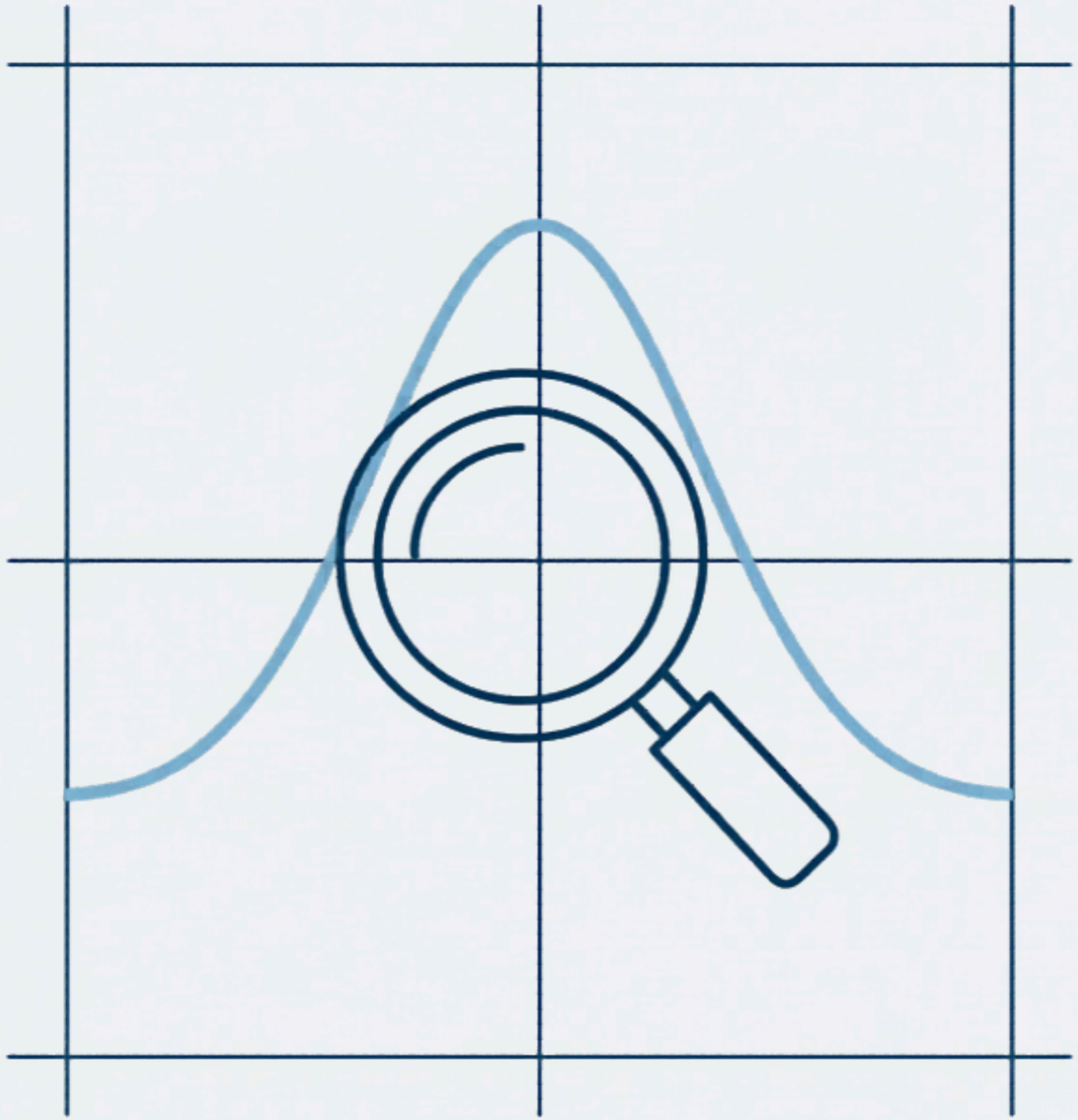
# Understanding Diagnostic and Screening Statistics in Clinical Practice



## For Family Medicine Residents

May 19, 2026

**Sorawat Sangkaew, MD PhD**

Department of Social Medicine,
Hatyai hospitalɔ; Hospital for Tropical Diseases,
Faculty of Tropical Medicine, Mahidol University

## Performance of an Antigen-Based Test for Asymptomatic and Symptomatic SARS-CoV-2 Testing at Two University Campuses — Wisconsin, September–October 2020

