Miscellaneous

Covered in this Handout are:

1. McNemar’s test for Paired Binomial Data
2. Introduction to Analysis of Variance (ANOVA)
3. Multiple comparisons and error rates

McNemar’s test for Paired Dichotomous data

McNemar’s test is analogous to the paired t-test, except that is applied to only dichotomous data.

We learned that when we want to compare the means in two groups of paired observations, the standard t-tests are not valid. This was because the variance of the difference in means was derived under the assumptions that the two groups are independent and so it ignore the covariance-correlation term (which can increase or decrease that term). So in this case, both the hypothesis tests and confidence intervals that are based on this assumptions will not provide the ‘correct’ answer.

Side note: By correct, I mean that test will reject more or less often that the specified type I error. In statistics, this is what we mean by correct: that the test has the properties we designed it to.

To solve this problem we reduced the data from two dimensions down to one, by subtracting the observations within a pair and analyzing the differences with a one sample t-test and confidence interval on the differences. This approach avoids the correlation problem because the estimated variance on the differences accounts for the correlation.

With dichotomous data the problem is more complicated, but a similar approach exists. It is called 'McNemar's test for paired binomial data'.

The basic idea is still to analyze the differences (because the difference in means, or in this case proportions, is still the average of the differences) and then use the variance of the differences instead of trying to estimate the correlation.

But rather than do this directly on the differences, we arrange everything in a 2x2 table. The catch is that we use a different test-statistic for this table.

Setup:
N pairs of (zero or one) responses, (X_i, Y_i), $i=1,\ldots,N$
X_i is a Bernoulli (θ_1) random variable
Y_i is a Bernoulli (θ_2) random variable

Here θ_1 is the probability of success on the first observation within the pair and the θ_2 is the probability of success on the second observation within the i^{th} pair.

An important note is that the probability of success, θ, does not depend on i. And we want to test if H: $\theta_1 = \theta_2$, i.e. is the probability of success different on the first trial than on the second.

Example: A recent screening study of 49,528 women (the DMIST trial) compared two different imaging modalities (mammogram, digital mammogram) for detecting breast cancer. Both modalities were preformed on each woman. If both exams were negative the women were followed for one year to be sure cancer was not present and if either exam was positive a biopsy was preformed.

(This was designed and analyzed at Brown University's Center for Statistical Sciences; Reference is Pisano et. al., NJEM, 2005)

Out of the 49,528 enrolled women only 42,555 were eligible, completed all exams and had pathology or follow-up information (called reference standard information).

In studies of diagnostic tests, one should always separate the true positive cases and the true negative cases as determined by reference standard information, and analyze them separately. In this case there were 334 women with breast cancer and 42,221 women without breast cancer.

Below is the data from the 334 women with breast cancer. Screen film mammograms detected 136 women, digital mammograms detected 138, but only 84 of these women were detect by both modalities. The data are displayed in the following 2x2 table :

Data on positive cases from DMIST trial.

		Screen Mammogram		
		Detected	Missed	
Digital Mammo	Detected	84	54	138
	Missed	52	144	196
		136	198	334

We want to see if the proportion of detected women differs between the modalities. It might be tempting to use a simply Chi-square test for this contingency table, but that would be wrong because that test is built to examine the assumption that the Row and columns are independent, which they are clearly not (because the same women are in both groups).

So the test we use is Mcnemar’s test.

McNemar's test:

		Time 2		
		Success	Failure	
Time 1	Success	a	b	a+b
	Failure	c	d	c+d
		a+c	b+d	N

Let
θ_1 = P(Success | Time 1) = (a+b)/N
θ_2 = P(Success | Time 2) = (a+c)/N

The null hypothesis is H_0: $\theta_1 = \theta_2$ which implies that H_0: (a+b)/N=(a+c)/N or b=c .

