Meta-analysis of Individual Participant Diagnostic Test Data

Ben A. Dwamena, MD

The University of Michigan Radiology & VAMC Nuclear Medicine, Ann Arbor, Michigan

Canadian Stata Conference, Banff, Alberta - May 30, 2019

University of Michigan
Medical School

Outline

University of Michigan
Medical School

Objectives

1. Review underlying concepts of medical diagnostic test evaluation
2. Discuss a recommended model for meta-analysis of aggregate diagnostic test data
3. Describe framework for meta-analysis of individual participant diagnostic test data
4. Illustrate implementation with MIDASIPD, a user-written STATA routine

University of Michigan
Medical School

Medical Diagnostic Test

Any measurement aiming to identify individuals who could potentially benefit from preventative or therapeutic intervention

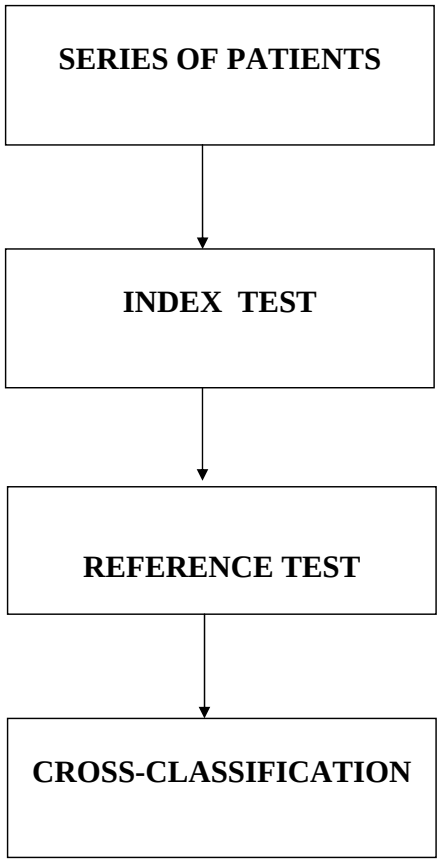
This includes:

1. Elements of medical history
2. Physical examination
3. Imaging procedures
4. Laboratory investigations
5. Clinical prediction rules

University of Michigan
Medical School

Diagnostic Accuracy Studies

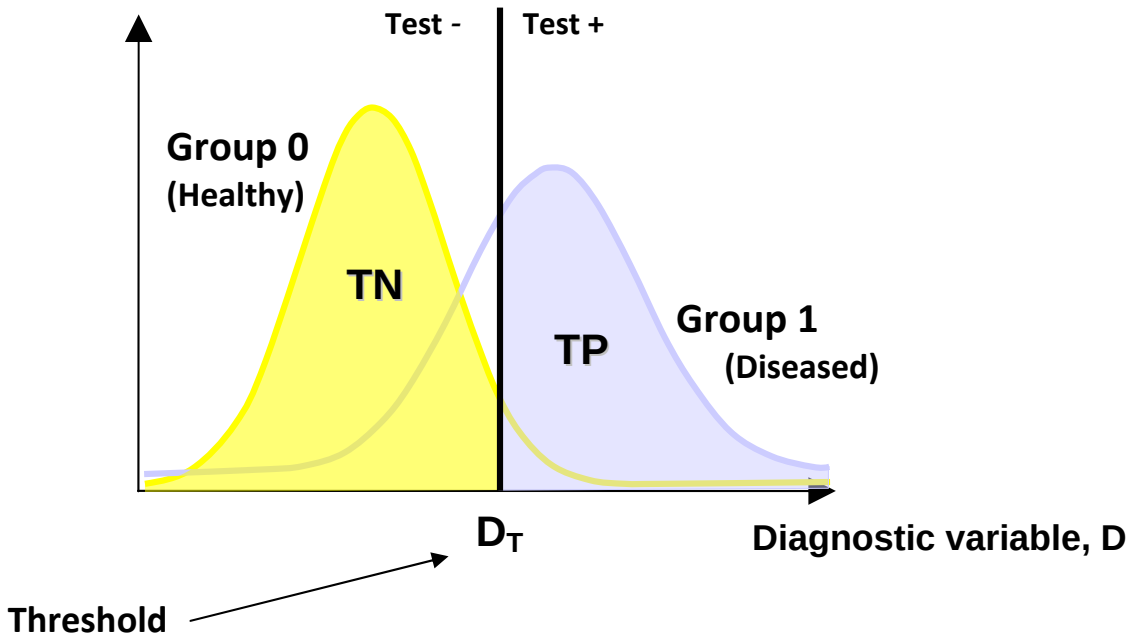
Figure: Basic Study Design



University of Michigan
Medical School

Diagnostic Accuracy Studies

Figure: Distributions of test result for diseased and non-diseased populations defined by threshold (DT)



University of Michigan
Medical School

Philosophical View Regarding Things

aka Epictetus (55-135 AD), Greek

1. They are what they appear to be
2. They neither are nor appear to be
3. They are but do not appear to be
4. They are not but appear to be

University of Michigan
Medical School

Diagnostic Test Results as Things

1. They are what they appear to be: True Positive
2. They neither are nor appear to be: True Negative
3. They are but do not appear to be: False Negative
4. They are not but appear to be: False Positive

University of Michigan
Medical School

Binary Test Accuracy: Data Structure

Data often reported as 2×2 matrix

	Reference Test (Diseased)	Reference Test (Healthy)
Test Positive	True Positive (a)	False Positive (b)
Test Negative	False Negative (c)	True Negative (d)

1. The chosen threshold may vary between studies of the same test due to inter-laboratory or inter-observer variation

2. The higher the cut-off value, the higher the specificity and the lower the sensitivity

University of Michigan
Medical School

Binary Test Accuracy

Measures of Test Performance

Sensitivity (true positive rate)	The proportion of subjects with disease who are correctly identified as such by test (a/a+c)
Specificity (true negative rate)	The proportion of subjects without disease who are correctly identified as such by test (d/b+d)
Positive predictive value	The proportion of test positive subjects who truly have disease (a/a+b)
Negative predictive value	The proportion of test negative subjects who truly do not have disease (d/c+d)

University of Michigan
Medical School

Binary Test Accuracy

Measures of Test Performance

Likelihood ratios (LR) The ratio of the probability of a positive (or negative) test result in the patients with disease to the probability of the same test result in the patients without the disease (sensitivity/1-specificity) or (1-Sensitivity/specificity)

Diagnostic odds ratio The ratio of the odds of a positive test result in patients with disease compared to the odds of the same test result in patients without disease (LRP/LRN)

University of Michigan Medical School

Diagnostic Meta-analysis

Critical review and statistical combination of previous research

Rationale

1. Too few patients in a single study
2. Too selected a population in a single study
3. No consensus regarding accuracy, impact, reproducibility of test(s)
4. Data often scattered across several journals
5. Explanation of variability in test accuracy
6. etc.