Ian W. Pray, PhD[1,2,3,*]; Laura Ford, PhD[1,2,*]; Devlin Cole, MD[3,4]; Christine Lee, PhD[1,5], John Paul Bigouette, PhD[1,2]; Glen R. Abedi, MPH[1]; Dena Bushman, MSN, MPH[1,2]; Miranda J. Delahoy, PhD[1,2]; Dustin Currie, PhD[1,2]; Blake Cherney, MS[1]; Marie Kirby, PhD[1]; Geroncio Fajardo, MD[1]; Motria Caudill, PhD[1,6]; Kimberly Langolf, MS[7]; Juliana Kahrs, MS[7]; Patrick Kelly, MD[4,8]; Collin Pitts, MD[4,8]; Ailam Lim, PhD[9]; Nicole Aulik, PhD[9]; Azaibi Tamin, PhD[1]; Jennifer L. Harcourt, PhD[1]; Krista Queen, PhD[1]; Jing Zhang, PhD[1]; Brett Whitaker, PhD[1]; Hannah Browne[1]; Magdalena Medrzycki, PhD[1]; Patricia Shewmaker, PhD[1]; Jennifer Folster, PhD[1]; Bettina Bankamp, PhD[1]; Michael D. Bowen, PhD[1]; Natalie J. Thornburg, PhD[1]; Kimberly Goffard, MBA[10]; Brandi Limbago, PhD[1]; Allen Bateman, PhD[7,11]; Jacqueline E. Tate, PhD[1]; Douglas Gieryn[10]; Hannah L. Kirking, MD[1]; Ryan Westergaard, MD, PhD[3,4]; Marie Killerby, VetMB[1]; CDC COVID-19 Surge Laboratory Group

**TABLE 2. Sensitivity, specificity, positive predictive value, and negative predictive value of Sofia SARS Antigen Fluorescent Immunoassay compared with real-time reverse transcription–polymerase chain reaction (RT-PCR) among asymptomatic and symptomatic persons — two universities, Wisconsin, September–October 2020**

| Antigen test result | RT-PCR result, no. | | | | | |
|---|---|---|---|---|---|---|
| | Asymptomatic (N = 871) | | | Symptomatic* (N = 227) | | |
| | Positive | Negative | Total | Positive | Negative | Total |
| Positive | 7 | 14 | **21** | 32 | 2 | **34** |
| Negative | 10 | 840 | **850** | 8 | 185 | **193** |
| **Total** | **17** | **854** | **871** | **40** | **187** | **227** |
| **Test evaluation, % (95% CI)** | | | | | | |
| Sensitivity | 41.2 (18.4–67.1) | | | 80.0 (64.4–90.9) | | |
| Specificity | 98.4 (97.3–99.1) | | | 98.9 (96.2–99.9) | | |
| Positive predictive value | 33.3 (14.6–57.0) | | | 94.1 (80.3–99.3) | | |
| Negative predictive value | 98.8 (97.8–99.4) | | | 95.9 (92.0–98.2) | | |

**Abbreviation:** CI = confidence interval.
* One or more symptoms reported.

- Cross-sectional diagnostic accuracy study comparing Sofia SARS antigen test with RT-PCR reference standard.
- Included asymptomatic and symptomatic university participants undergoing both tests.
- Calculated sensitivity, specificity, PPV, NPV, and 95% confidence intervals using 2×2 tables

- Can you calculate and interpret the sensitivity, specificity, PPV, and NPV of the test?
- Why is the sensitivity lower in the asymptomatic group?
- Why is the PPV much lower in the asymptomatic group?

