

Diagnostic screening

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Stat 205: Elementary Statistics for the Biological and Life Sciences

Two possibilities: diseased or not diseased

- We assume a state loosely termed **diseased** $D+$ or **not diseased** $D-$, but any event of interest works.
- **Examples:**
 - $D+$ = cardiovascular disease
 - $D+$ = hepatitis B
 - $D+$ = Parkinson's disease
 - $D+$ = recent use of illegal drugs
- Notice shades of gray and differences in these outcomes.
 - Cardiovascular disease is an umbrella term and can be tested for many different ways: exercise stress test, MRI, X-ray, Echocardiogram, CT scan, PET, SPECT, plus various blood tests. Usually diagnosis takes multiple tests into account.
 - Drug use is known to the person being tested!
 - Hepatitis B is either there or not.

Binary tests: result in one of two outcomes, either $T+$ or $T-$.

Examples:

- over the counter pregnancy tests
- rapid strep test
- cultures (either something grows or it doesn't)
- direct microscopic examination of body fluid (either see it or not)
- asking a potential employee if they've recently used illegal drugs

Continuous tests: result in a number Y . Typically as the number increases the likelihood of $D+$ increases.

Examples:

- Enzyme-Linked ImmunoSorbent Assay (ELISA) measures an inferred amount of antigen in a blood sample
- minutes of briskly walking on a treadmill before discomfort
- pathologist classifying a slide as (1) negative, (2) atypical squamous hyperplasia, (3) carcinoma *in situ* (not metastasized), (4) invasive carcinoma (metastasized)

Often a continuous test is made into a binary one by *dichotomizing*:

$$T+ \Leftrightarrow Y > k \text{ and } T- \Leftrightarrow Y \leq k.$$

Binary tests

An individual from a population will fall into one of four categories:

$(D+, T+)$, $(D+, T-)$, $(D-, T+)$, or $(D-, T-)$.

These are 'true positive', 'false negative', 'false positive', and 'true negative'.

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Two common measures of *binary* test accuracy are sensitivity and specificity:

$$Se = \Pr\{T + | D+\} \quad Sp = \Pr\{T - | D-\}.$$

- How well does the test do identifying those that really are $D+$? The *sensitivity* of a test, denoted Se , is the probability that a diseased person tests positive.
- How well does the test do identifying those that really are $D-$? The test's *specificity* is the probability that a nondiseased person tests negative.

Note, *gold standard* tests have perfect sensitivity and specificity. For example, western blot test for HIV; culture for strep. A measure for dichotomized tests that considers sensitivity and specificity over all possible cutoffs k will be discussed shortly.

Example: Rapid strep test

Sheeler et al. (2002) describe a modest prospective trial of $n = 232$ individuals complaining of sore throat who were given the rapid strep (*streptococcal pharyngitis*) test. Each individual was also given a gold standard test, a throat culture.

	D+	D-	Total
T+	44	4	48
T-	19	165	184
Total	63	169	232

Estimating sensitivity, specificity, and prevalence

	D+	D-	Total
T+	44	4	48
T-	19	165	184
Total	63	169	232

- An estimate of Se is $\widehat{Se} = \widehat{\Pr}\{T+ | D+\} = \frac{44}{63} = 0.70$.
- An estimate of Sp is $\widehat{Sp} = \widehat{\Pr}\{T- | D-\} = \frac{165}{169} = 0.98$.
- The estimated prevalence of strep among those complaining of sore throat $\Pr\{D+\}$ is $p = \widehat{\Pr}\{D+\} = \frac{63}{232} = 0.27$.

If we have a sore throat, and test positive, we may be interested in the probability we have strep

$$\begin{aligned}
 \Pr\{D+ | T+\} &= \frac{\Pr\{T+ | D+\}\Pr(D+)}{\Pr\{T+ | D+\}\Pr\{D+\} + \Pr\{T+ | D-\}\Pr\{D-\}} \\
 &= \frac{Se \times p}{Se \times p + (1 - Sp) \times (1 - p)} \\
 &\approx \frac{0.70 \times 0.27}{0.70 \times 0.26 + (1 - 0.98) \times (1 - 0.27)} \\
 &= 0.92.
 \end{aligned}$$

This is called the *predictive value positive* (PVP).

Similarly,

$$\begin{aligned}
 \Pr\{D- | T-\} &= \frac{\Pr\{T- | D-\}\Pr(D-)}{\Pr\{T- | D-\}\Pr\{D-\} + \Pr\{T- | D+\}\Pr\{D+\}} \\
 &= \frac{Sp \times (1 - p)}{Sp \times (1 - p) + (1 - Se) \times p} \\
 &\approx \frac{0.98 \times (1 - 0.27)}{0.98 \times (1 - 0.27) + (1 - 0.70) \times 0.27} \\
 &= 0.90.
 \end{aligned}$$

This is called the *predictive value negative* (PVN).

Sensitivity, specificity, PPV, and NPV

- These four numbers summarize how useful a test T is: sensitivity $\Pr\{T + |D+\}$, specificity $\Pr\{T - |D-\}$, positive predictive value $\Pr\{D + |T+\}$ and negative predictive value $\Pr\{D - |T-\}$.
- PPV and NPV are tied to how prevalent $\Pr\{D+\}$ the disease is in the population – useful to an individual.
- Se and Sp not tied to prevalence. Useful for picking a test in terms of cost of making a mistake.
- We ignored variability here and only reported *point estimates*. How reliable these estimates are depends on how many people were sampled. For example, $\widehat{Se} = 0.70$ but a 95% CI is $(0.57, 0.81)$; that's a large range. Similarly, $\widehat{Sp} = 0.97$ with 95% CI $(0.94, 0.99)$.

Which test is best?

