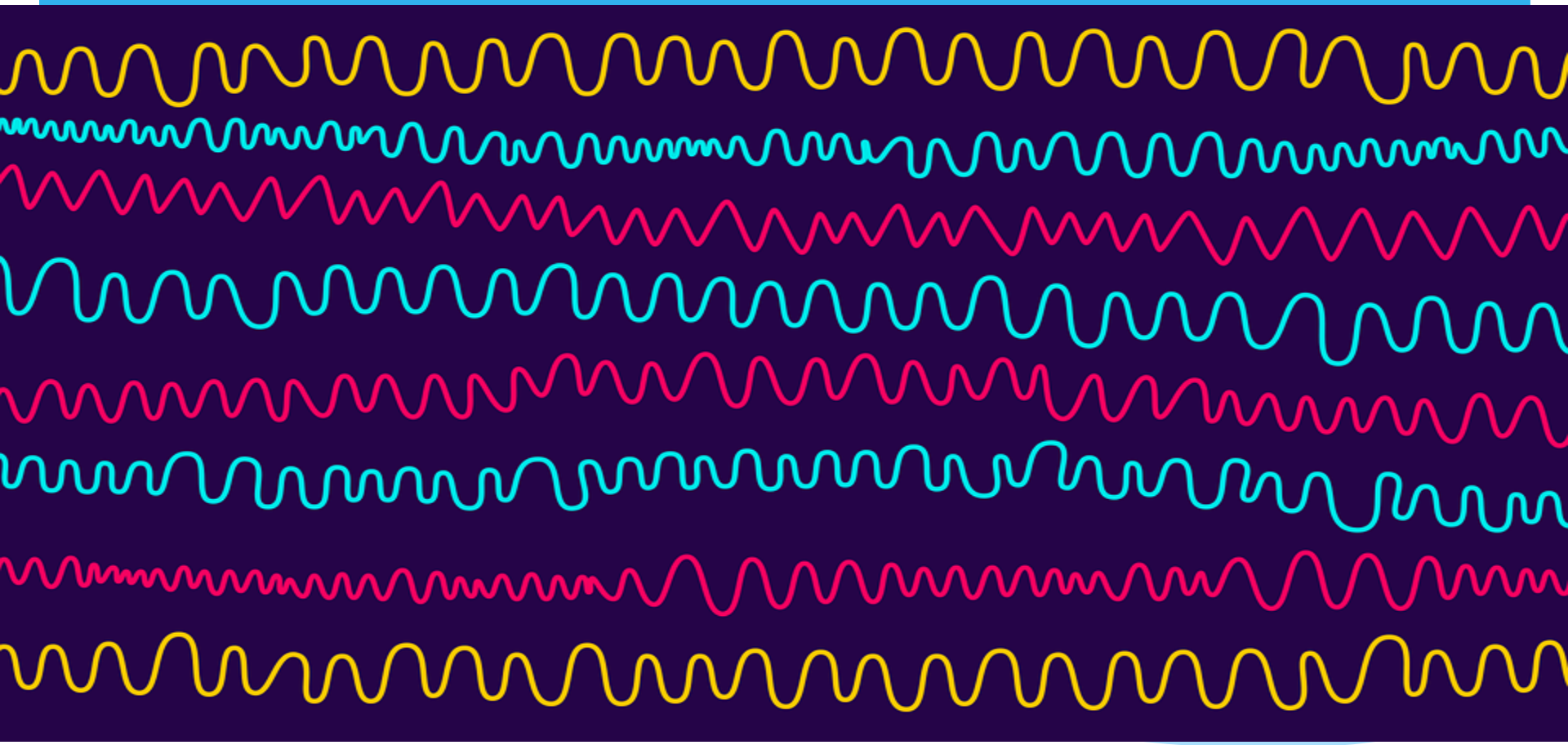
Evidence of diagnosis and screening



https://pixabay.com/illustrations/waves-background-screen-design-1789169/

Objectives

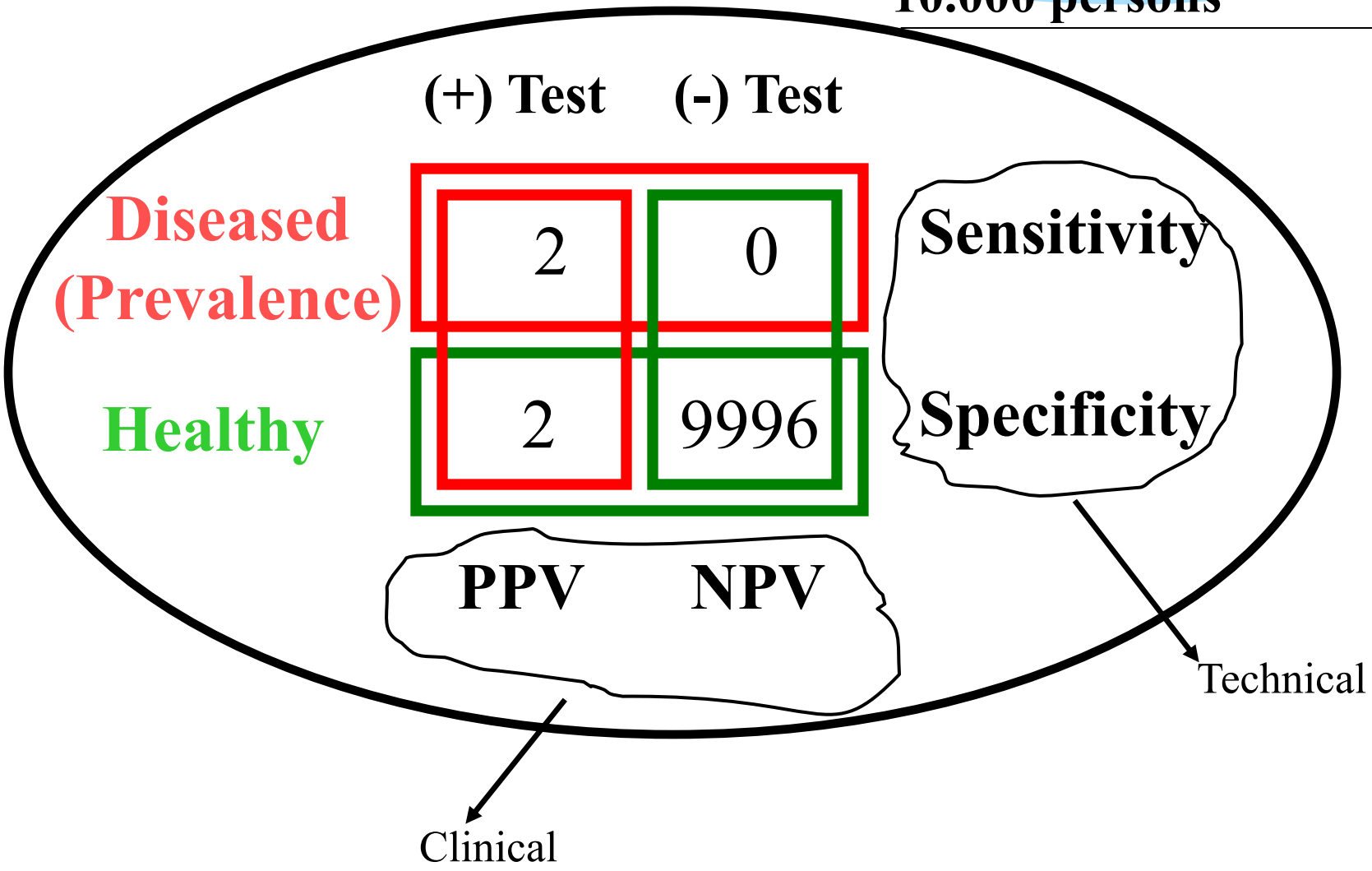
* This presentation aims to increase the paticipants' knowledge to appraise diagnostic articles and to calculate the pre & post-test probability for a laboratory test to diagnose common problems in clinical practice.
* At the end of this session, the participants are expected to;
  * Discuss diagnostic test characteristics: Sensitivity, Specificity, Predictive values, Likelihood ratios
  * Discuss-pre and post-test probabilities and the use of the Fagan's nomogram
  * Discuss the use of QUADAS-2 for assessing quality of a diagnostic test
  * Explain the place of ROC analysis in diagnostic tests

Technical vs. Clinical Precision

* "Baby Jeff": The case of screening for muscular dystrophy at Harrisburg Hospital
* Technical Precision of CPK test:
  * Sensitivity: 100%
  * Specificity: 99.98%
* **But**,

  • The prevalence of MD is 1 in 5000 (0.02%)

Technical vs. Clinical Precision



Ways to remember Sensitivity and Specificity

SENSITIVITY

* PID – positive in disease
* SnNOut: Tests with a high sensitivity rule OUT the disease

SPECIFICITY

* NIH – Negative in health
* SpPIn: Tests with a high specificity rule IN the disease

Does Baby Jeff have M.D.?

Of 100,000 males, 20 will have M.D.

(1 in 5,000, or 0.02% prevalence)

* The test will correctly identify all **20** who have the disease (sensitivity = 100%)

Does Baby Jeff have M.D.?