# Unveiling Post-COVID-19 syndrome: incidence, biomarkers, and clinical phenotypes in a Thai population

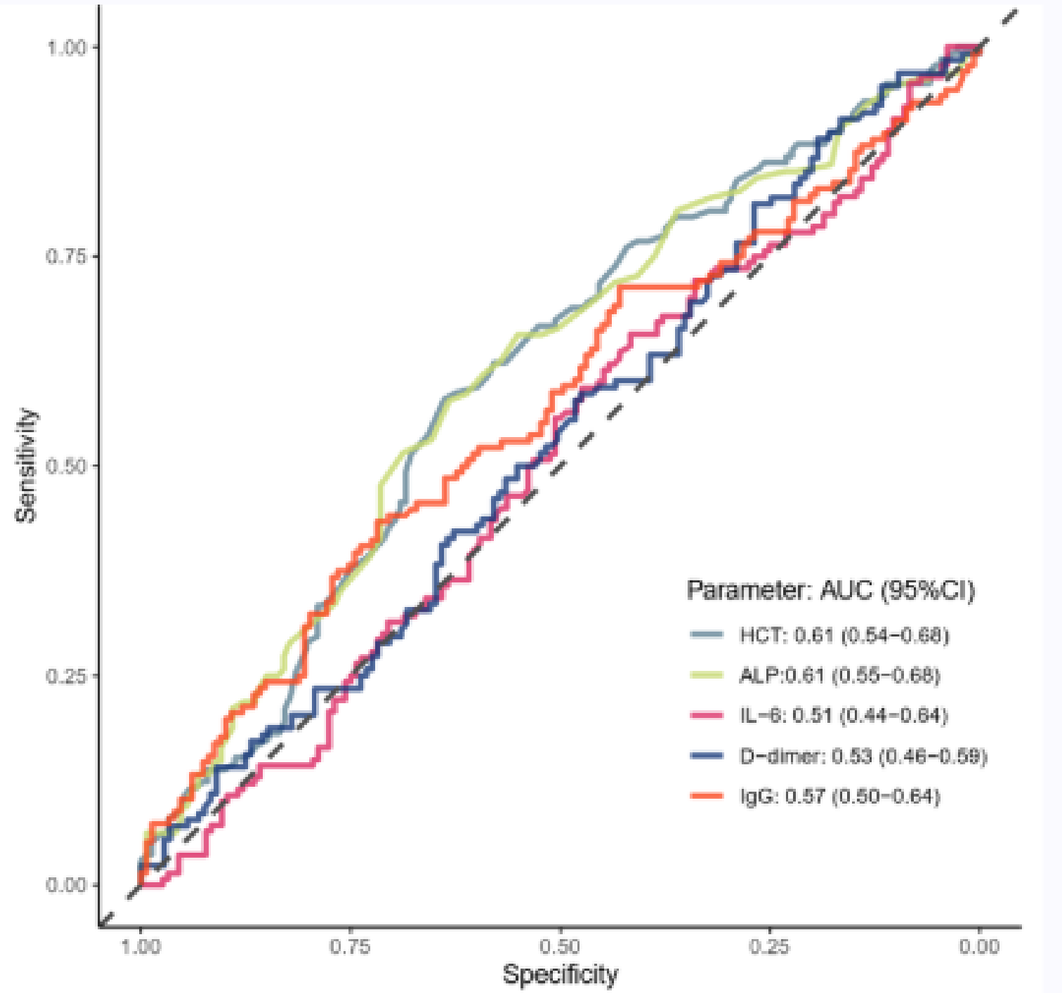
Sorawat Sangkaew[1,2*], Hathaitip Tumviriyakul[1], Chutima Cheranakhorn[3], Nopporn Songumpai[3], Nawamin Pinpathomrat[4], Bunya Seeyankem[4], Kameelah Yasharad[5], Palanthorn Loomcharoen[6], Wisitsak Pakdee[7], Chanunya Changawej[8], Dararat Dumrongkullachart[8], Amornrat Limheng[9] and Ilaria Dorigatti[10]

**Table 2** Association between biomarkers and post-COVID syndrome examined through univariate (crude) and multiple (adjusted) logistic regression analyses

| Biomarkers | Crude ORs (95% CI) | *p*-value | Adjusted ORs (95% CI) | *p*-value | AUROC (95% CI) |
|---|---|---|---|---|---|
| **Demographic and Clinical Characteristics** | | | | | |
| Age (year) | 1.01 (0.99–1.02) | 0.350 | 1 (0.99–1.02) | 0.607 | |
| Female | 3.20 (1.93–5.40) | **< 0.001** | 3.51 (2.06–6.12) | **< 0.001** | |
| BMI (kg/m$^2$) | 0.97 (0.92–1.02) | 0.200 | 0.97 (0.92–1.03) | 0.326 | |
| Number of underlying diseases | 3 (1.64–5.64) | **< 0.001** | 2.98 (1.55–5.93) | **0.001** | |
| Vaccine doses | 0.65 (0.49–0.84) | **< 0.001** | 0.66 (0.49–0.86) | **0.003** | |
| **Laboratory** | | | | | |
| HCT | **0.91 (0.85–0.96)** | **0.001** | 0.98 (0.91–1.06) | 0.605 | 0.61 (0.55–0.68) |
| WBC | 1.03 (0.91–1.17) | 0.663 | 1.03 (0.9–1.18) | 0.705 | 0.51 (0.44–0.57) |
| PLT | 1 (1–1) | 0.909 | 1 (1–1) | 0.741 | 0.53 (0.46–0.53) |
| NLR | 0.95 (0.72–1.23) | 0.691 | 0.93 (0.7–1.24) | 0.611 | 0.55 (0.49–0.62) |
| PLR | 1 (0.99–1) | 0.260 | 1 (0.99–1) | 0.194 | 0.52 (0.45–0.58) |
| AST | 1 (0.97–1.03) | 0.803 | 1.01 (0.98–1.04) | 0.652 | 0.48 (0.42–0.55) |
| ALT | 1 (0.99–1.01) | 0.805 | 1.01 (1–1.03) | 0.286 | 0.47 (0.40–0.54) |
| AST/ALT ratio | 1.18 (0.72–1.95) | 0.501 | 0.85 (0.49–1.46) | 0.557 | 0.53 (0.46–0.59) |
| ALP | **1.02 (1.01–1.03)** | **0.005** | **1.02 (1–1.03)** | **0.016** | 0.61 (0.55–0.68) |
| Albumin | 0.55 (0.25–1.18) | 0.128 | 1.26 (0.5–3.2) | 0.628 | 0.56 (0.50–0.63) |
| CRP | 1.02 (0.97–1.08) | 0.404 | 1.03 (0.98–1.09) | 0.303 | 0.52 (0.47–0.60) |
| D-dimers | 1 (1–1) | 0.364 | 1 (1–1) | 0.677 | 0.53 (0.46–0.60) |
| IL-6 | 1 (0.98–1.01) | 0.418 | 0.99 (0.98–1.01) | 0.340 | 0.51 (0.44–0.57) |
| log (IgG) | **0.78 (0.62–0.96)** | **0.024** | 0.84 (0.64–1.09) | 0.203 | 0.57 (0.50–0.64) |

