PBHS 32410 / STAT 22401 J. Dignam Winter 2023

Logistic Regression (continued)

- Recall that logistic regression provides a way of relating predictor variables X to binary (0,1) outcome variable Y. This outcome variable is an indicator for "yes/no", "event/non-event", etc
- The model actually predicts $\Pr(Y = 1|X)$. This equals the expected value (mean) of Y, as in linear regression. How?
  - Note that for a binary variable, the mean of Y and covariate X , $\sum_{j=1}^{N_i} Y_i/N_i = p_i$, or the proportion that equal 1.
  - For a binomial random variable (independent draws, probability p of success for each draw), this proportion equaling 1 is the same as $\Pr(Y = 1)$

Logistic Regression

- The model for $\Pr(Y = 1|X)$ is nonlinear. We model linearly via the logit transform:

$$\log\left\{\frac{p}{1-p}\right\} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_q X_q$$

- β_j in the model is the difference in log odds for a one unit increment in X_j. This is same as the **log odds ratio.** Exponentiating gives the **odds ratio**, reflecting the relative odds of event (being a '1') for a one-unit increment in X. Note that this is a multiplicative difference (rather than additive as in difference of means)

- Ex: $\beta_{age} = 0.336$. Then $\exp(0.336) = 1.4$. For a one-year increase in age, relative odds of event goes up by 1.4, or 40%

Logistic Regression

- The model can produce a probability of event for each case in the dataset, based on the predictors X, via the equation

$$\Pr(Y = 1|X) = \frac{\exp(\beta_0 + \beta_1 X_1 + \ldots + \beta_q X_q)}{1 + \exp(\beta_0 + \beta_1 X_1 + \ldots + \beta_q X_q)}$$

- With these values, one can assess how well individual cases may be classified with respect to outcome (will discuss shortly)

Logistic Regression - another example
model coefficient interpretation

- **Glioblastoma (GBM):** A randomized clinical trial was conducted comparing standard treatment (radiation + chemotherapy) to this treatment plus bevacizumab (Avastin) with the goal of improving two endpoints:
  - progression-free survival (time remaining alive and free of disease progression) and
  - survival time
- Here, we analyze PFS at 18 months from study entry
- While prognosis is generally unfavorable, important new tumor molecular markers are strongly associated w/outcomes and possibly treatment response. O(6)-methylguanine-DNA methyltransferase (MGMT) inactivation via methylation is also examined

Logistic Regression
model coefficient interpretation

Examining effects individually via tables:

```
. cc fail_18mo  trt

                                                          Proportion
                 |   Exposed   Unexposed  |      Total       exposed
-----------------+------------------------+------------------------
           Cases |       225          235  |        460        0.4891
        Controls |        87           74  |        161        0.5404
 ----------------+------------------------+------------------------
           Total |       312          309  |        621        0.5024

                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
      Odds ratio |           .81438       |    .5587526    1.185748 (exact)
                 +-----------------------------------------------
```

Modest treatment effect - 19% lower odds of failure

```
. cc fail_18mo  mgmt_grp

                                                      Proportion
                 |   Exposed   Unexposed  |      Total       exposed
-----------------+------------------------+------------------------
           Cases |       354         106  |        460        0.7696
        Controls |        92          69  |        161        0.5714
-----------------+------------------------+------------------------
           Total |       446         175  |        621        0.7182

                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
      Odds ratio |         2.504717       |    1.678978    3.724206 (exact)
                 +-----------------------------------------------
```

MGMT unmethylated have 2.5 times greater odds of failure

Logistic Regression
model coefficient interpretation

The model run:

```
. logit fail_18mo trt mgmt_grp

Iteration 0:   log likelihood = -355.38631
. . .
Iteration 3:   log likelihood = -343.79561

Logistic regression                             Number of obs     =        621
                                                LR chi2(2)        =      23.18
                                                Prob > chi2       =     0.0000
Log likelihood = -343.79561                     Pseudo R2         =     0.0326
------------------------------------------------------------------------------
   fail_18mo |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |  -.1996488   .1870863    -1.07   0.286    -.5663311    .1670335
    mgmt_grp |   .9167454   .1941661     4.72   0.000     .5361868    1.297304
       _cons |   .5330665   .1833776     2.91   0.004     .1736529    .8924801
------------------------------------------------------------------------------
```

Adjusted ORs: trt OR: $e^{-.19964} = 0.819$. MGMT OR: $e^{.91674} = 2.50$

Logistic Regression
model coefficient interpretation

We can generate 3 odds ratios relative to the reference group [no bev, MGMT methylate]d:

	Treatment	
MGMT Status	Placebo	Bevac
methylated	1.00	0.82
unmethylated	2.51	2.04

Note that 2.51 x. 0.82 = 2.04, i.e., the treatment effect is the same in both MGMT groups according to this model

