Prostate Specific Antigen (PSA) is an enzyme produced by the prostate. PSA values can be measured from a blood sample, and it is used for correlation to and prognosis of prostate cancer. A value greater than 4.0 ng/mL is commonly considered abnormal, and is often used to recommend a prostate biopsy.

In medicine, various tests are commonly used. It can be chemical, microbiological, radiological, immunological, genetic tests, as well as biomarker tests, and many more. So how do you know if a test is good or bad? What parameters describe accuracy?

To know if a test can detect a disease, it is important to know the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV):

- **Sensitivity**: How likely is the test to accurately detect the disease in someone with the disease (true positive)?
- **Specificity**: How likely is the test to detect the absence of a disease in someone without the disease (true negative)?
- **Positive predictive value**: How likely is someone with a positive test result to actually have the disease?
- **Negative predictive value**: How likely is someone with a negative test result to actually not have the disease?

Students can use the raw data, provided by Dr. Tomlin and used in his experiments, to calculate sensitivity, specificity, PPV and NPV for PSA in prostate cancer. This is subsequently obtained in a number of steps:

1. **Define a population to sample**, i.e. all the patients in the study.
2. **Define the disease of interest**, i.e. prostate cancer.
3. **Choose a test to determine the prevalence of disease**, i.e. PSA to detect prostate cancer.
4. **Determine the sensitivity, specificity, positive predictive value, and negative predictive value for this population**:
   a. **For people that have the characteristic (PSA > 4 ng/mL)**, record the number of people who tested positive and the number of people who tested negative. Do the same for people that do not have the characteristic (PSA < 4 ng/mL). The student will end up with four numbers. People with the characteristic AND tested positive are the **true positives (TP)**. People with the characteristic AND tested negative are the **false negatives (FN)**. People without the characteristic AND tested positive are the **false positives (FP)**. People without the characteristic AND tested negative are the **true negatives (TN)**. For example, let us suppose that student did the test on 1000 patients. Among the 100 patients with cancer, 95 of them tested positive, and 5 tested negative. Among the 900 patients without cancer, 90 tested positive, and 810 tested negative. In this case, TP=95, FN=5, FP=90, and TN=810.
b. **To calculate the sensitivity,** divide TP by (TP+FN). In the case above, that would be 95/(95+5)= 95%. Among all people that have the characteristic, what proportion will test positive? 95% sensitivity is regarded as acceptable.

c. **To calculate the specificity,** divide TN by (FP+TN). In the case above, that would be 810/(90+810)= 90%. Among all people without the characteristic, what proportion will test negative? 90% specificity is regarded as acceptable.

d. **To calculate the positive predictive value (PPV),** divide TP by (TP+FP). In the case above, that would be 95/(95+90)= 51.4%. Among all people that test positive, what proportion truly has the characteristic? 51.4% PPV means that if you test positive, you have a 51.4% chance of actually having the disease.

e. **To calculate the negative predictive value (NPV),** divide TN by (TN+FN). In the case above, that would be 810/(810+5)= 99.4%. Among all people that test negative, what proportion truly does not have the characteristic? 99.4% NPV means that if you test negative, you have a 99.4% chance of not having disease.

**Follow-up questions:**

- If a cutoff of 1.0 ng/mL was used, how would this affect the sensitivity and specificity of serum PSA for prostate cancer detection? If a cutoff of 10 ng/mL was used, how would this affect the sensitivity and specificity of serum PSA for prostate cancer detection?

- Why do you think the authors of the current study did not propose a cutoff for the urine TMPRSS2:ERG TMA test?

**More advanced activity:**

In Figure 1, the sensitivity and specificity of using TMPRSS2:ERG and PCA3 scores for predicting the presence of prostate cancer on biopsy is described. To analyze the data, a so called receiver operation characteristic (ROC) curve is generated. In a ROC curve, the true positive rate (sensitivity) is plotted as a function of the true negative rate (specificity) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two diagnostic groups (diseased vs. normal).

A test with perfect discrimination has a ROC curve that equals 1 and passes through the upper left corner (100% sensitivity, 100% specificity). Therefore the closer the ROC curve is to the upper left corner, the higher overall accuracy to the test. When the variable cannot distinguish between the two diagnostic groups, the area will be equal to 0.5 (the ROC curve will coincide with the diagonal).

Since Dr. Tomlin’s had data on TMPRSS2:ERG and PCA3 scores as well as biopsy results, he could estimate the sensitivity and specificity on the two variables (seen in Figure 1). By using Dr. Tomlin’s data, each student can make his or her own ROC curve and have a chance to learn more
about biomarkers and diagnostic sensitivity, specificity, positive and negative predictive values, area under the curve, and more.

Generation of ROC curves can also be challenging without statistical software. However, there is a nice web based program that can generate ROC curves, and could be used to generate curves from the data we provided for PSA, TMPRSS2:ERG and PCA3. http://www.rad.jhmi.edu/jeng/javarad/roc/formats.html
For interested students, a ROC curve can be constructed from the above web site.