Another form of the null hypothesis is H_0: $\theta_1/\theta_2=1$ or H_0: $\theta_1/(1-\theta_1)/\theta_2/(1-\theta_2)=1$ (Odds ratio of detection for Digital over screen is one)

$$\chi^2 = \frac{(b-c)^2}{(b+c)} \text{ with df=1}$$

Notice that $(\theta_1 - \theta_2)^2 = ((b-c)/N)^2$, so we see that the difference in proportions is indeed the top of the test statistic, keeping the connection between the Chi-square test and the Z-test for difference in proportions.

So McNemar's test, in this form, is an approximate test that requires large samples to be valid.

Back to our DMIST example comparing sensitivity:

		Screen Mammogram		
		Detected	Missed	
Digital Mammo	Detected	84	54	138
	Missed	52	144	196
		136	198	334

Here is the *Stata* output for our data:

```
. mcci 84 54 52 144

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+-----------
         Exposed |        84          54  |        138
       Unexposed |        52         144  |        196
-----------------+------------------------+-----------
           Total |       136         198  |        334

McNemar's chi2(1) =      0.04    Prob > chi2 = 0.8460
Exact McNemar significance probability       = 0.9227

Proportion with factor
        Cases       .4131737
        Controls    .4071856     [95% Conf. Interval]
                   ---------     --------------------
        difference   .005988     -.0574189    .069395
        ratio       1.014706      .8757299   1.175737
        rel. diff.   .010101     -.0912974   .1114995

        odds ratio  1.038462       .696309   1.549997
```

Three comments:

1) Some books, like Pagano and Gauvreau, suggest a slightly different version of this test to help when some cell counts are small. It is known as the continuity corrected version:

$$\chi^2 = \frac{(|b-c|-1)^2}{(b+c)} \text{ with df=1}$$

Opinions differ on when to use this, but typically it is used when any cell counts are less than 5. Same reasoning applies for the continuity corrected version of the Chi-square test.

2) There is no exact analytical formula for the variance of the difference of paired proportions. So the easiest way to get a confidence interval is to simply perform a hypothesis test for every null hypothesis (difference is zero, difference is 0.01, 0.02, 0.03 etc.) and use the set of null hypotheses that DO NOT reject as your confidence interval. This procedure is known as "inverting the hypothesis test", and this is how *Stata* gets the confidence interval for the difference in paired proportions.

3) You should ignore the proportions for cases and controls that Stata provides. What you really are comparing here are 138/334 versus 136/334, which has a relative risk of 138/136=1.014 and risk difference of 2/334 = .00598802 (See output).

We can do a similar analysis for the negative cases:

Data on negative cases from DMIST trial.

		Screen Mammogram		
		Detected	Missed	
Digital Mammo	Detected	40409	780	41189
	Missed	894	139	1032
		41302	919	42221

```
. mcci 40409 780 893 139

                 | Controls                |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+----------
         Exposed |     40409         780  |     41189
       Unexposed |       893         139  |      1032
-----------------+------------------------+----------
           Total |     41302         919  |     42221

McNemar's chi2(1) =      7.63    Prob > chi2 = 0.0057
Exact McNemar significance probability       = 0.0062

Proportion with factor
        Cases       .9755572
        Controls    .9782336     [95% Conf. Interval]
                   ---------     --------------------
        difference -.0026764     -.0045987  -.0007541
        ratio       .9972641      .9953276   .9992043
        rel. diff. -.1229597     -.2154003  -.0305192

        odds ratio  .8734602       .792443   .9626051
```

Notice that the p-value is significant (less than 0.05), but the estimated difference is tiny and of no clinical consequence (specificity is the same).

Based on these results, both screening modalities appear to have the same overall performance.

Interestingly, a similar analysis was done on the subgroup of women less than 50 years old: 72 of these women had breast cancer and 14,203 did not. The data for young positive women are as follows:

```
. mcci 18 17 7 30

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+----------
         Exposed |        18          17  |         35
       Unexposed |         7          30  |         37
-----------------+------------------------+----------
           Total |        25          47  |         72

McNemar's chi2(1) =      4.17    Prob > chi2 = 0.0412
Exact McNemar significance probability       = 0.0639

Proportion with factor
        Cases       .4861111
        Controls    .3472222     [95% Conf. Interval]
                   ---------     --------------------
        difference  .1388889     -.0044424   .2822202
        ratio            1.4      1.011942    1.93687
        rel. diff.   .212766      .0315035   .3940284

        odds ratio  2.428571       .957147    6.92694   (exact)
```

So it appears the sensitivity of these tests are different by about 13%.