University of Michigan
Medical School

Diagnostic Meta-analysis

Scope

1. Identification of the number, quality and scope of primary studies
2. Quantification of overall classification performance (sensitivity and specificity), discriminatory power (diagnostic odds ratios) and informational value (diagnostic likelihood ratios)
3. Assessment of the impact of technological evolution (by cumulative meta-analysis based on publication year), technical characteristics of test, methodological quality of primary studies and publication selection bias on estimates of diagnostic accuracy
4. Highlighting of potential issues that require further research

University of Michigan
Medical School

Diagnostic Meta-analysis

Methodological Concepts

1. Meta-analysis of diagnostic accuracy studies may be performed to provide summary estimates of test performance based on a collection of studies and their reported empirical or estimated smooth ROC curves

2. Statistical methodology for meta-analysis of diagnostic accuracy studies focused on studies reporting estimates of test sensitivity and specificity or two by two data

3. Both fixed and random-effects meta-analytic models have been developed to combine information from such studies

University of Michigan
Medical School

Methods for Aggregate Dichotomized Data

Examples

1. Meta-analysis of sensitivity and specificity separately by direct pooling or modeling using fixed-effects or random-efffects approaches

2. Meta-analysis of postive and negative likelihood ratios separately using fixed-effects or random-effects approaches as applied to risk ratios in meta-analysis of therapeutic trials

3. Meta-analysis of diagnostic odds ratios using fixed-effects or random-efffects approaches as applied to meta-analysis of odds ratios in clinical treatment trials

4. Summary ROC Meta-analysis using fixed-effects or random-efffects approaches

University of Michigan
Medical School

Methods for Aggregate Dichotomized Data

Bivariate Mixed Model

Level 1: Within-study variability: Approximate Normal Approach

$$\begin{pmatrix} \texttt{logit}(p_{Ai}) \\ \texttt{logit}(p_{Bi}) \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{Ai} \\ \mu_{Bi} \end{pmatrix}, C_i\right)$$

$$C_i = \begin{pmatrix} s^2_{Ai} & 0 \\ 0 & s^2_{Bi} \end{pmatrix}$$

p_{Ai} and p_{Bi} Sensitivity and specificity of the ith study

μ_{Ai} and μ_{Bi} Logit-transforms of sensitivity and specificity of the ith study

C_i Within-study variance matrix

s^2_{Ai} and s^2_{Bi} variances of logit-transforms of sensitivity and specificity

University of Michigan
Medical School

Methods for Aggregate Dichotomized Data

Bivariate Mixed Model

Level 1: Within-study variability: Exact Binomial Approach

$$y_{Ai} \sim Bin\left(n_{Ai}, p_{Ai}\right)$$

$$y_{Bi} \sim Bin\left(n_{Bi}, p_{Bi}\right)$$

n_{Ai} and n_{Bi} Number of diseased and non-diseased

y_{Ai} and y_{Bi} Number of diseased and non-diseased with true test results

p_{Ai} and p_{Bi} Sensitivity and specificity of the ith study

University of Michigan
Medical School

Methods for Aggregate Dichotomized Data

Bivariate Mixed Model

Level 2: Between-study variability

$$\begin{pmatrix} \mu_{Ai} \\ \mu_{Bi} \end{pmatrix} \sim N\left(\begin{pmatrix} M_A \\ M_B \end{pmatrix}, \Sigma_{AB}\right)$$

$$\Sigma_{AB} = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix}$$

μ_{Ai} and μ_{Bi} Logit-transforms of sensitivity and specificity of the ith study

M_A and M_B Means of the normally distributed logit-transforms

Σ_{AB} Between-study variances and covariance matrix

University of Michigan Medical School

Methods for Aggregate Dichotomized Data

Bivariate Mixed Binary Regression

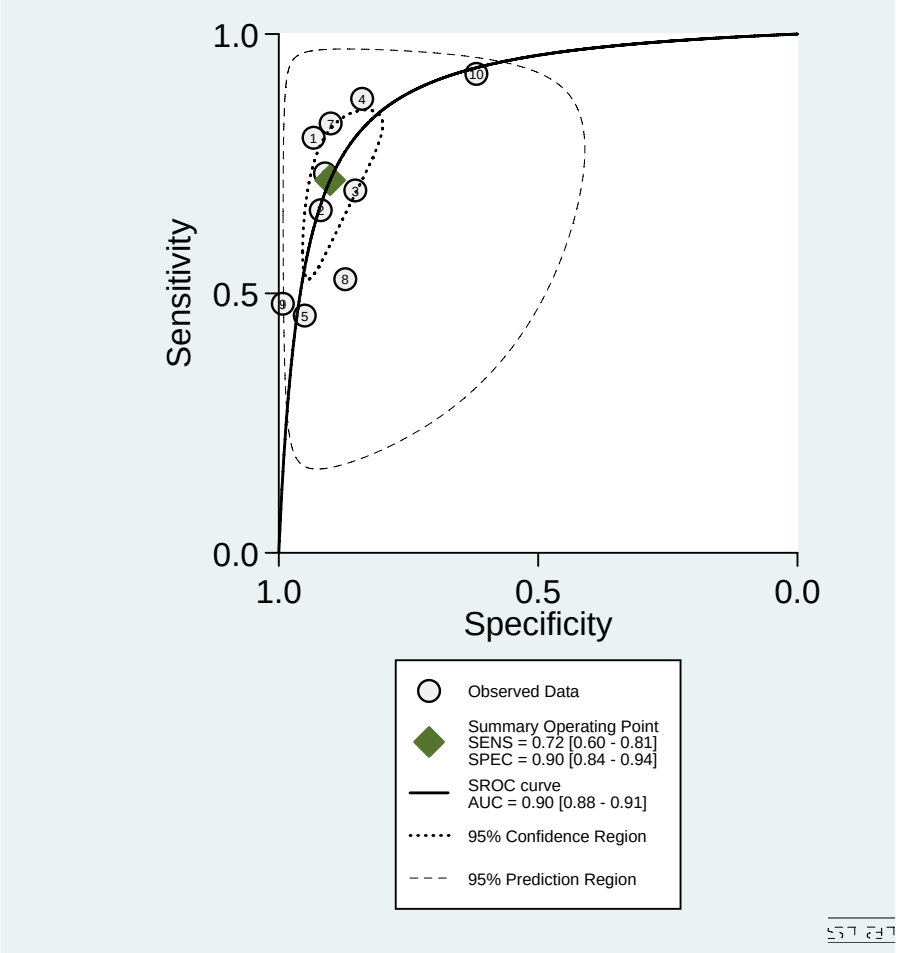
```
. midas tp fp fn tn

SUMMARY DATA AND PERFORMANCE ESTIMATES

Number of studies =  10
Reference-positive Units =  953
Reference-negative Units = 3609
Pretest Prob of Disease = 0.21
Parameter                      Estimate          95% CI
Sensitivity                     0.72 [    0.60,    0.81]
Specificity                     0.90 [    0.84,    0.94]
Positive Likelihood Ratio        7.3 [     4.9,    10.7]
Negative Likelihood Ratio       0.31 [    0.22,    0.44]
Diagnostic Odds Ratio             23 [      16,      34]
```