Logistic Regression - another model

We can add a treatment by MGMT interaction term to the model, permitting different trt effects in each MGMT group:

```
. logit fail_18mo trt mgmt_grp trt_by_mgmt
Iteration 0:   log likelihood = -355.38631
I . .
Iteration 3:   log likelihood =  -342.3045
Logistic regression                             Number of obs     =        621
                                                LR chi2(3)        =      26.16
                                                Prob > chi2       =     0.0000
Log likelihood =  -342.3045                     Pseudo R2         =     0.0368
------------------------------------------------------------------------------
   fail_18mo |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |  -.6310748   .3145175    -2.01   0.045    -1.247518   -.0146317
    mgmt_grp |    .561396   .2849644     1.97   0.049      .002876    1.119916
Interaction trt_by_mgmt |   .6745599   .3920708     1.72   0.085    -.0938848    1.443005
       _cons |   .7646061   .2329773     3.28   0.001     .3079791    1.221233
------------------------------------------------------------------------------
```

There is a suggestion of interaction between treatment and MGMT status

Logistic Regression - another model

We again generate 3 odds ratios relative to [no bev, MGMT methylated]: 1.00

	Treatment	
MGMT Status	Placebo	Bevac
methylated	1.00	0.53
unmethylated	1.75	1.83

Now note that

- Bev effect in methylated is larger, 47% reduction in odds of failure
- No Bevt effect in unmethylated, which we can see by computing 1.83/1.75 equals OR = 1.045. Another way to obtain is $e^{-.6311+.6745} = 1.045$. We can check these effects by estimating treatment effects separately by MGMT status.

Logistic Regression - Stratified Treatment Effect

```
. cc fail_18mo  trt if mgmt_grp==0
                                                              Proportion
                 |   Exposed   Unexposed  |      Total       exposed
-----------------+------------------------+------------------------
           Cases |        48           58  |        106       0.4528
        Controls |        42           27  |         69       0.6087
-----------------+------------------------+------------------------
           Total |        90           85  |        175       0.5143
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
      Odds ratio |         .5320197       |    .2736227    1.029957 (exact)
```

Unmethylated

```
. cc fail_18mo  trt if mgmt_grp==1
                                                              Proportion
                 |   Exposed   Unexposed  |      Total       exposed
-----------------+------------------------+------------------------
           Cases |       177          177  |        354       0.5000
        Controls |        45           47  |         92       0.4891
-----------------+------------------------+------------------------
           Total |       222          224  |        446       0.4978
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
      Odds ratio |         1.044444       |    .6430068    1.697515 (exact)
```

Methylated

Logistic Regression - Model Significance & Goodness of Fit

- As we discussed, a *likelihood ratio* test can be defined contrasting the model in question with a null model containing no predictors. This is analogous to the global F-test in SLR/MLR

- The test statistic:

$$D_{global} = -2(\text{log-likelihood}_{null} - \text{log-likelihood}_{full})$$

  is χ^2_{df} where degrees of freedom df $=$ number of predictors

- This same type of test is used for contrasting two nested models, say, dropping out 3 predictors out of 7 candidates

$$D_{nested} = -2(\text{log-likelihood}_{smaller\ model} - \text{log-likelihood}_{bigger\ model})$$

  is χ^2_3 (3 df) and tests whether the three parameters considered for dropping simultaneously have $\beta_j = 0$

Logistic Regression - Quantifying Fit

- The global LR test evaluates whether there is a worthwhile model relative to no model at all. What about a test against 'the best model available', or a perfect fit?

- In the case of discrete predictors (where tables can be formed), such as test is available and can give a sense of what is the model that predicts best with the least number of predictors.

- Model Goodness of Fit - Deviance: notation and definition

The quantity D above is known as the deviance and can be used to assess model fit: define

1. $\hat{L}_c$: the maximized likelihood (likelihood given the MLE) under the current model of interest
2. $\hat{L}_f$: the maximized likelihood under the model fits the data perfectly, which is termed the *full* or *saturated model*

Then the *Deviance:* $D = -2\log(\hat{L}_c/\hat{L}_f) = -2\{\log\hat{L}_c - \log\hat{L}_f\}$

- D measures the extent to which the current model deviates from the full model:
- Large D when $\hat{L}_c$ is small relative to $\hat{L}_f$, indicating the current model fit is poor.
- Small D when $\hat{L}_c$ is similar to $\hat{L}_f$, indicating 'good' current model fit.

- Model Goodness of Fit - Deviance: notation and definition

Deviance: formula

- Recall: the likelihood function based on observations y_i/n_i, for $i = 1, 2, ..., n$ groups defined by unique covariate combinations, with unknown p_i is

$$L = \prod_{i=1}^{n} \binom{n_i}{y_i} p_i^{y_i} (1 - p_i)^{n_i - y_i}$$

$$\log L = \sum_{i=1}^{n} \{\log \binom{n_i}{y_i} + y_i \log p_i + (n_i - y_i) \log(1 - p_i)\} \qquad (1)$$

- Let $\hat{p}_i,\ i = 1, ..., n$ be the fitted values under *current model*, then

$$\log \hat{L}_c = \sum_{i=1}^{n} \{\log \binom{n_i}{y_i} + y_i \log \hat{p}_i + (n_i - y_i) \log(1 - \hat{p}_i)\} \qquad (2)$$

- Define $\tilde{p}_i = y_i/n_i,\ i = 1, ..., n$ which are the actual probabilities in

these table cells. We define this as the *full model*:

$$\log\hat{L}_f = \sum_{i=1}^{n}\{\log\binom{n_i}{y_i} + y_i\log\tilde{p}_i + (n_i - y_i)\log(1-\tilde{p}_i)\} \qquad (3)$$