Mutlivariable logistic regression was adjusted for age, sex, comorbidity, and the number of received vaccine doses

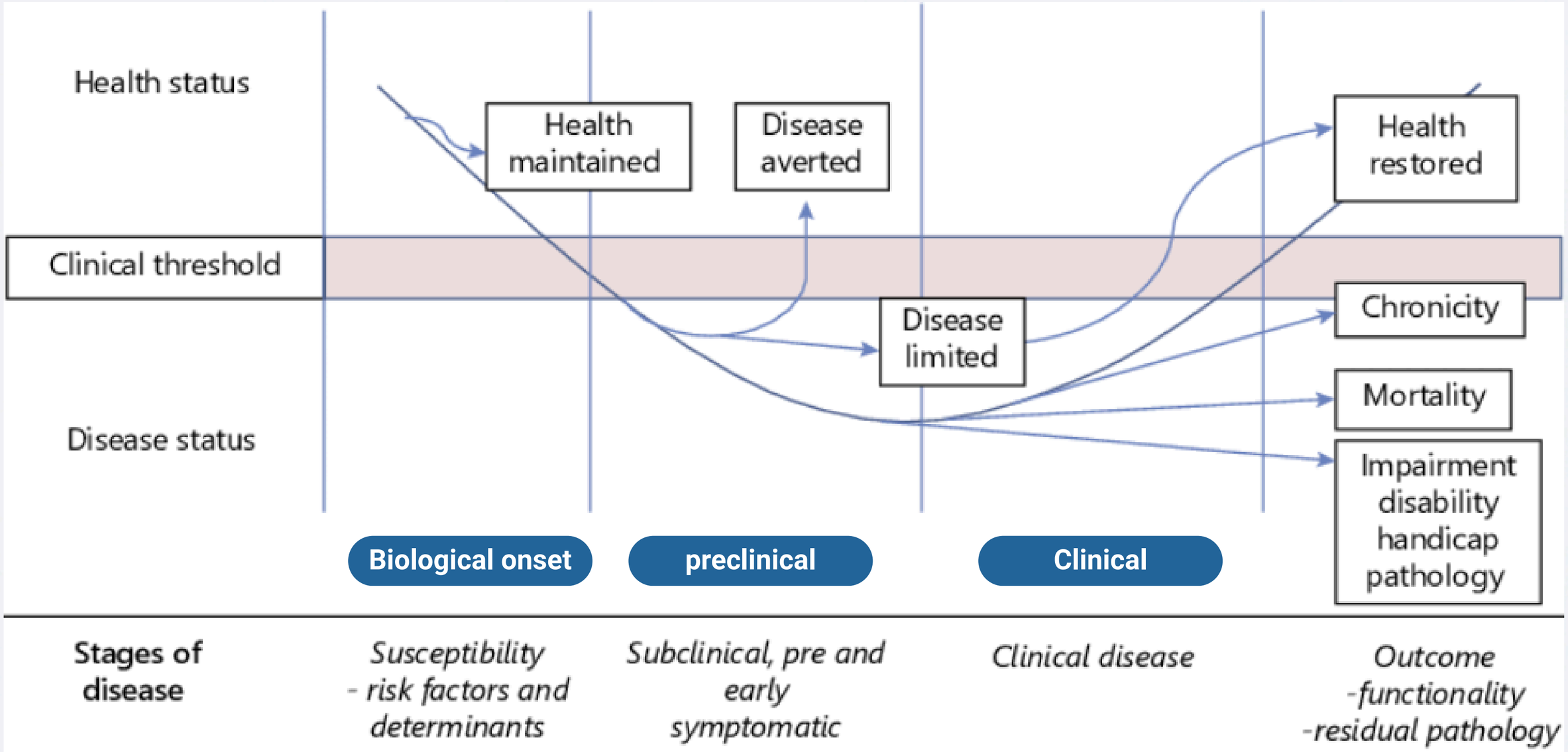
## Discriminative performance (ROC curve)