University of Michigan
Medical School

Methods for Aggregate Dichotomized Data

Bivariate Summary ROC Meta-analysis

```
. midas tp fp fn tn, sroc(curve mean data conf pred) level(95)
```



University of Michigan Medical School

Bivariate Random Effects Modeling of Individual Participant Data

Level 1: Within-study variability

$$y_{1ik} \sim Bernoulli\,(p_{1i})$$

$$y_{0ij} \sim Bernoulli\,(p_{0i})$$

y_{1ik} test response of patient k in study i who has disease

y_{0ij} test response of patient j in study i who does not have disease

y_{1ik} and y_{0ij} Equal to 1 if test response is correct and 0 otherwise

p_{1i} and p_{0i} Sensitivity and specificity of the ith study

University of Michigan Medical School

Modeling of Individual Participant Data

Level 2: Between-study variability

$$\begin{pmatrix} \beta_{1i} \\ \beta_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} mu_1 \\ mu_0 \end{pmatrix}, \Sigma_{AB}\right)$$

$$\Sigma_{12} = \begin{pmatrix} \sigma^2_{11} & \sigma_{12} \\ \sigma_{12} & \sigma^2_{22} \end{pmatrix}$$

β_{1i} and β_{0i} Logit-transforms of sensitivity and specificity of the ith study

mu_1 and mu_2 Means of the normally distributed logit-transforms

Σ_{12} Between-study variances and covariance matrix

University of Michigan Medical School

Explanation of Heterogeneity Beyond Chance

Investigate Accuracy-Covariate Effects

1. Significant heterogeneity than that due to chance alone re: diagnostic meta-analysis.
2. Addressed with covariate regression.
3. Covariate values may be binary, categorical or continuous
4. Across-study effects based on study-level variables
5. Within-study effects using patient-level variables
6. Mixed-study effects using both study-level and patient-level variables

University of Michigan
Medical School

Methods for Individual Dichotomized Data

Investigate Accuracy-Covariate Effects

1. Meta-analysis methods relying on AD estimate only the across-study effects using meta-regression
2. Across-study effect estimates are used to make inferences about the within-study effects
3. Assumption: across-study effects are unbiased estimates of the within-study effects
4. Ecological bias and confounding may affect this assumption

University of Michigan
Medical School

Modeling of Individual Participant Data

Covariate heterogeneity

1. PATIENT-LEVEL COVARIATES vary within studies (e.g. the age of patients) and across studies (e.g. the mean age of patients).

2. The WITHIN-STUDY EFFECTS describe relationship between diagnostic accuracy and individual covariate values; i.e. the sensitivity-covariate and specificity-covariate effects

3. The ACROSS-STUDY EFFECTS describe association between the mean covariate value in each study (e.g. mean age) and the underlying mean logit-sensitivity and mean logit-specificity across studies

University of Michigan
Medical School

Modeling of Individual Participant Data

Covariate heterogeneity

1. The WITHIN-STUDY EFFECTS: change in individual logit-sensitivity/logit specificity per a unit increase in patient level covariate value

2. The ACROSS-STUDY EFFECTS change in mean logit-sensitivity/logit-specificity per a unit increase in study level covariate value

University of Michigan
Medical School

Modeling of Individual Participant Data

Fisherian/Frequentist Model Estimation

Maximum Likelihood/Simulated Maximum Likelihood marginalizing study-specific logit-sensitivity and logit specificity over random effects

1. **meglm** with **family**(bernoulli), **link**(logit) and **covariance**(unstructured)
2. **melogit** using **family**(bernoulli) and **covariance**(unstructured)
3. **gllamm** using **denom**(1) and **link**(logit)

University of Michigan Medical School

Modeling of Individual Participant Data

Bayesian Model Estimation

Markov Chain Monte Carlo Simulation with Metropolis-Hastings Algorithm and Gibbs Sampling

1. **bayesmh** using likelihood(**dbernoulli**())
2. **bayesmh** using likelihood(**binlogit**)
3. **bayes** prefix **meglm** or **melogit**

University of Michigan
Medical School

Stata Code

Fisherian/Frequentist Model Estimation

```
meglm (parameter ‘logitsen’ ‘logitspe’ /// null fixed effects
‘wslogitsen’ ‘wslogitspe’ /// within-study effects
‘aslogitsen’ ‘aslogitspe’, noconstant) /// across-study effects
(‘_study’: ‘logitsen’ ‘logitspe’, noconstant cov(un)), /// var-cov
family(bernoulli) link(‘link’) /// likelihood
intmethod(‘intmethod’) intp(‘nip’)
```

University of Michigan
Medical School

Stata Code

Bayesian Model Estimation

```
bayes, remargl burn(5000)  mcmcs(5000) thin(2)  ///
saving("c:\ado\personal\bayesben.dta", replace) rseed(1356):
meglm (parameter ‘logitsen’ ‘logitspe’ ///null fixed effects
‘wslogitsen’ ‘wslogitspe’ ///within-study effects
‘aslogitsen’ ‘aslogitspe’, noconstant) /// across-study effects
(‘_study’: ‘logitsen’ ‘logitspe’, noconstant cov(un)), ///
family(bernoulli) link(‘link’) ///
intmethod(‘intmethod’) intp(‘nip’) nogroup nolrt
```

University of Michigan
Medical School

midasipd

Estimation Syntax

a wrapper for meglm programmed as an estimation command with replay and post-estimation graphics

```
#delimit;
syntax varlist(min=2 max=2)
[if] [in] , ID(varname) EFFects(string) COvar(varname) [
Link(string) INTegration(string) NIP(integer 30)
SORTby(varlist min=1) LEVEL(integer 95)
noTABLE noHSROC noFITstats noHETstats
REVman *];
#delimit cr
```

University of Michigan
Medical School

midasipd

Replay/Post-Estimation Syntax

```
#delimit;
syntax [if] [in] [, Level(cilevel)
noTABLE noHSROC noFITstats noHETstats
DIAGplot REVman UPVstats(numlist min=2 max=2)
FORest(string) BVroc(string) SROC(string)
FAGAN(numlist min=1 max=3) CONDIProb(string)
LRMAT(string) EBayes(string) BIASse(string)
*];
```