- The *Deviance* is then given by

$$\begin{aligned} D &= -2\{\log\hat{L}_c - \log\hat{L}_f\} \\ &= 2\sum_{i=1}^{n}\{y_i\log(\frac{\tilde{p}_i}{\hat{p}_i}) + (n_i - y_i)\log(\frac{1-\tilde{p}_i}{1-\hat{p}_i})\} \end{aligned} \qquad (4)$$

- Model Goodness of Fit - Deviance Statistic

- To use the deviance statistic, we have to have the following circumstances for the covariate set **X**:
  - We assume there is a model that reproduces the probability of event at a given X combination perfectly (from a table of response by X category, the $\tilde{p}$ from eqn. 4 above), and ...
  - there are model(s) with fewer parameters (for example, main effects only for $\mathbf{X}$, or a given X represented as a numeric index or on a continuous scale).
- Then, we can contrast models via estimated $\hat{p}$ and $\tilde{p}$

Logistic Regression - D as Goodness of Fit Measure

Deviance: distribution of the deviance statistic D

- We use D to evaluate the current model, and so we need to know it's distribution. Under H_0 that the *current model* requires no additional parameters to fit well, as the groups size $n_i \longrightarrow \infty$, D converges to χ^2_{n-p}, where $p = \sharp$ parameters fit, $n = \sharp$ of groups.

- Thus, for reasonably large groups, the deviance provides a goodness of fit test for the model, and $D \sim \chi^2_{n-p}$ approximately. In this case,
  - The value of deviance statistic, D, can be compared to tables of percentage points of the χ^2_{n-p} distribution. Note - here we expect a large statistic (small p-value) under bad fit.
  - Since mean of a χ^2_{n-p} r.v. is $n - p$, a useful rule of thumb is the D does not exceed $n - p$, the model may be satisfactory.

Logistic Regression - D as Goodness of Fit Measure

Deviance: distribution (continued): Case of 'continuous' X values:

- For the case where X is (in practical terms) on a continuous scale, so that for each X value there is only one response (0/1) for Y (and thus no natural way to form a table), $\log\hat{L}_f = 0$, and D depends only on the fitted success $\hat{p}_i$:
  $D = -2\sum_{i=1}^{n}\{\hat{p}_i \text{logit}(\hat{p}_i) + \log(1-\hat{p}_i)\}$. In this case, the deviance is uninformative about the goodness of fit of a model.
- In this case where $n_i = 1$, for all i, D is not even approximately χ^2.
- Even when the n_i all exceed unity (i.e, we have 'tables'), the χ^2 approximation may not be particularly good when the data are sparse, i.e., some of the binomial denominators n_i are very small.

We will look at an alternative test for this case a bit later . . .

Logistic Regression - D as Goodness of Fit Measure

Example: Donner Party: In 1846 the Donner and Reed families left Springfield, Illinois, for California by covered wagon. In July, the Donner Party, as it became known, reached Fort Bridger, Wyoming. There, 87 people and 20 wagons crossed the Wasatch Range and the desert west of the Great Salt Lake and entering the eastern Sierra Nevada mountains in late October (later than planned). Heavy snows stranded the group in the mountains, and by the time of complete rescue in April, 1847, 40 of the 87 members had died from famine and exposure.

What factors were related to survival?

Example - D as Goodness of Fit Measure

Listing of part of the data for 45 individuals

```
list AGE SEX STATUS in 5/20, noobs clean
```

AGE	SEX	STATUS
15	MALE	DIED
25	MALE	SURVIVED
25	MALE	DIED
22	FEMALE	SURVIVED
20	MALE	SURVIVED
24	FEMALE	SURVIVED
25	MALE	DIED
25	FEMALE	DIED
15	FEMALE	SURVIVED
18	MALE	SURVIVED
25	FEMALE	SURVIVED
23	FEMALE	SURVIVED
28	MALE	SURVIVED
28	MALE	SURVIVED
21	FEMALE	SURVIVED
28	MALE	DIED

Example - D as Goodness of Fit Measure

We form a discrete age categorical variable for illustrative purposes, classifying individuals as under 25 years or 25 and over.

The model:

```
. logistic died sex age25plus

Logistic regression                               Number of obs     =         45
                                                  LR chi2(2)        =       8.09
                                                  Prob > chi2       =     0.0175
Log likelihood = -26.868228                       Pseudo R2         =     0.1309
------------------------------------------------------------------------------
        died | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   3.597994   2.515823     1.83   0.067     .9138505    14.16595
   age25plus |    3.84985   2.832213     1.83   0.067     .9104196    16.27968
       _cons |   .2056279   .1604821    -2.03   0.043     .0445413    .9492959
------------------------------------------------------------------------------
Note: _cons estimates baseline odds.
```

We have two predictors of mortality: males and those over 25 have over 3-fold greater odds of death.