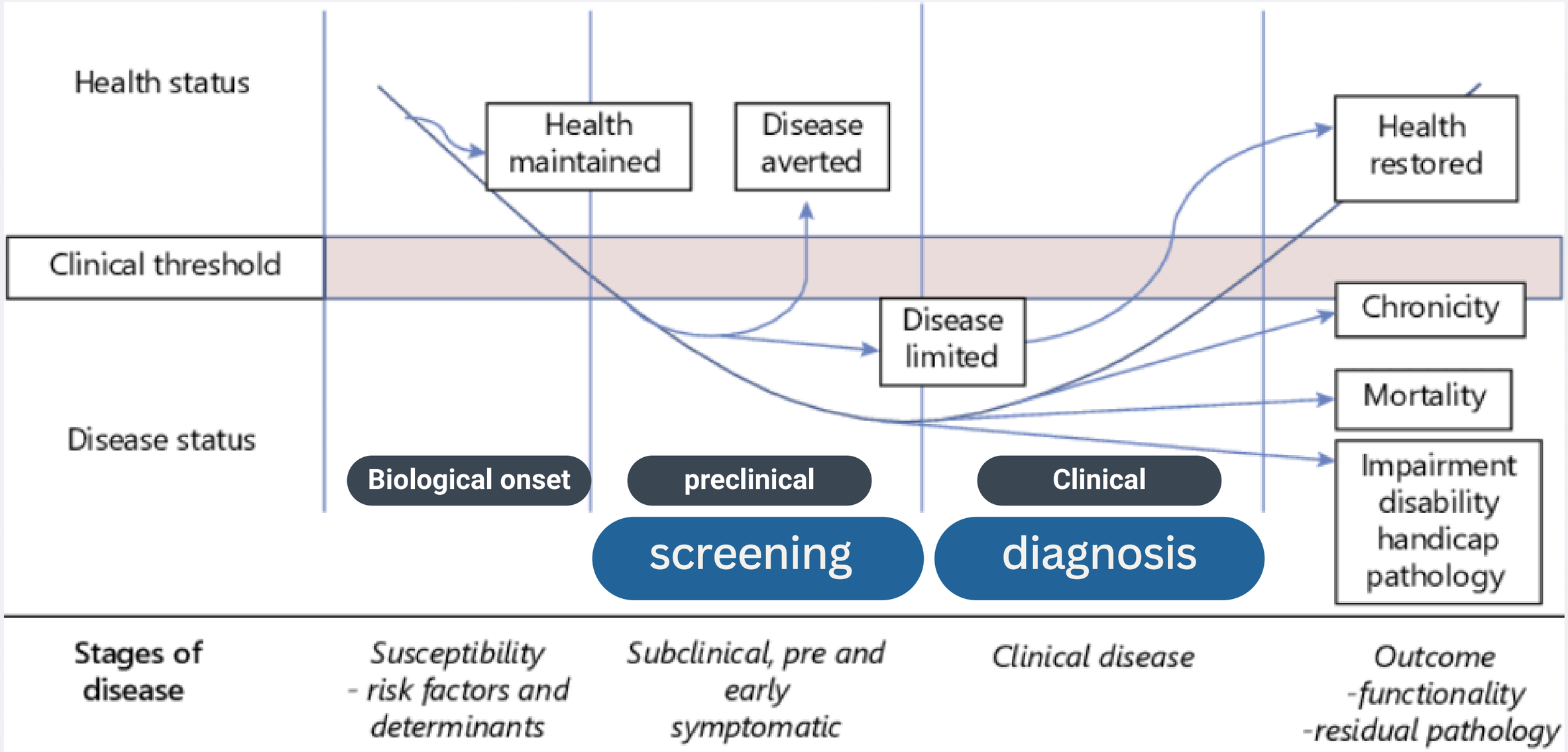
# Learning objectives

- Distinguish between random error and systematic bias.
- Calculate core metrics: Sensitivity, Specificity, PPV, NPV.
- Analyze the impact of disease prevalence on predictive values.
- Interpret ROC curves and Likelihood Ratios (LRs) clinically.
- Identify lead-time, length-time, and compliance biases in screening.