University of Michigan
Medical School

midasipd

Demonstration

Ultrasound for diagnosis of malignancy in women with breast masses

```
Number of studies                =        8

Number of participants           =     2824

Reference-positive Participants  =     1072

Reference-negative Participants  =     1752

Pretest Prob of Disease          =     0.39
```

University of Michigan
Medical School

midasipd

Demonstration

```
discard
cd c:/ado/personal/
use "E:\statacanadadata1.dta", clear
//set trace on
midasipd y dtruth, id(author) eff(across) covar(age)
midasipd, forest(generic)
midasipd, fagan(0.5)
midasipd, fagan(0.25 0.5 0.75)
midasipd, condiprob(full)
midasipd, condiprob(trunc)
```

University of Michigan
Medical School

midasipd

Demonstration

```
discard
use "E:\statacanadadata2.dta"", clear
midasipd y dtruth, id(author) eff(none) covar(age)
midasipd, diagplot
midasipd, bvroc(weighted mean confe predr lgnd)
midasipd, sroc( cregion tcurve lgnd)
midasipd, lrmat(colregion)
```

University of Michigan
Medical School

Summary Test Performance

WITHIN

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Sens	0.8818	0.0259	34.0694	0.0000	0.8311	0.9325
Spec	0.7652	0.0562	13.6123	0.0000	0.6550	0.8754
DOR	3.1908	0.2336	13.6571	0.0000	2.7329	3.6487
LRP	3.7554	0.8286	4.5322	0.0000	2.1314	5.3794
LRN	0.1545	0.0275	5.6253	0.0000	0.1007	0.2083

ACROSS

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Sens	0.9751	0.0767	12.7093	0.0000	0.8247	1.1255
Spec	0.7416	0.8720	0.8505	0.3950	-0.9674	2.4507
DOR	4.7233	3.7544	1.2581	0.2084	-2.6352	12.0818
LRP	3.7741	12.5681	0.3003	0.7640	-20.8590	28.4072
LRN	0.0335	0.0869	0.3860	0.6995	-0.1367	0.2038

MIXED

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Sens	0.9821	0.0571	17.1881	0.0000	0.8701	1.0941
Spec	0.8004	0.7165	1.1171	0.2639	-0.6039	2.2047
DOR	5.3922	3.1435	1.7153	0.0863	-0.7690	11.5534
LRP	4.9201	17.4572	0.2818	0.7781	-29.2955	39.1356
LRN	0.0224	0.0588	0.3809	0.7032	-0.0928	0.1376

University of Michigan Medical School

Extent of heterogeneity

WITHIN

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Isqsen	0.9526	0.0217	43.9303	0.0000	0.9101	0.9951
Isqspe	0.7960	0.1035	7.6911	0.0000	0.5932	0.9989
Isqbiv	0.8368	0.0173	48.3878	0.0000	0.8029	0.8707

ACROSS

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Isqsen	0.9569	0.1031	9.2852	0.0000	0.7549	1.1589
Isqspe	0.4290	0.7699	0.5572	0.5774	-1.0800	1.9379
Isqbiv	0.5001	0.7587	0.6591	0.5098	-0.9869	1.9871

MIXED

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Isqsen	0.9465	0.1509	6.2710	0.0000	0.6507	1.2423
Isqspe	0.3654	0.7533	0.4851	0.6276	-1.1110	1.8419
Isqbiv	0.6301	0.2699	2.3349	0.0195	0.1012	1.1591

University of Michigan
Medical School

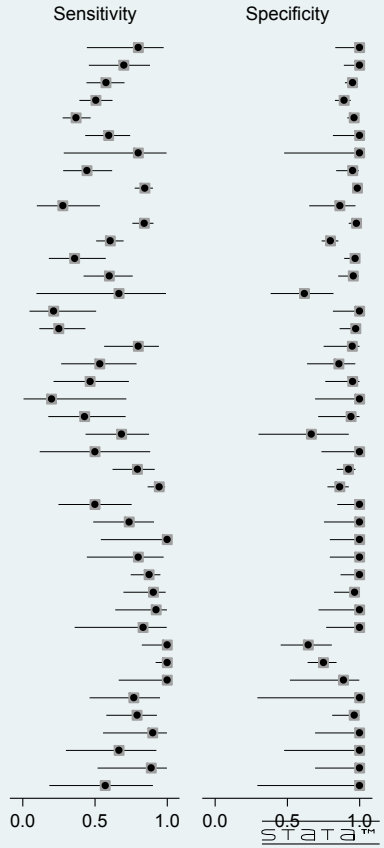
FOREST PLOT

code:

```
midasipd, forest(cochrane) nohead noestimates
```

result:

Studyid	TP	FP	FN	TN	Sensitivity (95% CrI)	Specificity (95% CrI)
Heuser	8	0	2	20	0.80 [0.44 - 0.97]	1.00 [0.83 - 1.00]
Fuster	14	0	6	32	0.70 [0.46 - 0.88]	1.00 [0.89 - 1.00]
Ueda	34	6	25	118	0.58 [0.44 - 0.70]	0.95 [0.90 - 0.98]
Cermik	40	15	39	125	0.51 [0.39 - 0.62]	0.89 [0.83 - 0.94]
Veronesi	38	5	65	128	0.37 [0.28 - 0.47]	0.96 [0.91 - 0.99]
Chung	25	0	17	18	0.60 [0.43 - 0.74]	1.00 [0.81 - 1.00]
Stadnik	4	0	1	5	0.80 [0.28 - 0.99]	1.00 [0.48 - 1.00]
Kumar	16	2	20	40	0.44 [0.28 - 0.62]	0.95 [0.84 - 0.99]
Gil-Rendo	120	2	22	131	0.85 [0.77 - 0.90]	0.98 [0.95 - 1.00]
Weir	5	3	13	19	0.28 [0.10 - 0.53]	0.86 [0.65 - 0.97]
Zornoza	90	2	17	91	0.84 [0.76 - 0.90]	0.98 [0.92 - 1.00]
Wahl	66	40	43	159	0.61 [0.51 - 0.70]	0.80 [0.74 - 0.85]
Lovrics	9	2	16	63	0.36 [0.18 - 0.57]	0.97 [0.89 - 1.00]
Inoue	21	2	14	44	0.60 [0.42 - 0.76]	0.96 [0.85 - 0.99]
Fehr	2	8	1	13	0.67 [0.09 - 0.99]	0.62 [0.38 - 0.82]
Barranger	3	0	11	18	0.21 [0.05 - 0.51]	1.00 [0.81 - 1.00]
Van_Hoeven	8	1	24	37	0.25 [0.11 - 0.43]	0.97 [0.86 - 1.00]
Rieber	16	1	4	19	0.80 [0.56 - 0.94]	0.95 [0.75 - 1.00]
Nakamoto2	8	3	7	18	0.53 [0.27 - 0.79]	0.86 [0.64 - 0.97]
Nakamoto1	7	1	8	20	0.47 [0.21 - 0.73]	0.95 [0.76 - 1.00]
Kelemen	1	0	4	10	0.20 [0.01 - 0.72]	1.00 [0.69 - 1.00]
Guller	6	1	8	16	0.43 [0.18 - 0.71]	0.94 [0.71 - 1.00]
Danforth	13	3	6	6	0.68 [0.43 - 0.87]	0.67 [0.30 - 0.93]
Yang	3	0	3	12	0.50 [0.12 - 0.88]	1.00 [0.74 - 1.00]
Schirrmeister	27	6	7	73	0.79 [0.62 - 0.91]	0.92 [0.84 - 0.97]
Greco	68	13	4	82	0.94 [0.86 - 0.98]	0.86 [0.78 - 0.93]
Yutani2	8	0	8	22	0.50 [0.25 - 0.75]	1.00 [0.85 - 1.00]
Ohta	14	0	5	13	0.74 [0.49 - 0.91]	1.00 [0.75 - 1.00]
Hubner	6	0	0	16	1.00 [0.54 - 1.00]	1.00 [0.79 - 1.00]
Yutani1	8	0	2	16	0.80 [0.44 - 0.97]	1.00 [0.79 - 1.00]
Rostom	42	0	6	26	0.88 [0.75 - 0.95]	1.00 [0.87 - 1.00]
Smith	19	1	2	28	0.90 [0.70 - 0.99]	0.97 [0.82 - 1.00]
Noh	12	0	1	11	0.92 [0.64 - 1.00]	1.00 [0.72 - 1.00]
Palmedo	5	0	1	14	0.83 [0.36 - 1.00]	1.00 [0.77 - 1.00]
Adler2	19	11	0	20	1.00 [0.82 - 1.00]	0.65 [0.45 - 0.81]
Utech	44	20	0	60	1.00 [0.92 - 1.00]	0.75 [0.64 - 0.84]
Scheidhauer	9	1	0	8	1.00 [0.66 - 1.00]	0.89 [0.52 - 1.00]
Bassa	10	0	3	3	0.77 [0.46 - 0.95]	1.00 [0.29 - 1.00]
Avril	19	1	5	26	0.79 [0.58 - 0.93]	0.96 [0.81 - 1.00]
Crowe	9	0	1	10	0.90 [0.55 - 1.00]	1.00 [0.69 - 1.00]
Hoh	6	0	3	5	0.67 [0.30 - 0.93]	1.00 [0.48 - 1.00]
Adler1	8	0	1	10	0.89 [0.52 - 1.00]	1.00 [0.69 - 1.00]
Tse	4	0	3	3	0.57 [0.18 - 0.90]	1.00 [0.29 - 1.00]



University of Michigan
Medical School

SUMMARY ROC

1. Logit estimates of sensitivity, specificity and respective variances are used to construct a hierarchical summary ROC curve.

2. The summary ROC curve may be displayed with or without
   - Observed study data,
   - Summary operating point,
   - 95% Confidence region and/or
   - 95% Prediction region.

University of Michigan
Medical School

SUMMARY ROC

1. The 95% confidence region around the summary estimate of sensitivity and specificity may be viewed as a two-dimensional confidence interval.

2. The main axis of the 95% confidence region reflects the correlation between sensitivity and specificity (threshold effect).

3. The 95% prediction region depicts a two-dimensional standard deviation of the individual studies.

4. The area of the 95% prediction region beyond the 95% confidence region reflects extent of between-study variation.

University of Michigan
Medical School

SUMMARY ROC

1. The area under the curve (AUROC), serves as a global measure of test performance.
2. The AUROC is the average TPR over the entire range of FPR values.
3. The following guidelines have been suggested for interpretation of intermediate AUROC values:
   - **low** accuracy (0.5>= AUC <= 0.7),
   - **moderate** accuracy (0.7 >= AUC <= 0.9), or
   - **high** accuracy (0.9 >= AUC <= 1)

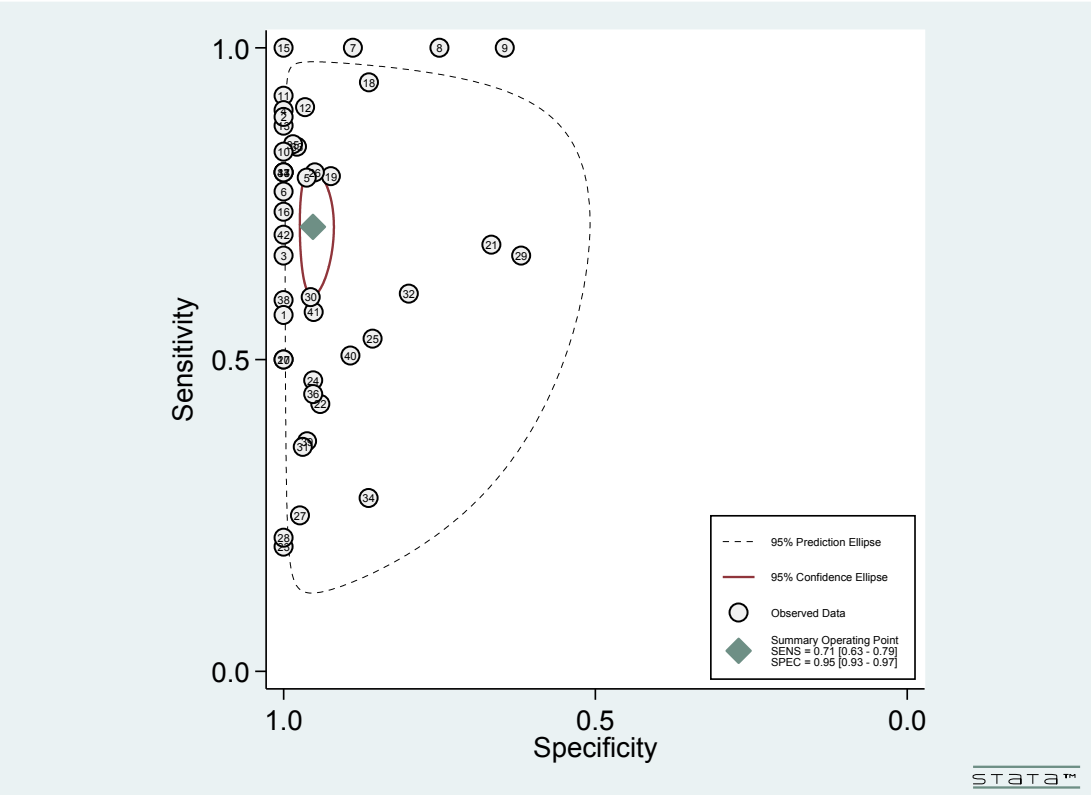
University of Michigan Medical School

SUMMARY ROC

code:

```
midasipd, sroc(mean prede confe data lgnd) ///
nohead noestimates
```

result:



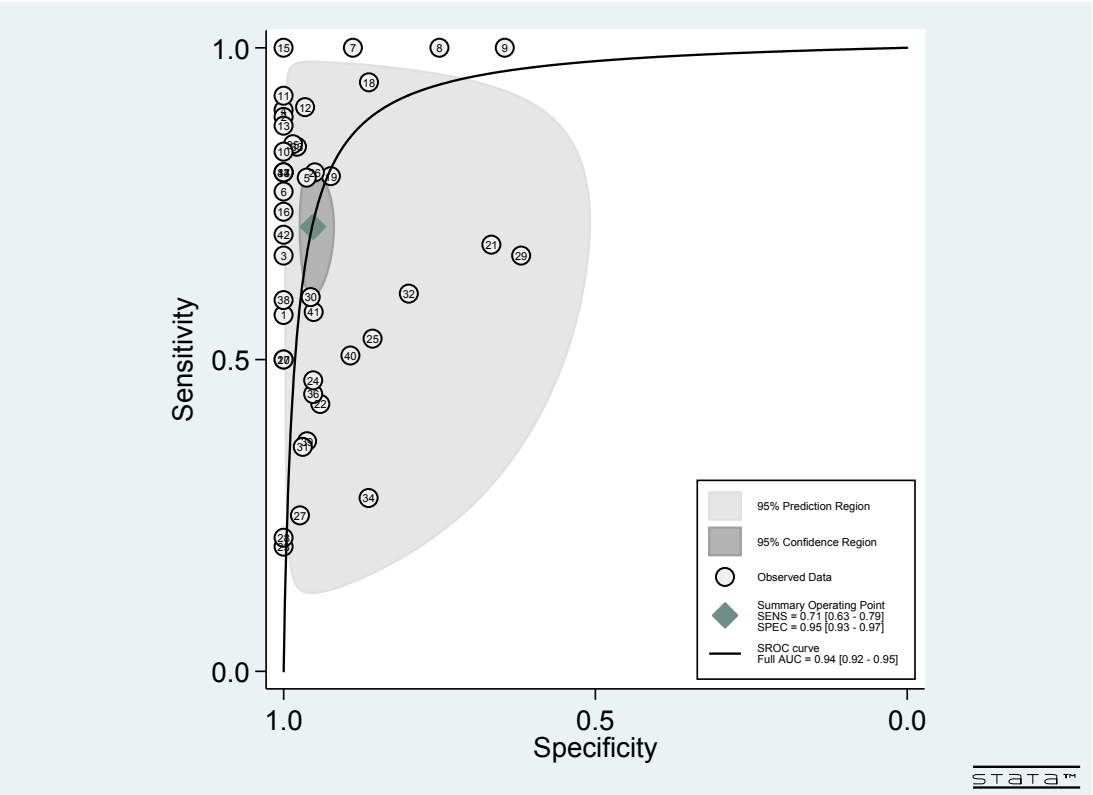
University of Michigan
Medical School

SUMMARY ROC

code:

```
midasipd, sroc(fcurve predr confr data lgnd)  ///
nohead noestimates
```

result:



University of Michigan
Medical School

FAGAN NOMOGRAM

1. The patient-relevant utility of a diagnostic test is evaluated using the likelihood ratios to calculate post-test probability(PTP) as follows: Pretest Probability=Prevalence of target condition PTP= LR $\times$ pretest probability/[(1-pretest probability)$\times$ (1-LR)]

2. This concept is depicted visually with Fagan's nomograms.

3. When Bayes theorem is expressed in terms of log-odds, the posterior log-odds are linear functions of the prior log-odds and the log likelihood ratios.

University of Michigan
Medical School

FAGAN NOMOGRAM

1. A Fagan plot consists of a vertical axis on the left with the prior log-odds, an axis in the middle representing the log-likelihood ratio and an vertical axis on the right representing the posterior log-odds.

2. Lines are then drawn from the prior probability on the left through the likelihood ratios in the center and extended to the posterior probabilities on the right.