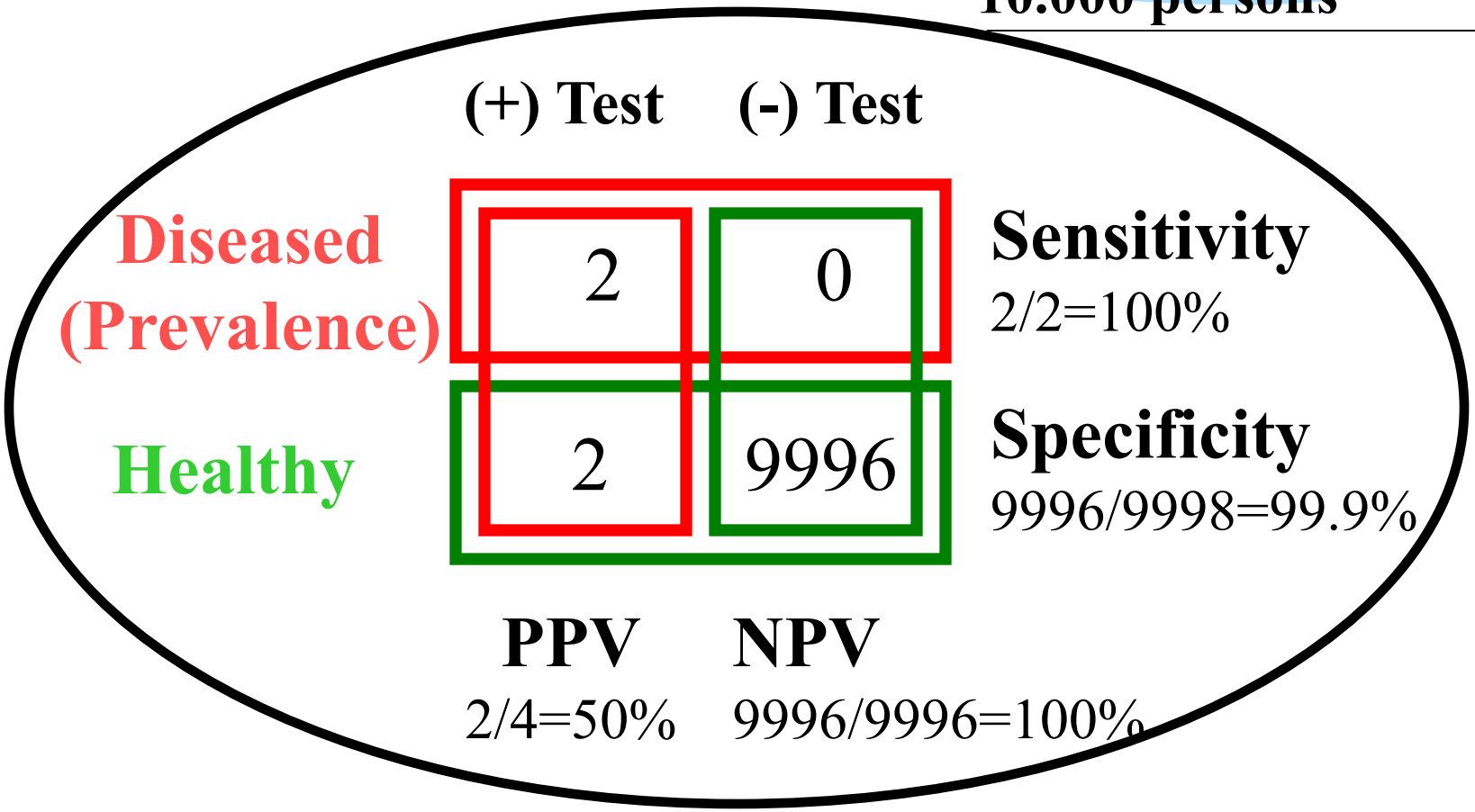
* Of the 99,980 without M.D.
  * Specificity = 99.98%
  * 99,980 x 0.9998 = 99,960 will be negative
  * Hence, false positives = **20**

“. . . The Rest of the Story”

* Therefore,
  * Out of 100,000 infants, **20** will be truly positive, while **20** will be false positive
  * Positive predictive value = 50%
  * The child with a positive screening test only has a 50/50 chance of actually having MD!

Technical vs. Clinical Precision

10.000 persons



Bayes theorem

* Decisions we are giving are based on previous assumptions
  * Imagine: 5 year old child coming with 38 ° C axillary temp.
    * If you are a doctor in Zambia, your most probable diagnosis may be **malaria** http://www.rbm.who.int/amd2003/amr2003/ch1.htm
    * If you are a doctor in Georgia, your most probable diagnosis may be **common cold**
    * Why?
      * Malaria prevalence in Zambian children under five is around 60%
      * Most common cause of fever among European children is common cold

Bayes theorem

* Adapting a theory of conditional probability from the 18th century statistician Thomas Bayes solves the problem of calculating posttest disease probability.
* This theory allows pretest probability to be separated from a term that describes the strength of the diagnostic test—likelihood ratio.