# Natural history of diseases



# Natural history of diseases



# Seeking the Clinical Truth

### The Goal

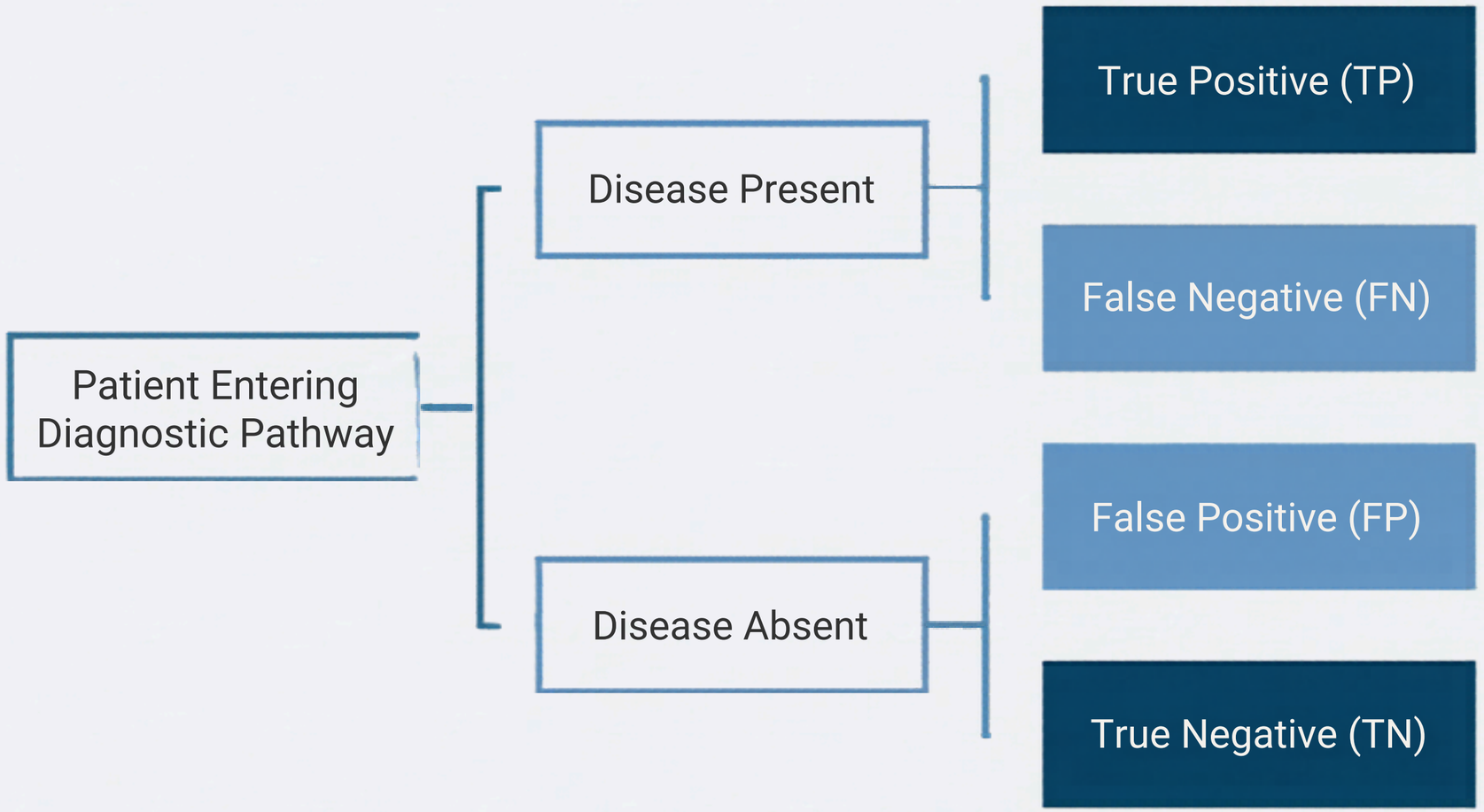
Accurately detect the underlying physiological truth