Example - D as Goodness of Fit Measure

A full or saturated model here would include the sex by age group interaction, which will reproduce exactly the probabilities for the sex by age group by died/survived 3-way table:

```
. logit died sex age25plus agebysex
. . .
Iteration 10:  log likelihood = -25.096587

Logistic regression                               Number of obs     =         45
                                                  LR chi2(3)        =      11.63
                                                  Prob > chi2       =     0.0088
Log likelihood = -25.096587                       Pseudo R2         =     0.1882
------------------------------------------------------------------------------
        died |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   17.63652   2388.794     0.01   0.994    -4664.313    4699.586
   age25plus |   17.57199   2388.794     0.01   0.994    -4664.378    4699.522
    agebysex |  -17.03307   2388.794    -0.01   0.994    -4698.983    4664.917
       _cons |  -17.34885   2388.794    -0.01   0.994    -4699.298      4664.6
------------------------------------------------------------------------------
```

Example - D as Goodness of Fit Measure

The coefficient estimates 'go crazy' since the (female, under 25) group has zero deaths, but the model accurately reproduces the observed probabilities of death in the 4 unique groups. The log likelihood statistic (the part we need (-25.096587)) is provided.

The Deviance statistic $D = -2\{\log\hat{L}_{current} - \log\hat{L}_{full}\}$ is then

$$D = -2\{-26.868228 - (-25.096587)\} = 3.5432$$

The associated p-value for a χ^2_1 distribution is 0.06. So, the model with two predictors passes as a 'barely' suitable model relative to the 'perfect' model

Example - D as Goodness of Fit Measure

To do this in Stata, need to install a module called *ldev* and run after the model of interest

```
. ldev

Logistic model deviance goodness-of-fit test

         number of observations =      45
   number of covariate patterns =       4
      deviance goodness-of-fit =    3.54
            degrees of freedom =       1
                  Prob > chi2 =       0.0598
```

Goodness of Fit Measures - continuous covariates

- **What if we have continuous predictors (no tables or very sparse tables)?**

- the Hosmer-Lemeshow test goodness of fit measure in logistic regression groups the n observations into groups(according to their estimated probability of event) and calculates the corresponding generalized Pearson χ^2 statistic. Usually deciles (10 groups) are used.

$$H = \sum_{g=1}^{G} \frac{(O_g - E_g)^2}{n_g(\hat{p}_g(1-\hat{p}_g))}$$

Where O_g is the number of events in group g and $E_g = n_g * \hat{p}_g$ is the expected number of events

- In this type of test, a *large* p-value (> 0.05) indicates good correspondence between observed and predicted outcomes.

Goodness of Fit Measures - HL Test

The test can also be run on discrete data - Donner party data

```
. estat gof

Logistic model for died, goodness-of-fit test

       number of observations =        45
 number of covariate patterns =        28
            Pearson chi2(25) =        24.35
                 Prob > chi2 =         0.4991
```

Logistic Regression - Model Significance and Goodness of Fit Measures

```
. logit sta typ age

Iteration 0:   log likelihood = -100.08048
Iteration 1:   log likelihood = -87.895217
. . .
Iteration 5:   log likelihood = -86.537821

Logistic regression                                     Number of obs     =        200
                                                        LR chi2(2)        =      27.09
                                                        Prob > chi2       =     0.0000
Log likelihood = -86.537821                             Pseudo R2         =     0.1353
------------------------------------------------------------------------------
         sta |      Coef.   Std. Err.      z    P>|z|     [95\% Conf. Interval]
-------------+----------------------------------------------------------------
         typ |   2.453535     .75257     3.26   0.001      .978525    3.928545
         age |   .0340162   .0106944     3.18   0.001     .0130556    .0549767
       _cons |  -5.508762   1.033511    -5.33   0.000    -7.534407   -3.483118
------------------------------------------------------------------------------

. estat gof, group(10) table
```

```
Logistic model for sta, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)
  +--------------------------------------------------------+
  | Group |   Prob | Obs_1 | Exp_1 | Obs_0 | Exp_0 | Total |
  |-------+--------+-------+-------+-------+-------+-------|
  |     1 | 0.0362 |     0 |   0.5 |    20 |  19.5 |    20 |
  |     2 | 0.0478 |     1 |   0.9 |    20 |  20.1 |    21 |
  |     3 | 0.0812 |     1 |   1.2 |    18 |  17.8 |    19 |
  |     4 | 0.1209 |     2 |   1.8 |    18 |  18.2 |    20 |
  |     5 | 0.1916 |     2 |   3.1 |    18 |  16.9 |    20 |
  |-------+--------+-------+-------+-------+-------+-------|
  |     6 | 0.2531 |     7 |   4.6 |    14 |  16.4 |    21 |
  |     7 | 0.2936 |     6 |   6.1 |    16 |  15.9 |    22 |
  |     8 | 0.3376 |     5 |   5.8 |    13 |  12.2 |    18 |
  |     9 | 0.3846 |     8 |   7.3 |    12 |  12.7 |    20 |
  |    10 | 0.5186 |     8 |   8.7 |    11 |  10.3 |    19 |
  +--------------------------------------------------------+

       number of observations =       200
             number of groups =        10
    Hosmer-Lemeshow chi2(8) =         2.95
                Prob > chi2 =         0.9372
```

Logistic Regression - Goodness of Fit Measures

This result looks very positive - good fit. However, Pseudo-$R^2 = 13\%$, so not that much variation explained.