Notice that the exact and approximate p-values are different and that the confidence interval for the odds ratio includes 1, but the confidence interval for the relative risk (‘ratio’) does not. Discuss!

Looking at the proportion of positive cases that were detected compares the sensitivity. To examine specificity, we look at the group of negative cases. The data for young negative women are as follows:

```
. mcci 13535 285 331 52

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+----------
         Exposed |     13535         285  |      13820
       Unexposed |       331          52  |        383
-----------------+------------------------+----------
           Total |     13866         337  |      14203

McNemar's chi2(1) =      3.44    Prob > chi2 = 0.0638
Exact McNemar significance probability       = 0.0697

Proportion with factor
        Cases       .9730339
        Controls    .9762726     [95% Conf. Interval]
                   ---------     --------------------
        difference -.0032388     -.0067337   .0002562
        ratio       .9966825      .9931863   1.000191
        rel. diff. -.1364985     -.2903823   .0173853

        odds ratio  .8610272      .7323123   1.011859
```

So it appears that the two tests differ slightly with respect to specificity, although the difference is small and likely uninteresting.

Digital mammograms appears to have better sensitivity (and the same specificity) for women under 50 and would therefore be a (slightly) better screening test.

Exact p-values for McNemar’s test

Because McNemar’s test is based on the information only in the discordant pairs (the b and c off diagonal cells) the calculations of exact p-values is quite simple.

If the null hypothesis is true, then it implies that the b and c cells should be equal, i.e., H_0 b=c. These cells are just counts of people, so the underlying distribution has to be Binomial where ½ of the counts should be in each cell.

That is, under the null hypothesis

b~Binomial(b+c,0.5)

So an exact p-value is P(b>b_{obs} |n=b+c and θ=1/2).

Example: in the subgroup of women less than 50 years old 72 of these women had breast cancer. Here b=17 and c=7, so

$$P(X \geq 17 \mid n = 24, \theta = 1/2) = \sum_{i=17}^{24} \binom{24}{k} 0.5^{24} = 0.03196$$

$$\text{two sided p - value} = 2(.03196) = .06391$$

```
. mcci 18 17 7 30
    … (See page 10)

McNemar's chi2(1) =      4.17    Prob > chi2 = 0.0412
Exact McNemar significance probability       = 0.0639
```

One Way Analysis of Variance (ANOVA)

We know how to test the equality of two normal means: Two samples, having $n_1, \bar{x}_1, s_1$, and $n_2, \bar{x}_2, s_2$.

Model (assumptions): Independent observations from two normal distributions with means μ_1, μ_2 and *common variance* σ^2 .

To test the hypothesis $H_0 : \mu_1 = \mu_2$ (means are equal) vs. $H_A : \mu_1 \neq \mu_2$ we use the test statistic

$$\frac{|\bar{x}_1 - \bar{x}_2|}{\sqrt{s_p^2 \left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

We reject H_0 if the observed value of the test statistic exceeds the critical value found in t-table using n_1+n_2-2 degree of freedom.

Example: For $n_1=10$ and $n_2=82$, the two-sided 5% critical value is 2.120.

This is the same thing if we checked to see if the square of the observed test statistic is bigger than $(2.120)^2 = 4.4944$.

Mathematically, we have

$$\frac{(\bar{x}_1-\bar{x}_2)^2}{s_p^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}=\frac{n_1(\bar{x}_1-\bar{x})^2+n_2(\bar{x}_2-\bar{x})^2}{s_p^2}$$

$$=\frac{n_1(\bar{x}_1-\bar{x})^2+n_2(\bar{x}_2-\bar{x})^2}{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2}{n_1+n_2-2}}>(t_{\alpha/2})^2$$

where the sample mean without a subscript is the overall mean obtained from the combined sample. This is sometimes called the 'grand mean'.