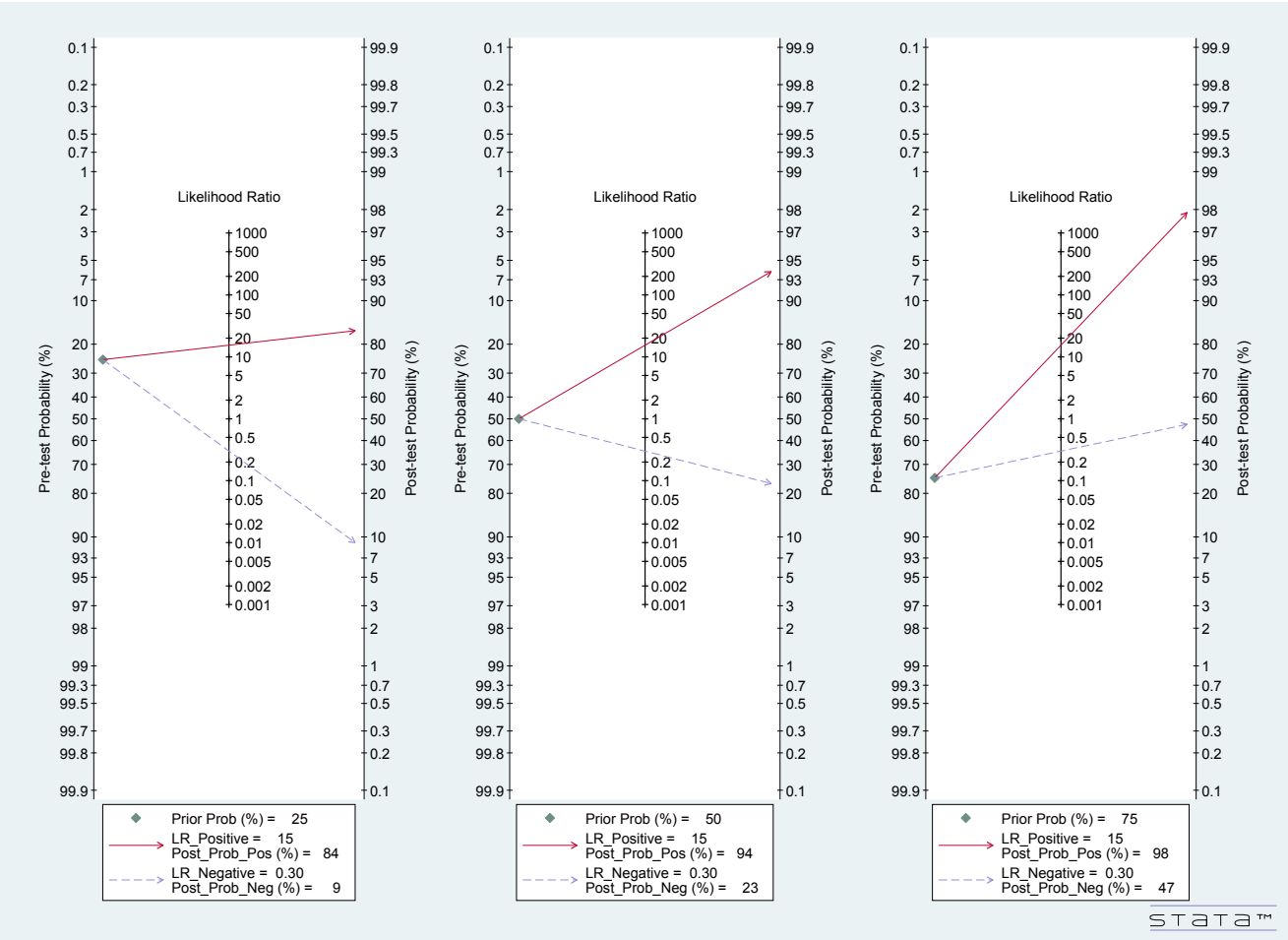
University of Michigan
Medical School

FAGAN NOMOGRAM

code:

```
midasipd, fagan(0.25 0.50 0.75) nohead noestimates
```

result:



University of Michigan Medical School

CONDITIONAL PROBABILITY PLOTS

1. The conditional probability of disease given a positive OR negative test, the so-called positive (negative) predictive values are critically important to clinical application of a diagnostic procedure.

2. They depend not only on sensitivity and specificity, but also on disease prevalence (p).

3. The probability modifying plot is a graphical sensitivity analysis of predictive value across a prevalence continuum defining low to high-risk populations.

4. It depicts separate curves for positive and negative tests.

5. The user draws a vertical line from the selected pre-test probability to the appropriate likelihood ratio line and then reads the post-test probability off the vertical scale.

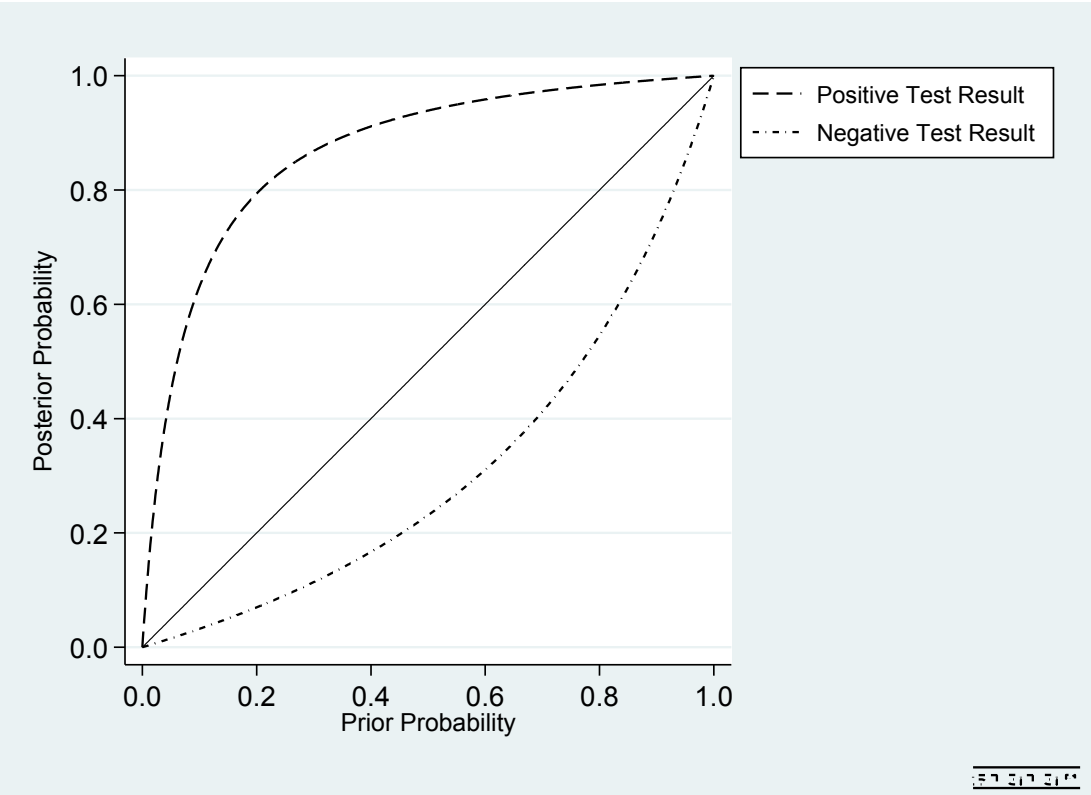
University of Michigan
Medical School

CONDITIONAL PROBABILITY PLOTS

code:

```
midasipd, condiprob(full) nohead noestimates
```

result:



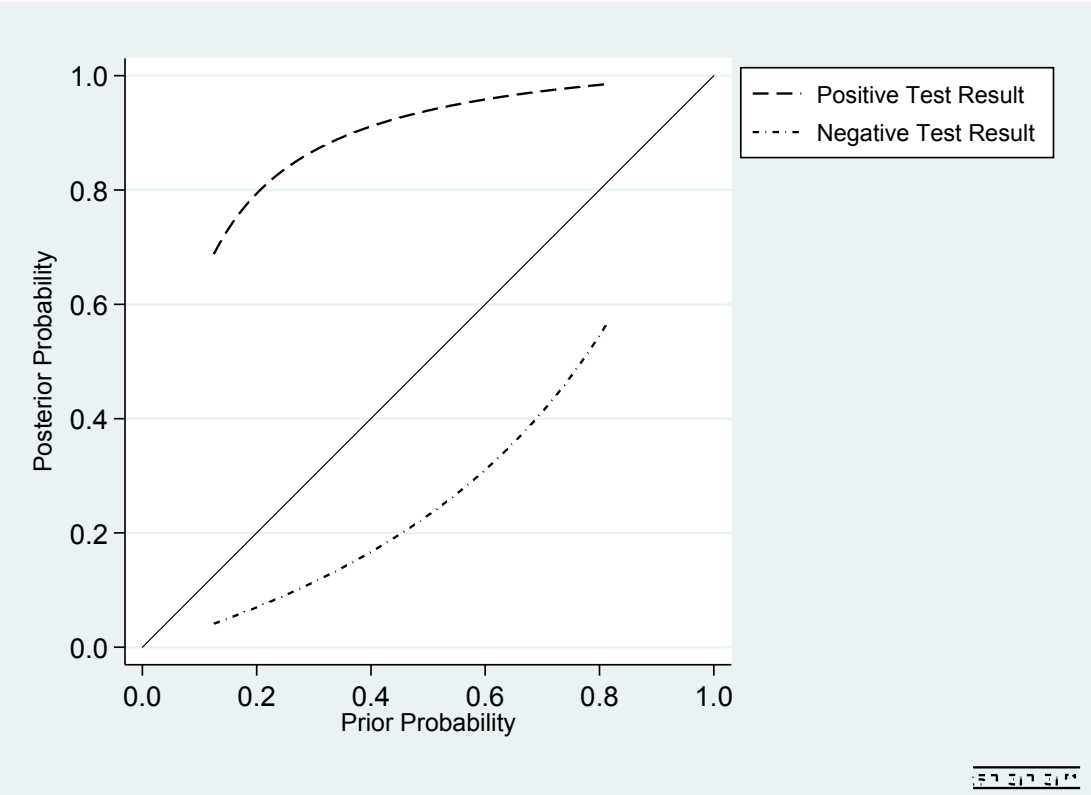
University of Michigan
Medical School

CONDITIONAL PROBABILITY PLOTS

code:

```
midasipd, condiprob(trunc) nohead noestimates
```

result:



University of Michigan
Medical School

UNCONDITIONAL PREDICTIVE VALUES

1. General summary statistics have also been introduced for when it may be of interest to evaluate the effect of prevalence(p) on predictive values: unconditional positive and negative predictive values, which permit prevalence heterogeneity.

2. These measures are obtained by integrating their corresponding conditional (on p) versions with respect to a prior distribution for p.

3. The prior posits assumptions about the risk level in a hypothetical population of interest, e.g. low, high, moderate risk, as well as the heterogeneity in the population.

University of Michigan
Medical School

UNCONDITIONAL PREDICTIVE VALUES

code:

```
midasipd, upv(0.25 0.75) nohead noestimates
```

result:

```
Prevalence Heterogeneity/Unconditional Predictive Values
--------------------------------------------------------------------
Prior Distribution (Uniform)                 =   0.25 - 0.75

Unconditional Positive Predictive Value      =   0.93 [0.93 - 0.93]

Unconditional Negative Predictive Value      =   0.75 [0.75 - 0.75]
--------------------------------------------------------------------
```

University of Michigan
Medical School

SUMMARY

1. Meta-analysis of diagnostic IPD Useful for unbiased estimation of impact of patient- and study level covariate heterogeneity
2. Meta-analysis of diagnostic IPD may mitigate ecological bias and confounding associated with meta-regression of AD
3. **midasipd** facilitates both frequentist and bayesian meta-analysis of diagnostic IPD using Stata
4. **midasipd** is an estimation command with multiple post-estimation graphical analyses
5. **midasipd** allows the separation of within-study and across-study effects of a covariate

University of Michigan
Medical School

References I


Aertgeerts B., Buntinx F., and Kester A.
The value of the CAGE in screening for alcohol abuse and alcohol dependence in general clinical populations: a diagnostic meta-analysis.
J clin Epidemiol 2004;57:30-39


Arends L.R., Hamza T.H., Von Houwelingen J.C., Heijenbrok-Kal M.H., Hunink M.G.M. and Stijnen T.
Bivariate Random Effects Meta-Analysis of ROC Curves.
Med Decis Making 2008;28:621-628


Begg C.B. and Mazumdar M.
Operating characteristics of a rank correlation test for publication bias.
Biometrics 1994;50:1088-1101


Chu H. and Cole S.R.
Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach.
J Clin Epidemiol 2006;59:1331-1332


Dendukuri N., Chui K. and Brophy J.M.
Validity of EBCT for coronary artery disease: a systematic review and meta-analysis.
BMC Medicine 2007;5:35

References II


Dukic V. and Gatsonis C.
Meta-analysis of diagnostic test accuracy studies with varying number of thresholds.
Biometrics 2003;59:936-946


Dwamena, B.
midas: Module for Meta-Analytical Integration of Diagnostic Accuracy Studies
Boston College Department of Economics, Statistical Software Components 2007; s456880: http://ideas.repec.org/c/boc/bocode/s456880.html.


Ewing J.A.
Detecting Alcoholism: The CAGE questionnaire.
JAMA 1984;252:1905-1907


Harbord R.M., Deeks J.J., Egger M., Whitting P. and Sterne J.A.
Unification of models for meta-analysis of diagnostic accuracy studies.
Biostatistics 2007;8:239-251


Harbord R.M., Whitting P., Sterne J.A.C., Egger M., Deeks J.J., Shang A. and Bachmann L.M.
An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary
Journal of Clinical Epidemiology 2008;61;1095-1103

References III


Harbord R.M., and Whitting P.
metandi: Meta-analysis of diagnostic accuracy using hierarchical logistic regression
Stata Journal 2009;2:211-229


Irwig L., Macaskill P., Glasziou P. and Fahey M.
Meta-analytic methods for diagnostic test accuracy.
J Clin Epidemiol 1995;48:119-30


Kester A.D.M., and Buntinx F.
Meta-Analysis of ROC Curves.
Med Decis Making 2000;20:430-439


Littenberg B. and Moses L. E.
Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method.
Med Decis Making 1993;13:313-321


Macaskill P.
Empirical Bayes estimates generated in a hierarchical summary ROC analysis agreed closely with those of a full Bayesian analysis.
J Clin Epidemiol 2004;57:925-932

References IV


Moses L.E., Shapiro D. and Littenberg B.
Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic
approaches and some additional considerations.
Stat Med 1993;12:1293-13116


Pepe M.S.
Receiver Operating Characteristic Methodology.
Journal of the American Statistical Association 2000;95:308-311


Pepe M.S.
The Statistical Evaluation of Medical Tests for Classification and Prediction.
2003; Oxford: Oxford University Press


Reitsma J.B., Glas A.S., Rutjes A.W.S., Scholten R.J.P.M., Bossuyt P.M. and Zwinderman A.H.
Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews.
J Clin Epidemiol 2005;58:982-990


Riley R.D., Dodd S.R., Craig J.V., Thompson J.R. and Williamson P.R.
Meta-analysis of diagnostic test studies using individual patient data and aggregate data
Stat Med 2008;27:6111-6136

References V


Rutter C.M., and Gatsonis C.A.
A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations
Stat Med 2001;20:2865-2884


Toledano A. and Gatsonis C.A.
Regression analysis of correlated receiver operating characteristic data.
Academic Radiology 1995;2:S30-S36


Tosteson A.A. and Begg C.B.
A general regression methodology for ROC curve estimation.
Medical Decision Making 1988;8:204-215


Williams R.
Using Heterogeneous Choice Models To Compare Logit and Probit Coefficients Across Groups
Sociological Methods and Research 2009;37: 531-559


White I.R.
Multivariate Random-effects Meta-analysis.
Stata Journal 2009;1:40-56