Pseudo-R^2 measures proportion reduction in log-likelihood over null model. This is a useful measure, but more like another F-test than a measure of model explanatory power.

The Hosmer-Lemeshow g.o.f. test is more valuable as a means to identify major systematic variation that is not explained. Large p-value does not assure that prediction will be highly accurate, etc.

Logistic Regression - Goodness of Fit for the Donner Data

With continuous age predictor and sex:

```
. logistic died sex AGE

Logistic regression                               Number of obs     =         45
                                                  LR chi2(2)        =      10.57
                                                  Prob > chi2       =     0.0051
Log likelihood = -25.628142                       Pseudo R2         =     0.1710
------------------------------------------------------------------------------
        died | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   4.939645   3.731909     2.11   0.034       1.1236    21.71599
         AGE |   1.081343   .0403206     2.10   0.036     1.005135     1.16333
       _cons |   .0395411   .0548425    -2.33   0.020     .0026089    .5992974
------------------------------------------------------------------------------
Note: _cons estimates baseline odds.
```

```
. estat gof, group(10) table

Logistic model for died, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)
  +--------------------------------------------------------+
  | Group |   Prob | Obs_1 | Exp_1 | Obs_0 | Exp_0 | Total |
  |-------+--------+-------+-------+-------+-------+-------|
  |     1 | 0.1928 |     0 |   0.8 |     5 |   4.2 |     5 |
  |     2 | 0.3257 |     1 |   1.3 |     4 |   3.7 |     5 |
  |     3 | 0.4827 |     1 |   1.8 |     3 |   2.2 |     4 |
  |     4 | 0.5662 |     3 |   2.2 |     1 |   1.8 |     4 |
  |     5 | 0.5798 |     7 |   4.6 |     1 |   3.4 |     8 |
  |-------+--------+-------+-------+-------+-------+-------|
  |     6 | 0.6226 |     1 |   0.6 |     0 |   0.4 |     1 |
  |     7 | 0.6637 |     3 |   3.2 |     2 |   1.8 |     5 |
  |     8 | 0.6878 |     3 |   2.7 |     1 |   1.3 |     4 |
  |     9 | 0.8770 |     2 |   4.0 |     3 |   1.0 |     5 |
  |    10 | 0.9692 |     4 |   3.8 |     0 |   0.2 |     4 |
  +--------------------------------------------------------+

      number of observations =        45
            number of groups =        10
    Hosmer-Lemeshow chi2(8) =        10.94
                Prob > chi2 =         0.2049
```

Logistic Regression - Predictive Ability

Since the model generates $\Pr(Y = 1)$ for all cases, we can assess how well we might predict failure or success with the model. Specifically:

- We can simply assess how many correct and incorrect for a given $\Pr(Y = 1)$ criterion, such as 0.5. Ordinary sensitivity/specificity type calculations can be used to assess the result

- We can try to select a probability value that optimizes the above parameters. Note that as in sensitivity/specificity problems, there is a trade-off between predicting cases and non-cases correctly

Logistic Regression - Example of Predictive Ability

Glioblastoma (GBM) randomized clinical trial comparing standard treatment (radiation + chemotherapy) to same plus bevacizumab (Avastin), Analysis of survival

We will additionally include MGMT and composite prognostic indicator known as *RPA class*, as predictors

(Gilbert et al *NEJM* 2014)

Logistic Regression - Predictive Ability

- GBM data:

```
.* TRT effect = exposed here is trt = 1 (bev), use cohort with MGMT
. cc survival trt if cohort==1
                                                              Proportion
                 |   Exposed   Unexposed  |      Total     Exposed
-----------------+------------------------+------------------------
           Cases |       210         193  |        403       0.5211
        Controls |        97         108  |        205       0.4732
-----------------+------------------------+------------------------
           Total |       307         301  |        608       0.5049
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
      Odds ratio |         1.211474       |    .8530073    1.721077 (exact)
 Attr. frac. ex. |         .1745591       |   -.1723229    .4189684 (exact)
 Attr. frac. pop |         .0909613       |
                 +-------------------------------------------------
                              chi2(1) =     1.25  Pr>chi2 = 0.2639
```

```
.* MGMT effect - exposed here is bad marker value (=1)
. cc survival mgmt_grp if cohort==1
                                                              Proportion
                 |   Exposed   Unexposed  |      Total      Exposed
-----------------+------------------------+------------------------
           Cases |       321           82  |        403       0.7965
        Controls |       115           90  |        205       0.5610
-----------------+------------------------+------------------------
           Total |       436          172  |        608       0.7171
                 |                         |
                 |      Point estimate     |    [95% Conf. Interval]
                 |-------------------------+------------------------
      Odds ratio |         3.063627        |    2.085235    4.496513 (exact)
 Attr. frac. ex. |         .6735895        |    .5204378    .7776055 (exact)
                 +-------------------------------------------------
                              chi2(1) =    37.16  Pr>chi2 = 0.0000
```

- No treatment benefit for survival (trt/control OR = 1.21, indicating 21% *greater odds* of failure on Avastin, although not significantly different from 1.0). MGMT- unmethylated patients have 3-fold greater risk of death. In GBM, this marker represents significant heterogeneity in prognosis