### Random Error

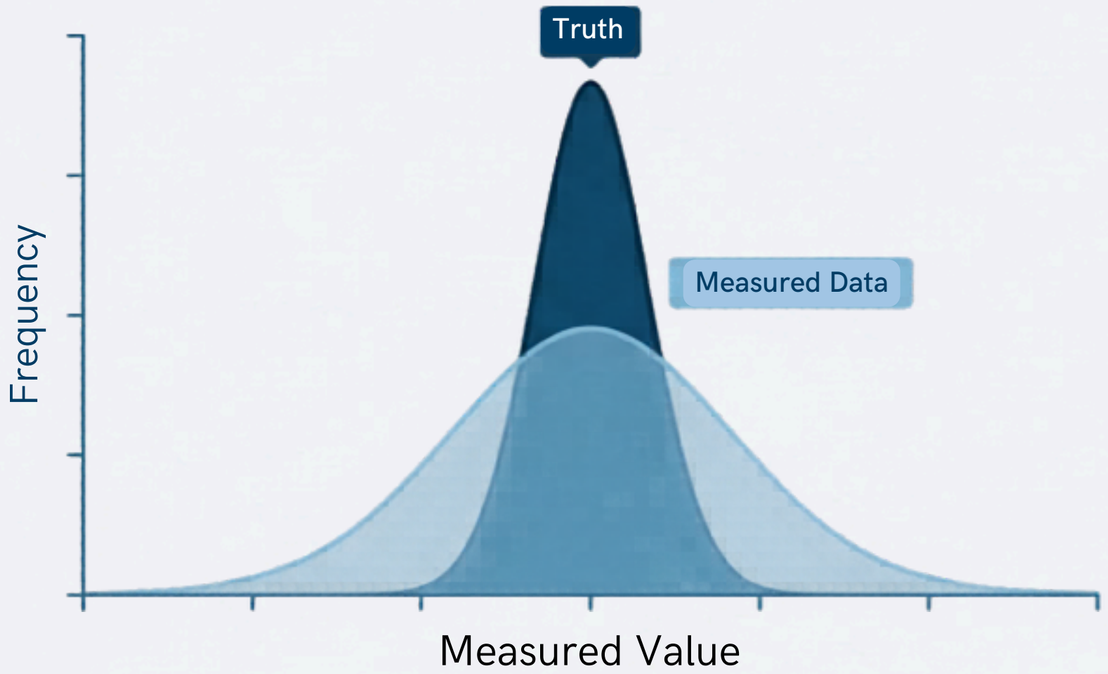
Inherent, unpredictable measurement variability.

### Systematic Error (Bias)

Consistent deviation from the truth due to flawed study design or conduct.

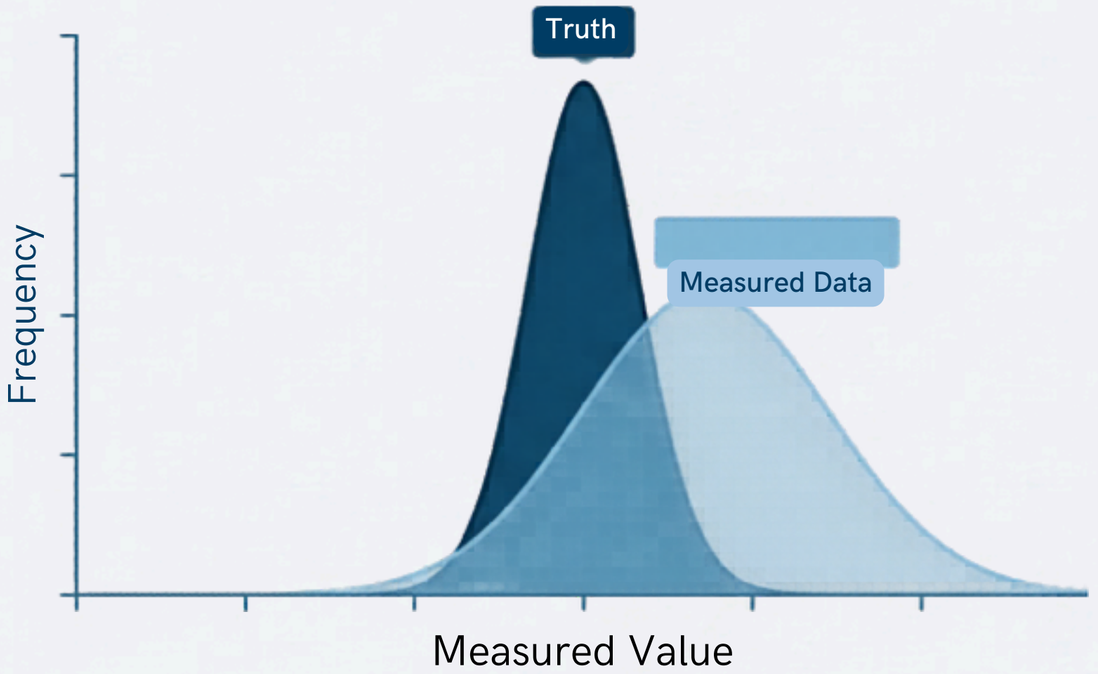


# Visualizing Error: Random vs. Systematic




## Random Error

Wider distribution, but the average remains centered exactly around the true clinical value.