Posttest Odds = Pretest Odds X Likelihood Ratio

Likelihood Ratio

* Converts a pre-test probability to a post-test probability
* Compares the likelihood of a positive result in someone with the disease as compared with someone without the disease (or vice-versa)
* Incorporates both sensitivity and specificity

$$LR^{+}=Sensitivity/(1-Specifity)=1/(1-0.9998)=5000$$

Likelihood Ratio

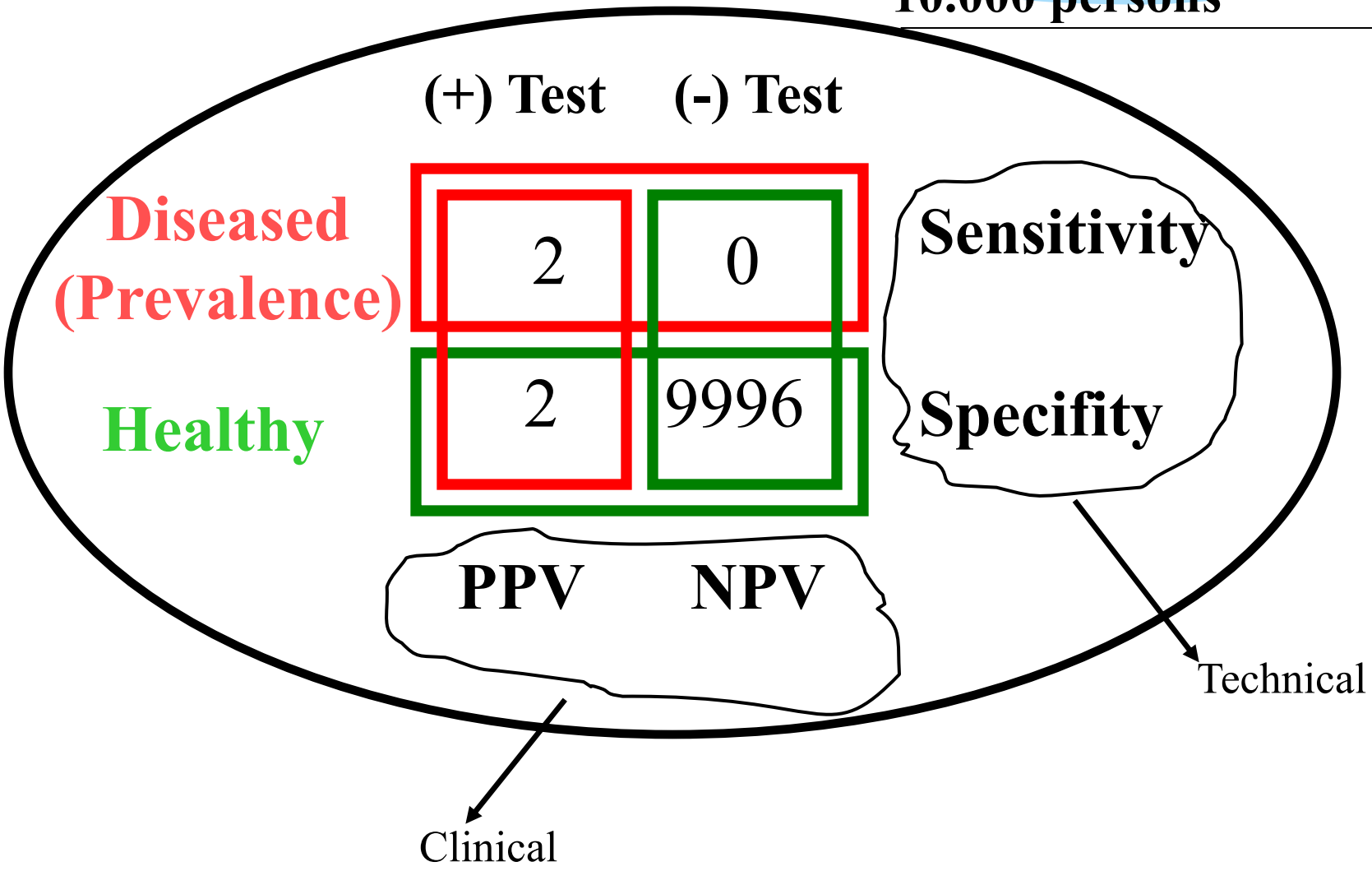
* Clinically more useful than sensitivity and specificity
* Can be used to calculate the probability of disease in a patient (the clinical question)
* Positive LR
  * How many times more likely the test is positive in patients with the disease than those without the disease?
* Negative LR
  * How many times more likely the test is negative in patients with the disease than those without the disease?

