in Ohio. At two months of age and on subsequent visits, however, Brian's weight begins to drop, which causes some concern by his pediatrician, Dr. Kidd. He reviews the information from Brian's grow chart and finds that Brian's weight has crossed from his original weight at the 75th percentile to less than the 3rd percentile. Based on his weight for length being below the third percentile, Dr. Kidd diagnoses Brian with "failure to thrive." Numerous formula changes and caloric supplementation are attempted without success.

PROBING QUESTIONS
7. What is immunoreactive trypsinogen? Is this a

and Michelle want to know how this could happen, since they had prenatal CF screening and were told that Greg's screening test was negative for CF.

PROBING QUESTION

9. Brianõs parents screened ònegativeó, how could this happen? How could Brian still end up with CF?

Screening tests differ from diagnostic tests and must fulfill certain requirements:

Disorder must have complications that can be averted if managed

negative test means that none of the mutations were found. A mutation could be present that is not detectable by the screen. The risk of mutation is reduced (table 1), but it is not zero.

7. What is immunoreactive trypsinogen? Is this a screening or diagnostic test? What is newborn screening? (LO 4)

Immunoreactive trypsinogen (IRT) is a screening test recently implemented (2006-2007) in the state of Ohio. It measures for an elevation of trypsinogen which is present due to pancreatic damage present at birth in children with CF. The student's do not need to know how trypsinogen is made or transported. If the IRT is elevated, our state follows up with DNA testing for common CF mutations. If one or more mutations are found, or if the IRT is above a certain level, the child is referred to a regional CF Newborn screening clinic, such as the combined program here at Rainbow Babies & Children's and the Center for Human Genetics, for confirmatory testing.

The newborn screening program in Ohio and other states dictate that all newborns be tested after 24 hours of birth for 32 serious diseases in the neonatal and childhood period (http://www.odh.ohio.gov/odhPrograms/phl/newbrn/nbrn1.aspx). Blood spots are taken with a heel stick and sent to the Ohio state laboratory. Most of the conditions tested at this time are rare inherited metabolic conditions where implementation of life saving diet and other therapies has been shown to avert early death and decrease the severity of illness. The CF program attempts to identify infants in Ohio with CF -724

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content is analyzed. If it is greater than 60 meq/L, the "sweat test" is positive. If two tests return positive, the diagnosis of CF is confirmed. However, this test also has a false negative rate and is estimated to detect 90% of affected children.

Other tests for CF include the transepithelial nasal potential difference test that measures electrical potential across the nasal epithelial cells. Abnormalities in the transport of sodium and potassium due to CFTR disregulation will alter