Logistic Regression - Predictive Ability

Examine treatment, MGMT, and RPA class (a baseline prognostic class indicator) together via logistic regression

```
. logit survival trt mgmt_grp rpa_class, or

Iteration 0:   log likelihood = -388.59785
Iteration 1:   log likelihood = -361.36406
. . .
Iteration 4:   log likelihood = -361.10958

Logistic regression                                     Number of obs   =        608
                                                        LR chi2(3)      =      54.98
                                                        Prob > chi2     =     0.0000
Log likelihood = -361.10958                             Pseudo R2       =     0.0707
------------------------------------------------------------------------------
    survival | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         trt |   1.253899   .2259569     1.26   0.209     .8807916    1.785057
    mgmt_grp |   3.354802   .6471911     6.27   0.000     2.298569    4.896394
   rpa_class |   1.967377   .3278095     4.06   0.000     1.419248    2.727201
       _cons |   .0507661   .0358217    -4.22   0.000     .0127335    .2023957
------------------------------------------------------------------------------
```

- Predict probabilities and assess

```
. predict phat
. list trt mgmt_grp rpa_class survival phat in 20/40, clean

      trt   mgmt_grp   rpa_cl~s   survival      phat
 20.    1          1          3          1   .6192176
 21.    1          1          5          1   .8629051
 22.    1          1          4          0   .7618647
 23.    1          1          4          0   .7618647
 24.    0          1          5          1   .8338792
 25.    1          1          3          0   .6192176
  . . .
 34.    1          1          4          0   .7618647
 35.    1          0          4          0   .4881366
 36.    1          1          3          1   .6192176
 37.    1          1          4          1   .7618647
 38.    0          1          3          1   .5646291
 39.    1          0          3          0   .3264767
 40.    1          1          4          1   .7618647
```

One can 'assign' all those with, say, $phat > .5$, to failure, and compare to actual failure outcome

phat < 0.5 for non-failure

- **A summary function to do this is provided in Stata**

```
. estat classification
Logistic model for survival
              -------- True --------
Classified |         D             ~D  |      Total
-----------+--------------------------+-----------
     +     |       340            131  |        471
     -     |        63             74  |        137
-----------+--------------------------+-----------
   Total   |       403            205  |        608

Classified + if predicted Pr(D) >= .5
True D defined as survival != 0
-------------------------------------------------
Sensitivity                     Pr( +| D)   84.37%
Specificity                     Pr( -|~D)   36.10%
Positive predictive value       Pr( D| +)   72.19%
Negative predictive value       Pr(~D| -)   54.01%
-------------------------------------------------
Correctly classified                        68.09%
-------------------------------------------------
```

default cut-off is 0.5

PPV

NPV

- **The above rule uses 0.5 as a classification probability.** What about other values? List the predicted probabilities.

```
. tab phat

Pr(survival)|    Freq.     Percent        Cumul.
------------+-----------------------------------
      .2788 |          9        1.48        1.48
   .3264767 |         11        1.81        3.29
   .4319939 |         56        9.21       12.50
   .4881366 |         61       10.03       22.53
   .5646291 |         38        6.25       28.78
   .5994036 |         17        2.80       31.58
   .6192176 |         25        4.11       35.69
   .6523169 |         18        2.96       38.65
    .718427 |        141       23.19       61.84
   .7618647 |        161       26.48       88.32
   .8338792 |         40        6.58       94.90
   .8629051 |         31        5.10      100.00
------------+-----------------------------------
      Total |        608      100.00
```

Re-run the classification with all those with predicted probability greater than 0.66 declared failures

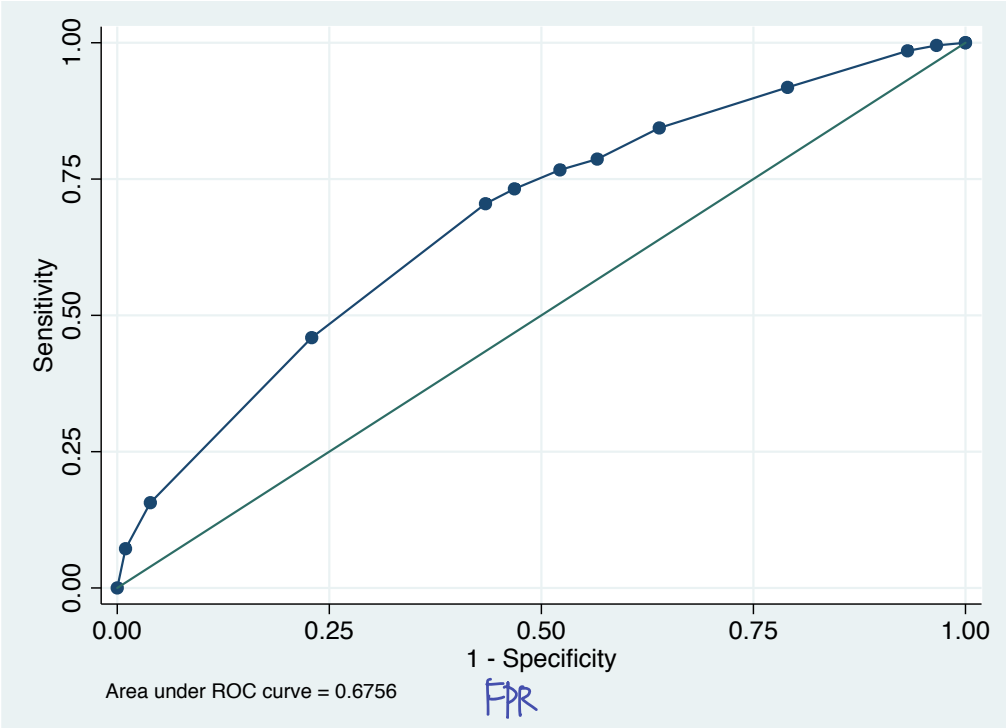
```
. estat classification, cutoff(.667)
Logistic model for survival
              -------- True --------
Classified |         D            ~D  |      Total
-----------+--------------------------+-----------
     +     |       284             89  |        373
     -     |       119            116  |        235
-----------+--------------------------+-----------
   Total   |       403            205  |        608

Classified + if predicted Pr(D) >= .667
True D defined as survival != 0
-------------------------------------------------
Sensitivity                     Pr( +| D)   70.47%
Specificity                     Pr( -|~D)   56.59%
Positive predictive value       Pr( D| +)   76.14%
Negative predictive value       Pr(~D| -)   49.36%
-------------------------------------------------
Correctly classified                        65.79%
-------------------------------------------------
```