Comparing tests

Say we have two tests, T_1 and T_2 , with:

$$Se_1 = 0.8, Sp_1 = 0.99, Se_2 = 0.99, Sp_2 = 0.8.$$

Which is better?

It depends which is worse: a false negative or a false positive.

- If a false positive is worse – perhaps resulting in unnecessary surgery or a regimen of pharmaceuticals with harmful side effects – then we want the false positive rate to be as small as possible \Leftrightarrow want specificity to be high. Here we'd pick T_1 .
- If a false negative is worse – perhaps letting a toxically diseased (think mad cow) proceed to slaughter, or a home pregnancy test – we want the false negative rate to be as small as possible \Leftrightarrow want sensitivity to be high. Here's we'd pick T_2 .

Evaluating continuous tests: ROC Curves

Recall that *dichotomizing* a continuous test Y makes a new binary test T :

$$Y > k \Rightarrow T+ \text{ and } Y \leq k \Rightarrow T-.$$

- Magnitude of the individual test scores ignored \Rightarrow information loss
- Predictive probability of disease is same for *all* $T+$ (or $T-$) individuals regardless of actual test scores
- Subjects w/ very large scores Y are identical to those barely above the cutoff
- BUT, expect probability of disease to be an increasing function of Y ...

Picking one cutoff has implications...

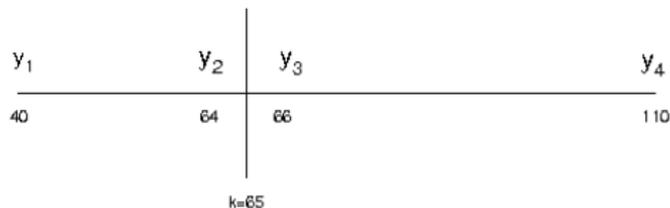


Figure: Four serology scores dichotomized using cutoff $k = 65$.

- Individuals 1 & 2 are $T-$; individuals 3 & 4 are $T+$.
- Individuals 1 and 2 $T-$, test scores differ by 24 units.
Individuals 3 and 4 $T+$, test scores differ by 44 units.
- Individuals 2 and 3 different although differ by only 2 units.

Underlying densities of Y for diseased and non-diseased

Dichotomizing can oversimplify the analysis but gives easily interpretable parameters: Se , Sp , PVP, and PVN.

Let G_0 and G_1 be distribution of Y from non-diseased and diseased populations.

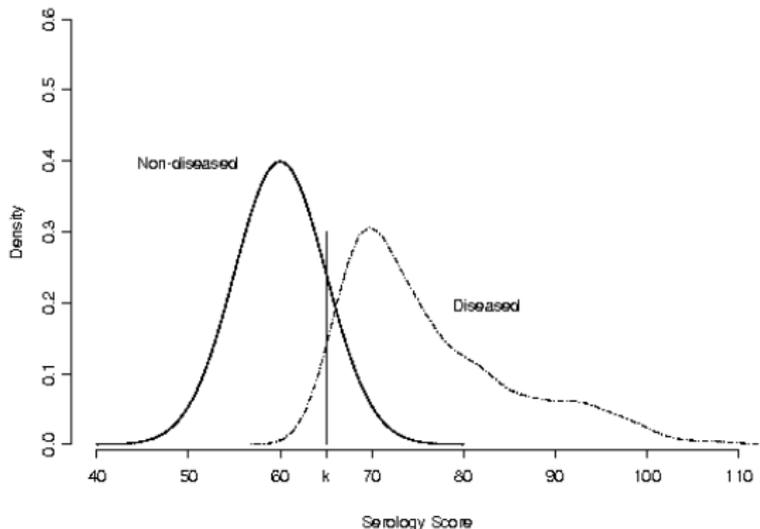


Figure: Cutoff $k = 65$ used to dichotomize continuous serology scores distributed according to G_0 (non-diseased) or G_1 (diseased).

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The receiver operator characteristic (ROC) curve plots $(1 - Sp(k), Se(k))$ for all cutoff values k .

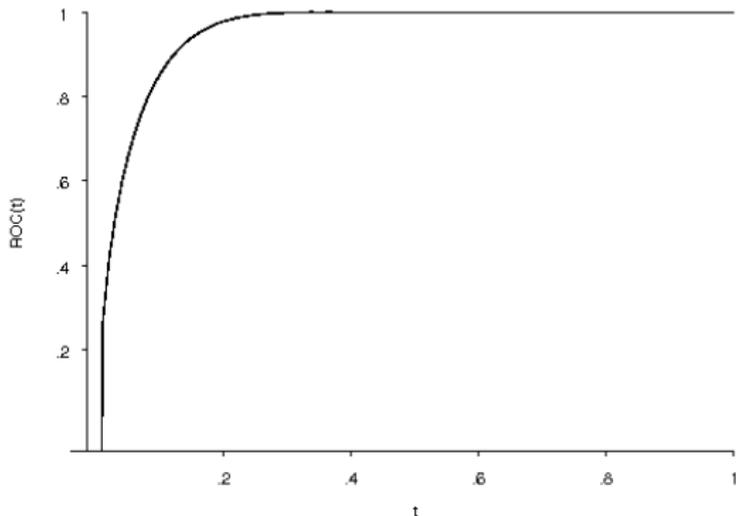


Figure: ROC curve corresponding to the distributions G_0 and G_1 .

Overall test accuracy

- ROC curve graphically illustrates a continuous test's X usefulness in terms of all error rates.
- Good tests have $Se(k)$ close to one and $1 - Sp(k)$ close to 0 for most k – translates into a concave curve with area underneath close to one.
- Area under the curve (AUC) is measure of tests overall diagnostic accuracy. Often reported in publications.
- The AUC is the probability of an infected having a larger Y than a non-infected – for reasonable tests, this should be larger than 0.5.