⇨ This squared form of the test statistic is important because it shows us how to generalize the test for more than two groups.

For three groups $n_1, \bar{x}_1, s_1,\ n_2, \bar{x}_2, s_2$ and $n_3, \bar{x}_3, s_3$, we have the same assumptions: Independent observations from three normal distributions with means μ_1, μ_2, μ_3 and common variance σ^2.

To test the hypothesis $H_0 : \mu_1 = \mu_2 = \mu_3$ (all means equal, or no differences among means) versus H_A: not all means are equal, we use the following test statistic:

$$\frac{\dfrac{n_1(\bar{x}_1 - \bar{x})^2 + n_2(\bar{x}_2 - \bar{x})^2 + n_3(\bar{x}_3 - \bar{x})^2}{2}}{\dfrac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2 + (n_3 - 1)s_3^2}{n_1 + n_2 + n_3 - 3}} = \frac{s_b^2}{s_w^2}$$

where $\bar{x}$ is the grand mean of all $n = n_1 + n_2 + n_3$ observations:

$$\bar{x} = \frac{n_1 \bar{x}_1 + n_2 \bar{x}_2 + n_3 \bar{x}_3}{n_1 + n_2 + n_3}$$

Under H_0 this statistic has an "*F*-distribution with 2 and n-3 degrees of freedom." The F-distribution is the square of the t-distribution just like the Chi-square is the square of the Z-distribution.

More generally, when there are k groups:

$$\begin{gathered} n_1,\ \bar{x}_1,\ s_1 \\ n_2,\ \bar{x}_2,\ s^2 \\ \vdots \\ n_k,\ \bar{x}_k,\ s_k \end{gathered}$$

The test statistic is

$$F_{k-1,\,n-k} = \frac{\sum_{i=1}^{k} n_i\left(\bar{x}_i - \bar{x}\right)^2}{k-1} \div \frac{\sum_{1}^{k} (n_i - 1)\, s_i^2}{n-k}$$

$$= \quad s_b^2 \quad / \quad s_w^2$$

Clever statisticians have proved that $E(s_w^2) = \sigma^2$, and that when H_0 is true, $E(s_b^2) = \sigma^2$ as well. But when H_A is true, $E(s_b^2) > \sigma^2$.

The bigger the *F*-statistic, the stronger the evidence that the population means are not all equal.

Moreover when H_0 is true the ratio s_b^2 / s_w^2 has an *F* probability distribution with $k - 1$ and $n - k$ degrees freedom (Pagano Table A.3).

To test H_0 at level 5%, find the critical value in the *F*-table and reject if the observed value s_b^2 / s_w^2 exceeds the critical value. Or find the p-value in the table, *p* = $P(F_{k-1,n-k} > F_{observed})$, and reject if it is smaller than 5%.

When k is two, the $F_{1,\ n-2}$ is the same as $\left(T_{n-2}\right)^2$. For example, we found that at 5% the critical value of *T* with 16 df is 2.120, so the critical value of T^2 is 4.494.

Table A.3 shows that this (4.49) is indeed the critical value of *F* with 1 and 16 df.

ANOVA is built from the same materials as the two sample t-test, and the same assumptions are required: normal distributions with equal variances.

As with the t-test, the ANOVA tests are robust (relatively insensitive) to failure of the normality assumption.

There is a nonparametric alternative test (the Kruskal-Wallis test) that is based on the ranks of the observations, and does not require that the underlying distributions be normal.

What do you do after the *F*-test rejects the hypothesis of no difference among the *k* population means, and you want to know <u>which</u> pairs of means are different?

There are various complicated approaches: The simplest is to test all of the possible pairs using two-sample t-tests (with s_w^2 replacing s_p^2, so you have *n-k* df), performing all $\binom{k}{2}$ tests at the level $\alpha/\binom{k}{2}$. This is known as a Bonferroni-adjusted α–level.