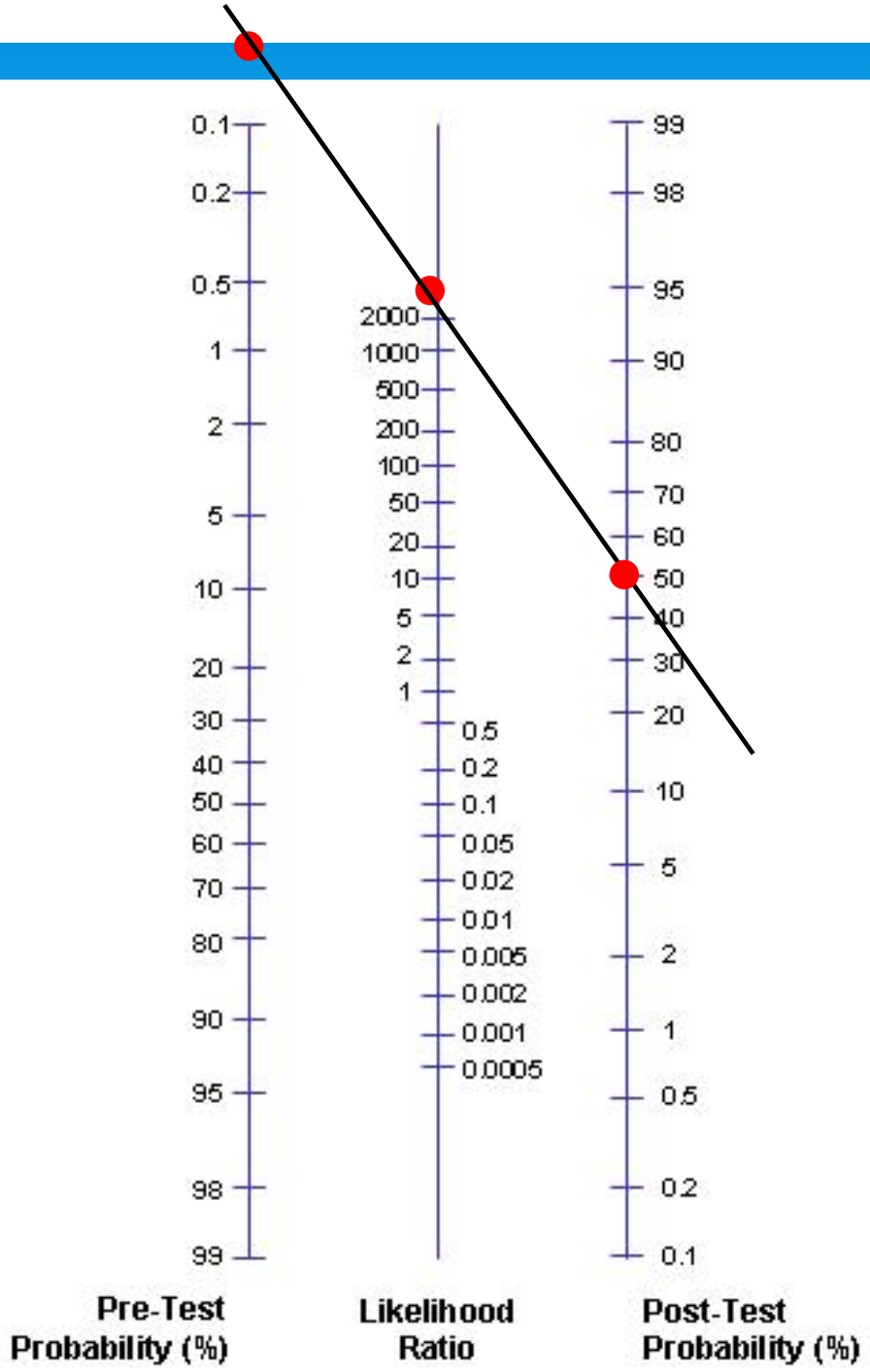
Likelihood Ratio

Qualitative Strength	LR(+)	LR(-)
Excellent	10	0.1
Very good	6	0.2
Fair	2	0.5
Useless	1	1

Mayer D. Essential Evidence-based Medicine. Cambridge University Press. 2004.

Technical vs. Clinical Precision




0.1
0.2
0.5
1
2
5
10
20
30
40
50
60
70
80
90
95
98
99
2000
1000
500
200
100
50
20
10
5
2
1
0.5
0.2
0.1
0.05
0.02
0.01
0.005
0.002
0.001
0.0005
99
98
95
90
80
70
60
50
40
30
20
10
5
2
1
0.5
0.2
0.1
Pre-Test Probability (%)
Likelihood Ratio
Post-Test Probability (%)

Online Calculator

* You may use online calculators

Diagnostic Test Calculator

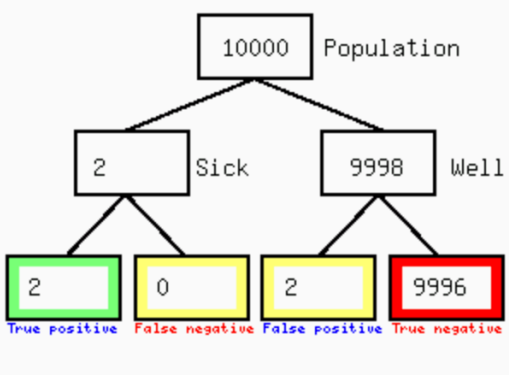
This calculator can determine diagnostic test characteristics (sensitivity, specificity, likelihood ratios) and/or determine the post-test probability of disease given given the pre- and test characteristics. Given sample sizes, confidence intervals are also computed.