- This rule is better on some measures, worse on others. To look at all probability cutoff values at once, use ROC curve (command *lroc*

Logistic Regression - ROC Curve for Prediction

- Receiver Operating Characteristic (ROC) curve: plot of Sensitivity ($\Pr(\text{predict } +|\text{case is } +)$ vs. False Positive Rate ($\Pr(\text{predict } +|\text{case is -})$) for all possible probability cut points.



Logistic Regression - ROC Curve for Prediction

- **Area under curve is the metric of interest.** Perfect prediction has area = 1.0. Area under 'Guessing' line = 0.50. Area can be thought of as equalling, if given two cases (event and non-event), the probability of correctly classifying one as event and other and non-event

- Point closest to upper left corner is the best classifier (best trade-off between sensitivity and specificity)

- This model has area = 0.68, best probability cutpoint near sensitivity specificity= 75%, specificity = 50%. Can examine ordered list of predicted probabilities to find (`lroc` in Stata will not list plot values (?)

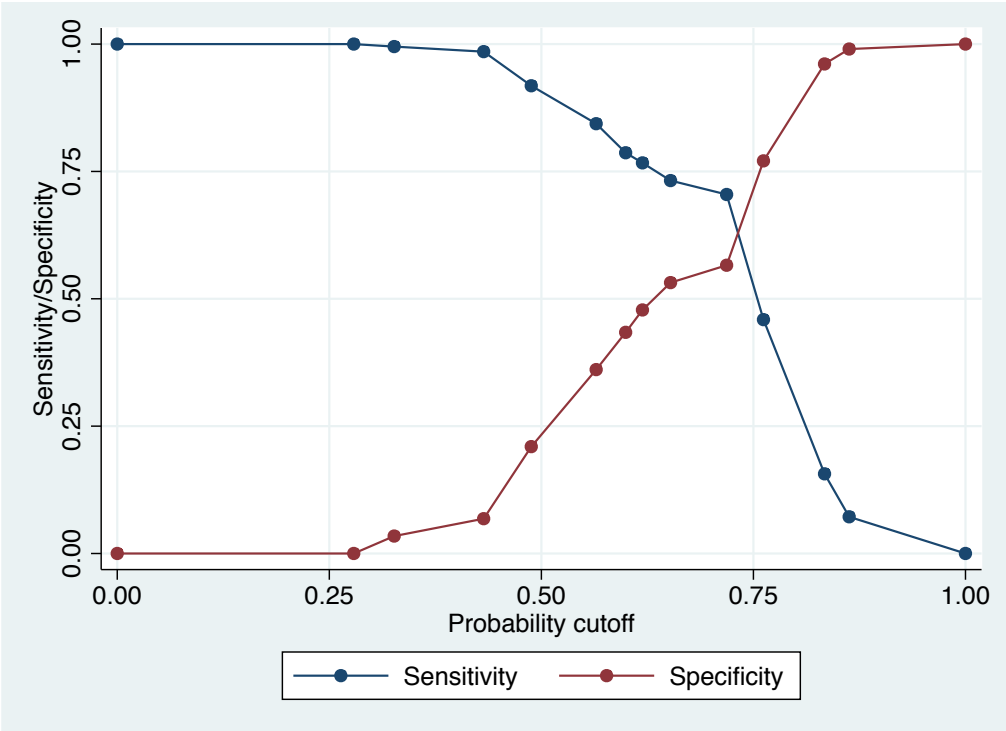
  A related option `lsens` in Stata will provide the sensitivity/specificity values at each model predicted probability.