Adjusting the alpha (α) level

There are times when it is necessary to control the overall Type I error and keep it from inflating. For example, if you design a study of a new drug with two primary endpoints and you consider the test a success if the drug performs better on *either* endpoint. You may constrain the overall type I error to an α-level by testing each endpoint at the $\alpha/2$ level, so that the total chance of making a Type I error in this study would be α.

There are a variety of opinions about whether this makes sense. The basic conflict is in figuring out which error you want to control: the error for an individual endpoint or the overall error for a study.

Controlling the overall error can lead to weird results because now rejection of one endpoint depends on how many other endpoints you decide to test.

For example, one endpoint might yield a p-value of 0.04, which would reject the null at the 5% level and conclude the drug works. But if you have two endpoints and constrain the overall error to 5% by testing each endpoint a 2.5% level, then you would fail to reject and conclude the drug does not work.

To make matters worse, both procedures have an overall 5% error rate. So you can only claim rejection at the 5% level in either case.

Procedures like this make people wonder if statisticians really have their head screwed on straight: The drug works if you did not test the other endpoint, but it does not work if you did.

This is a fascinating, but endless debate. The problem is that modern statistics uses one quantity (the tail area, either as a p-value or type I error) to do two things: (1) measure the strength of evidence against the null hypothesis and (2) tell me how often I make a mistake.

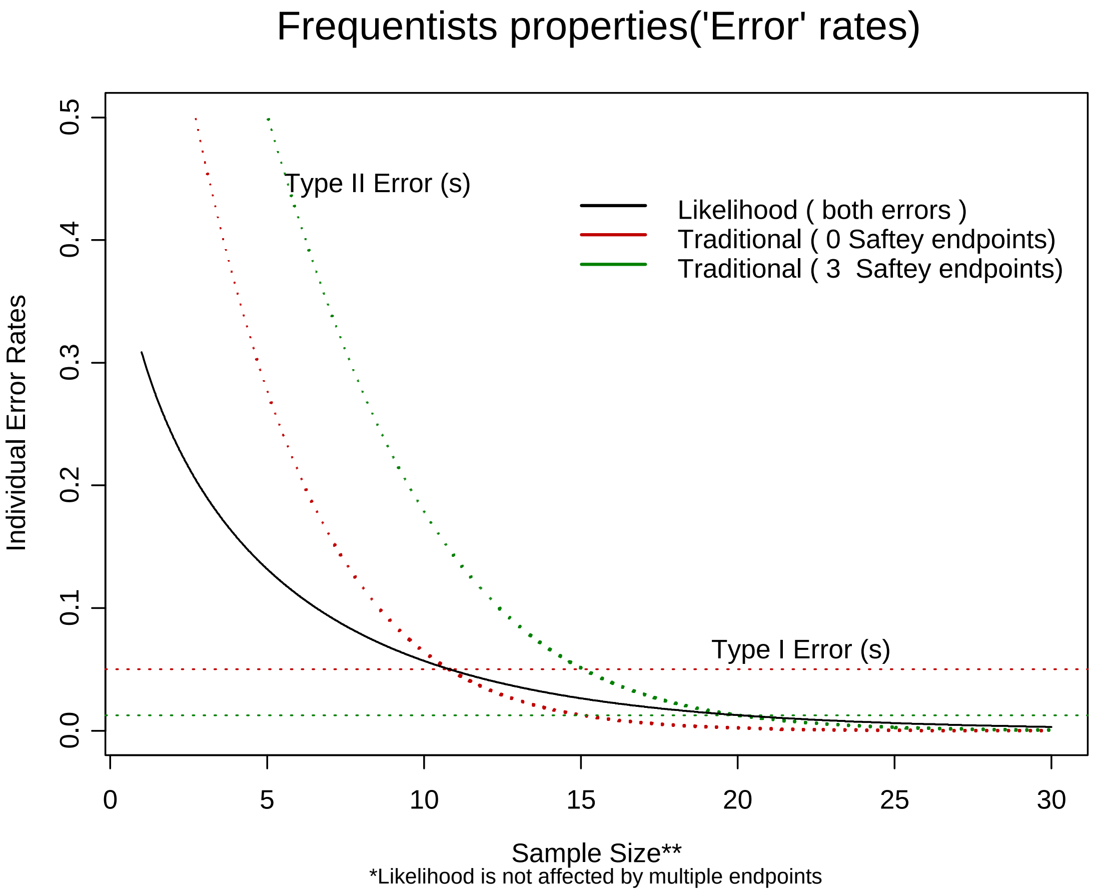
And it makes sense to adjust #2, but not #1. The only way this can be resolved is to trash this approach and try something new (like using a likelihood ratio to measure the strength of evidence and calculating its Type I and Type II error).