Fill out one of the sections below on the left, and then click on the 'Compute' button. Sections you don't fill out will be computed for you, and the nomogram on the right will probability that a patient has the disease after a positive or negative test.

Numbers of patients with and without the disease who test positive and negative:

	Disease present	Disease absent	Total
Test positive	2	2	4
Test negative	0	9996	9996
Total	2	9998	10000

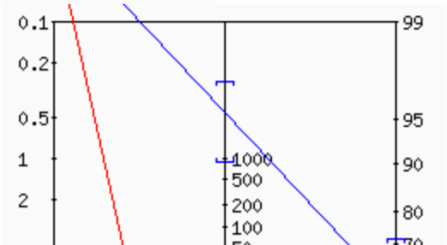
Compute



or
disease prevalence, test sensitivity, and test specificity (and, optionally, sample size):

Prevalence (e.g. 0.10):	0.000200
Sensitivity (e.g. 0.80):	1.000
Specificity (e.g. 0.80):	1.000
Total sample size:	10000

http://araw.mede.uic.edu/cgi-bin/testcalc.pl



Key message

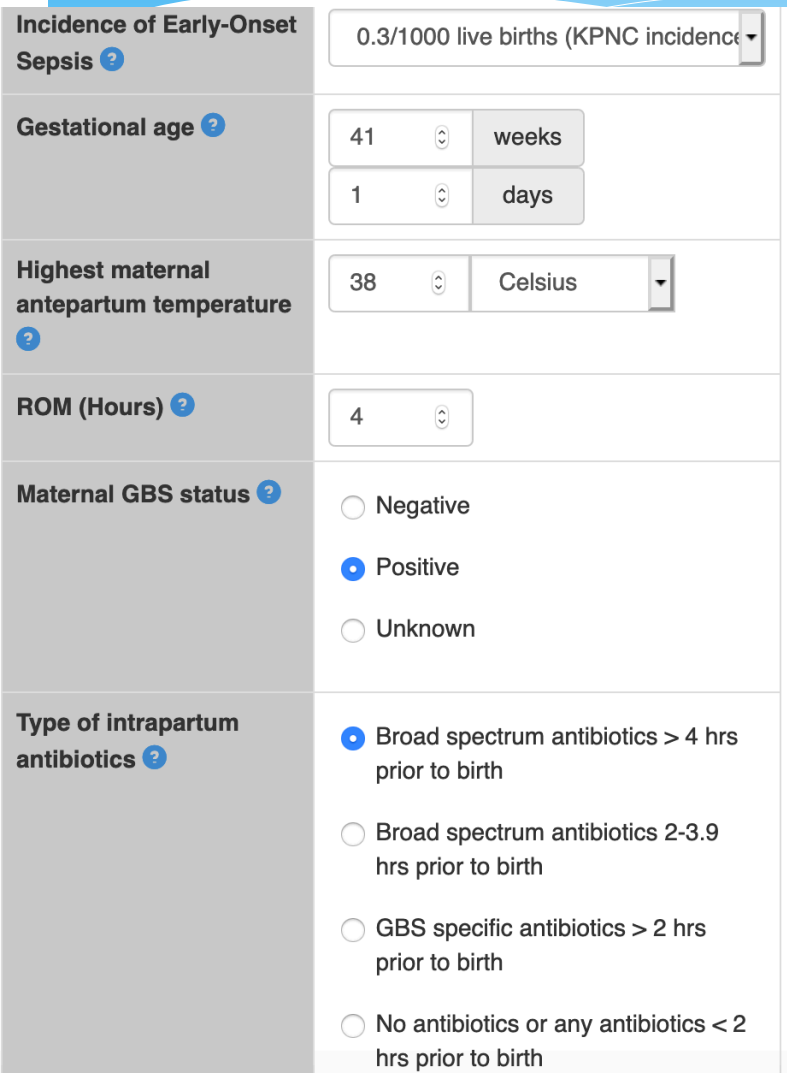
* The value of a test in clinical practice depends on:
  * its sensitivity!
  * its specifity!
  * the prevalence of the given disease in the relevant context!
  * other tests/information available

Prevalence and Predictive Values

Prevalence (%)	Positive predictive value (%)	Negative predictive value (%)
5	40	99
10	62	98
20	76	95
40	89	87
50	93	82
60	96	76