Logistic Regression - ROC Curve for Prediction

```
. lsens, gense(sensval) gensp(specval)
. list p sensval specval in 1/12, clean

             p    sensval    specval
  1.   .8629051   0.000000   1.000000
  2.   .8338792   0.071960   0.990244
  3.   .7618647   0.156328   0.960976
  4.    .718427   0.459057   0.770732
  5.   .6523169   0.704715   0.565854
  6.   .6192176   0.732010   0.531707
  7.   .5994036   0.766749   0.478049
  8.   .5646291   0.786600   0.434146
  9.   .4881366   0.843672   0.360976
 10.   .4319939   0.918114   0.209756
 11.   .3264767   0.985112   0.068293
 12.      .2788   0.995037   0.034146
```

- These are the points on the ROC curve. A plot is also produced



- IMPORTANT NOTE: Optimizing cut point on a given dataset does not establish that classifier will work on novel data - requires validation in an independent sample (not used to build the predictor model)

Classification - Donner Party Data

```
. estat classification
Logistic model for died
              -------- True --------
Classified |         D             ~D  |      Total
-----------+--------------------------+-----------
     +     |        23              8  |         31
     -     |         2             12  |         14
-----------+--------------------------+-----------
   Total   |        25             20  |         45

Classified + if predicted Pr(D) >= .5. True D defined as died != 0
-------------------------------------------------
Sensitivity                     Pr( +| D)   92.00%
Specificity                     Pr( -|~D)   60.00%
Positive predictive value       Pr( D| +)   74.19%
Negative predictive value       Pr(~D| -)   85.71%
-------------------------------------------------
False + rate for true ~D        Pr( +|~D)   40.00%
False - rate for true D         Pr( -| D)    8.00%
False + rate for classified +   Pr(~D| +)   25.81%
False - rate for classified -   Pr( D| -)   14.29%
-------------------------------------------------
Correctly classified                        77.78%
```

Classification - Donner Party Data

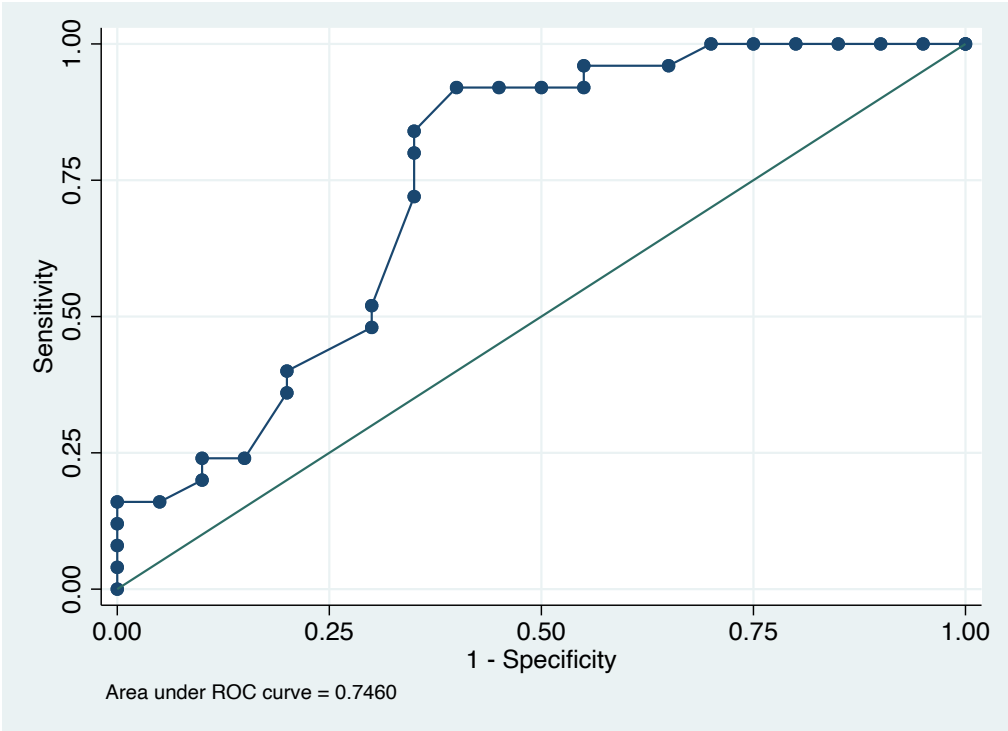
All possible cutpoints (except the extremes):

```
. predict phat
.  list phat sensval specval, clean
. . .
 10.   .6636918   0.360000   0.800000
 11.    .635664   0.400000   0.800000
 12.   .6094921   0.480000   0.700000
 13.   .5798071   0.520000   0.700000
 14.   .5716949   0.720000   0.650000
 15.   .5606443   0.800000   0.650000
 16.    .541299   0.840000   0.650000
 17.   .4827471   0.920000   0.600000
 18.   .4744595   0.920000   0.550000
 19.   .4438758   0.920000   0.500000
 20.   .3869718   0.920000   0.450000
 21.   .3256594   0.960000   0.450000
 . . .
```

probability cutpoint around 0.54 is best, as also shown in the ROC curve

Classification - Donner Party Data

```
.* get ROC curve
. lroc
```



Summary: Logistic Regression Models

- Several diagnostic quantities, aiming to detect outliers and influential points, are defined (C&H 12.5, not covered in SPRM). These borrow concepts from linear regression, discussed next . . .