Blume and Peipert "What your statistician never told you about p-values" (2003) has a nice discussion of this point.

"*In fact, as a matter of principle, the infrequency with which, in particular circumstances, decisive evidence is obtained, should not be confused with the force, or cogency, of such evidence*." [Fisher, 1959]

Miscellaneous

Single endpoint:
Frequentist error rates (Type I and Type II; reject when in the tails) along with likelihood error rates (reject when the likelihood ratio is greater than 1). Adjusting the Type I error to keep it at 5%.



*Likelihood is not affected by multiple endpoints

**Sample Size is relative to this example; but ordering holds in general

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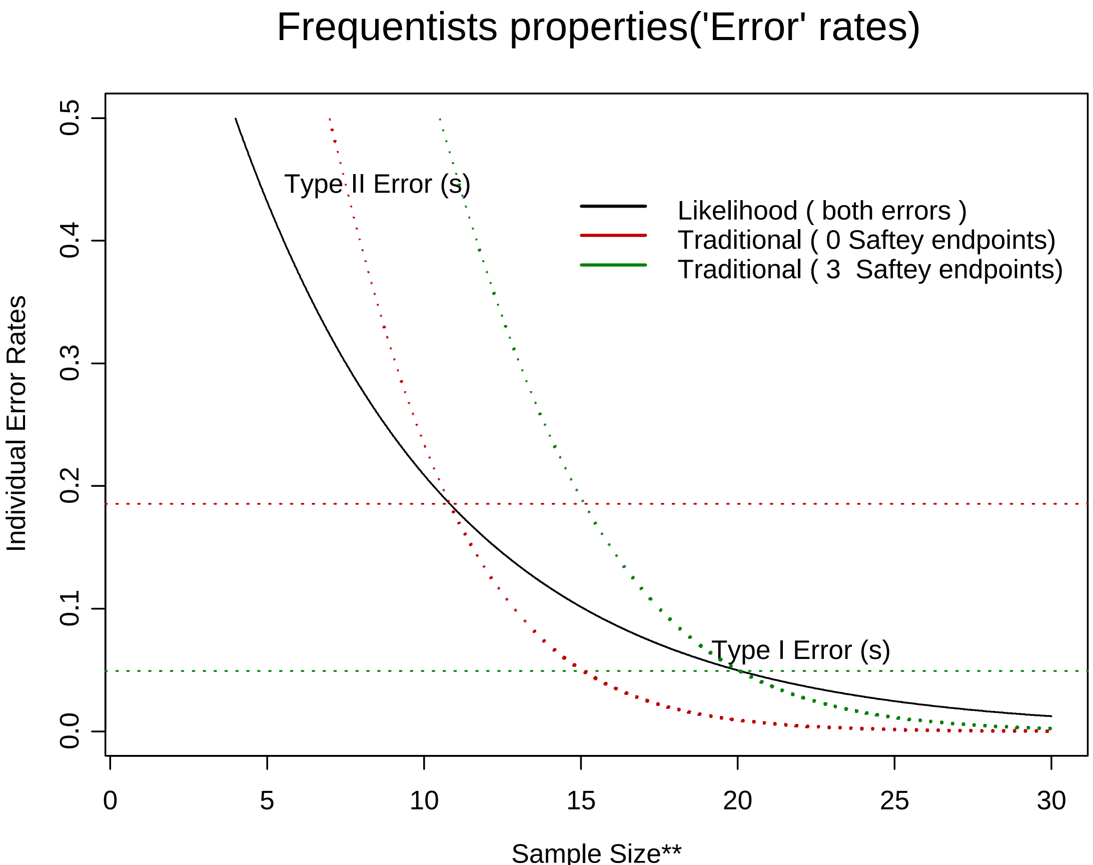