Akobeng 2007, Acta Pediatrica https://onlinelibrary.wiley.com/doi/full/10.1111/j.1651-2227.2006.00180.x

https://neonatalsepsiscalculator.kaiserpermanente.org/



Risk per 1000/births	
EOS Risk @ Birth	0.19

EOS Risk after Clinical Exam	Risk per 1000/births	Clinical Recommendation	Vitals
Well Appearing	0.08	No culture, no antibiotics	Routine Vitals
Equivocal	0.96	No culture, no antibiotics	Routine Vitals
Clinical Illness	4.05	Empiric antibiotics	Vitals per NICU

Classification of Infant's Clinical Presentation Clinical Illness Equivocal Well Appearing

Incidence of Early-Onset Sepsis	0.5/1000 live births (CDC national in
Gestational age	41 weeks 1 days
Highest maternal antepartum temperature	38 Celsius
ROM (Hours)	4
Maternal GBS status	○ Negative ● Positive ○ Unknown
Type of intrapartum antibiotics	● Broad spectrum antibiotics > 4 hrs prior to birth ○ Broad spectrum antibiotics 2-3.9 hrs prior to birth ○ GBS specific antibiotics > 2 hrs prior to birth ○ No antibiotics or any antibiotics < 2 hrs prior to birth

Risk per 1000/births	
EOS Risk @ Birth	**0.32**

EOS Risk after Clinical Exam	Risk per 1000/births	Clinical Recommendation	Vitals
Well Appearing	**0.13**	No culture, no antibiotics	Routine Vitals
Equivocal	**1.60**	Blood culture	Vitals every 4 hours for 24 hours
Clinical Illness	**6.75**	Empiric antibiotics	Vitals per NICU

Classification of Infant's Clinical Presentation **Clinical Illness** **Equivocal** **Well Appearing**

If you have a continuous outcome

* Defining a threshold levels may help you deciding
* Receiver operating characteristic curves may be used

The role of C-reactive protein to lymphocyte ratio in the differentiation of acute and perforated appendicitis

* A CRP/lymphocyte ratio cut-off value of 0.4 in predicting PA:

Table 2. ROC curve analyses of CLR

	Value	Lower	Upper
Sensitivity	0.700	0.457	0.881
Specificity	0.964	0.910	0.990
Positive Predictive Value	0.78	0.57	0.92
Negative Predictive Value	0.95	0.87	0.99
Positive Likelihood Ratio	19.4	7.2	53
Negative Likelihood Ratio	0.3	0.16	0.61

CLR: CRP/lymphocyte ratio.