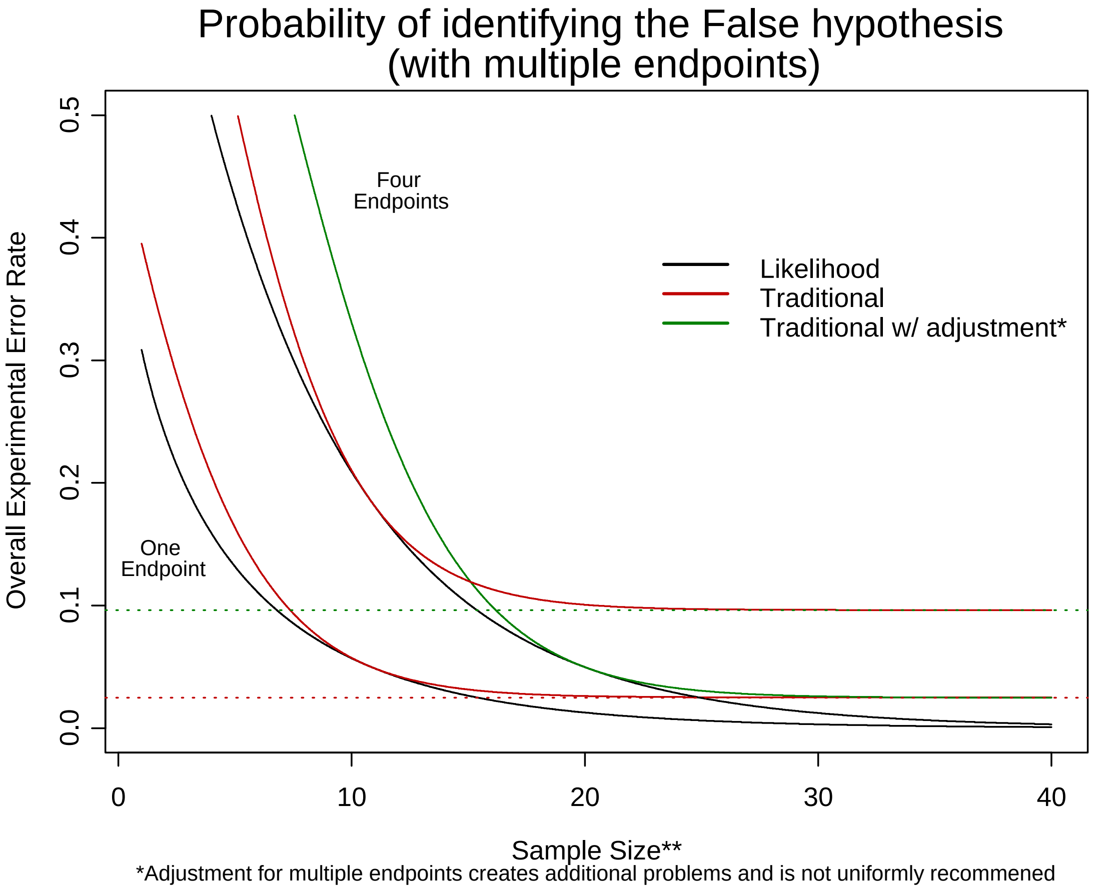
Overall endpoints:
Frequentist error rates (Type I and Type II; reject when in the tails) along with likelihood error rates (reject when the likelihood ratio is greater than 1). Adjusting the Type I error to keep it at 5%.



*Likelihood is not affected by multiple endpoints
**Sample Size is relative to this example; but ordering holds in general

Plots of the average error rates ((type I+ type II)/2) for hypothesis testing and likelihood inference. Multiple endpoints are included along with the adjusted and not adjusted results for hypothesis testing.



*Adjustment for multiple endpoints creates additional problems and is not uniformly recommened

**Sample Size is relative to this example; but ordering holds in general