https://jag.journalagent.com/travma/pdfs/UTD-47973-CLINICAL_ARTICLE-KOYUNCU.pdf

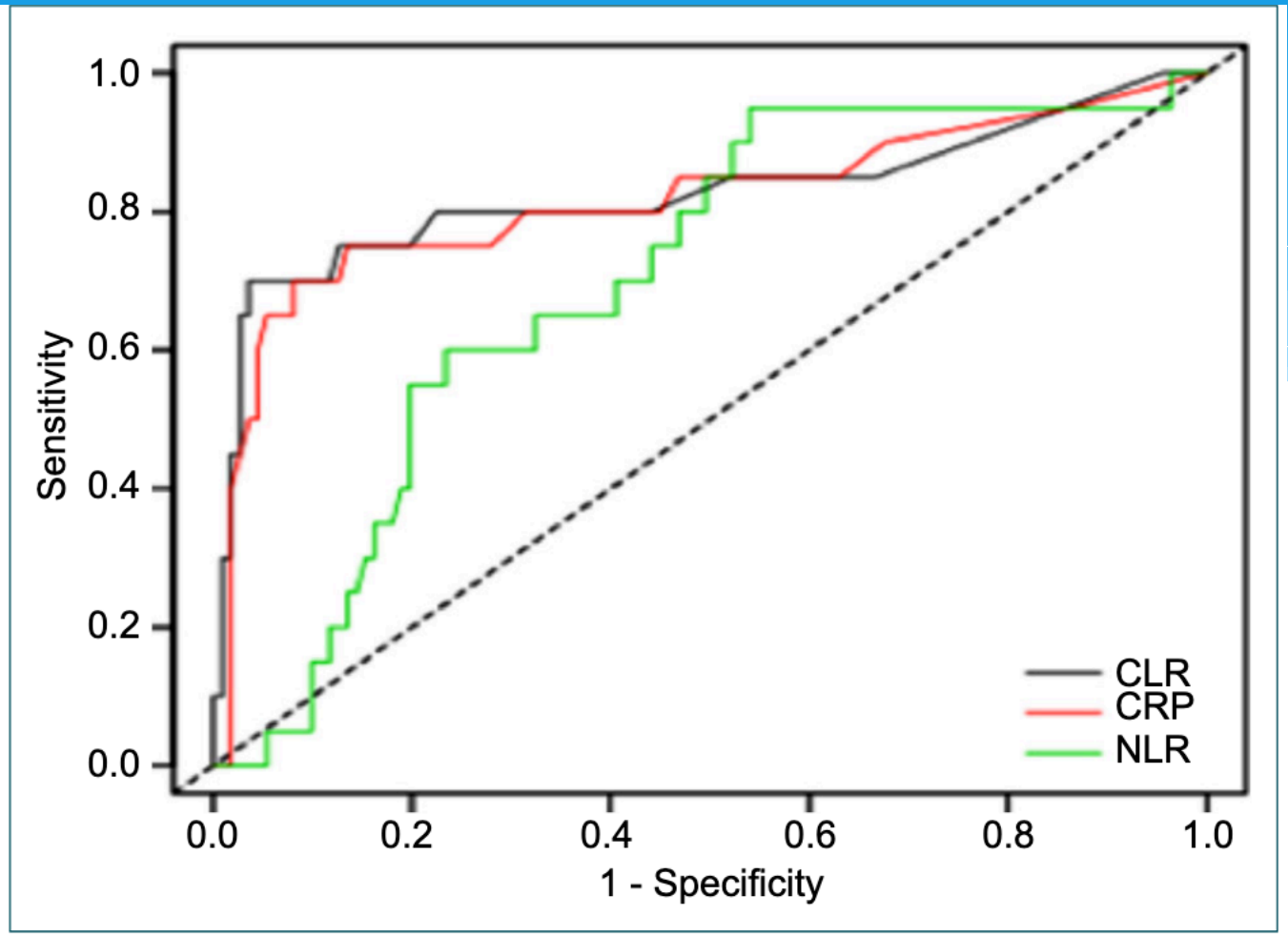


Figure 2. ROC analysis in the evaluation of PA (CLR: (CRP/lymphocyte ratio)x100; CRP: C-reactive protein; NLR: neutrophil/lymphocyte ratio).

https://jag.journalagent.com/travma/pdfs/UTD-47973-CLINICAL_ARTICLE-KOYUNCU.pdf

QUADAS-2

* QUADAS-2: A Revised Tool for the Quality Assessment of DiagnosticAccuracy Studies

Table 2. **Suggested Tabular Presentation for QUADAS-2 Results**

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
1	☺	☺	☺	☺	☹	☺	☺
2	☺	☺	☺	☺	☹	☺	☺
3	☹	☹	☺	☺	☹	☺	☺
4	☹	☹	☺	☺	☹	☺	☺
5	☹	?	☺	☺	☹	☺	☺
6	☹	?	☺	☺	☹	?	☺
7	☹	?	☺	☺	☹	☺	☺
8	☹	?	☺	☺	☹	?	☺
9	☹	?	☺	☺	☹	☺	☺
10	☹	?	☺	☹	☹	☺	☺
11	☺	?	☺	☹	☺	☺	☺

☺ = low risk; ☹ = high risk; ? = unclear risk.

https://www.acpjournals.org/doi/10.7326/0003-4819-155-8-201110180-00009?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed&

QUADAS 2

Assessing the validity of diagnostic tests

* Four domains
  * Patient selection
    * Risk of bias and concerns regarding applicability
  * Index test
    * Risk of bias and concerns regarding applicability
  * Reference standard
    * Risk of bias and concerns regarding applicability
  * Flow and timing
    * Only risk of bias

Patient (Participant) Selection

* Was a consecutive or random sample of patients enrolled?
* Was a case–control design avoided?
* Did the study avoid inappropriate exclusions?

☺ = low risk; ☹ = high risk; ? = unclear risk.

Index Test

* Were the index test results interpreted without knowledge of the results of the reference standard?

* If a threshold was used, was it prespecified?

☺ = low risk; ☹ = high risk; ? = unclear risk.

Reference Standard

* Was an independent gold-standard test used?
* Is the reference standard likely to correctly classify the target condition?
* Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?

☺ = low risk; ☹ = high risk; ? = unclear risk.

Patient Flow and Timing

* Was there an appropriate interval between index tests and reference standard?
* Did all patients receive a reference standard (Was it applied to all patients, irrespective of the results of the diagnostic test)?
* Did all patients receive the same reference standard?
* Were all patients included in the analysis?

☺ = low risk; ☹ = high risk; ? = unclear risk.

Applicability

* Are there concerns that the following do not match the review question?
* Included patients - was the diagnostic test evaluated in an appropriate spectrum of patients (not just florid or asymptomatic patients)?
* Index test, its conduct, or interpretation
* Reference standard

☺ = low risk; ☹ = high risk; ? = unclear risk.

Summary

* Discuss diagnostic test characteristics: Sensitivity, Specificity, Predictive values, Likelihood ratios
* Discuss-pre and post-test probabilities and the use of the Fagan's nomogram
* Discuss the use of QUADAS-2 for assessing quality of a diagnostic test
* Explain the place of ROC analysis in diagnostic tests