## Systematic Error (Bias)

Shifts the entire data distribution away from the true physiological reality. The average is fundamentally flawed.

# Statistics in Diagnostic Research

Sensitivity and specificity

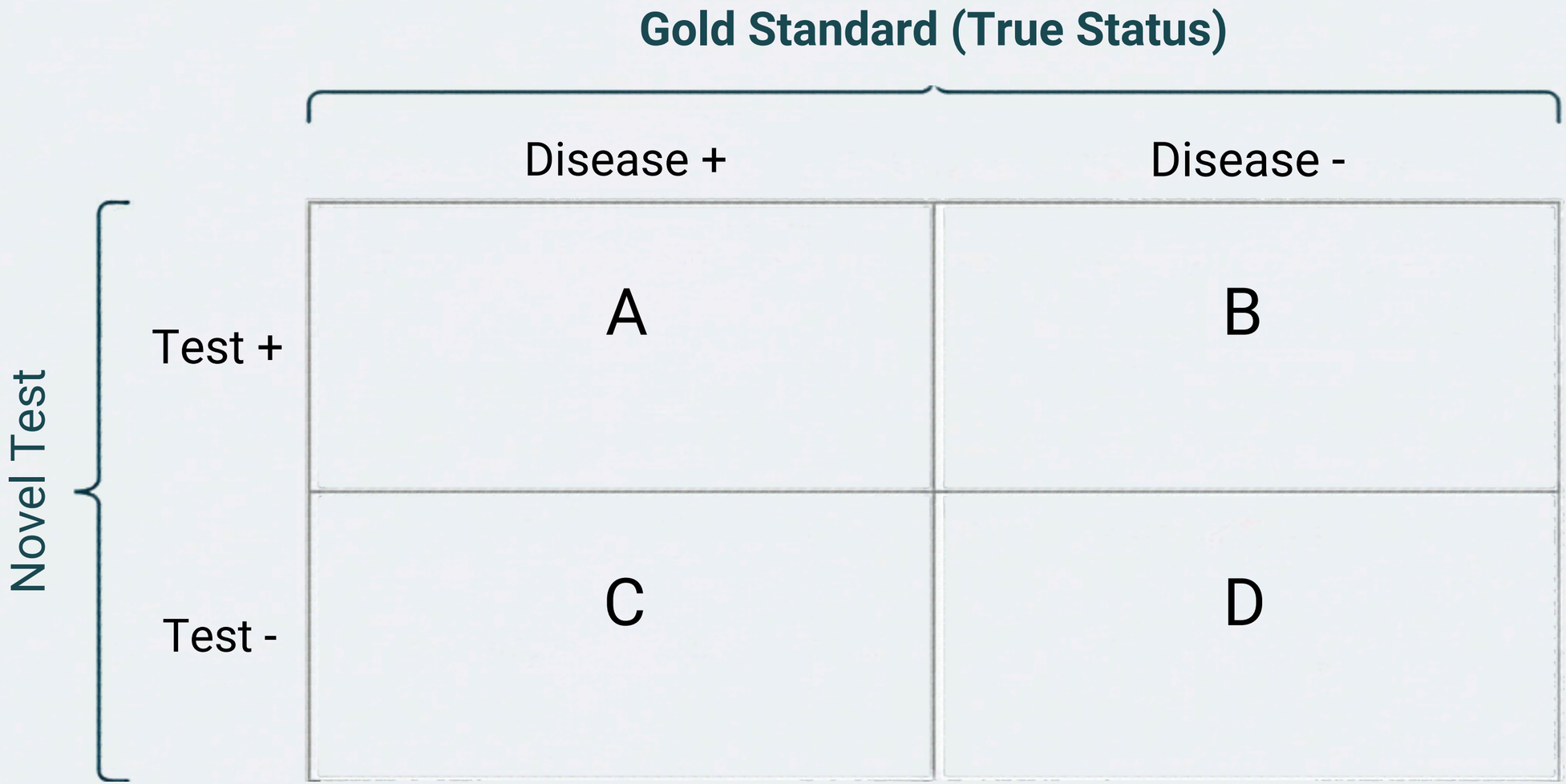
Positive and negative predictive value

Positive and negative likelihood ratio

Likelihood ratio nomogram

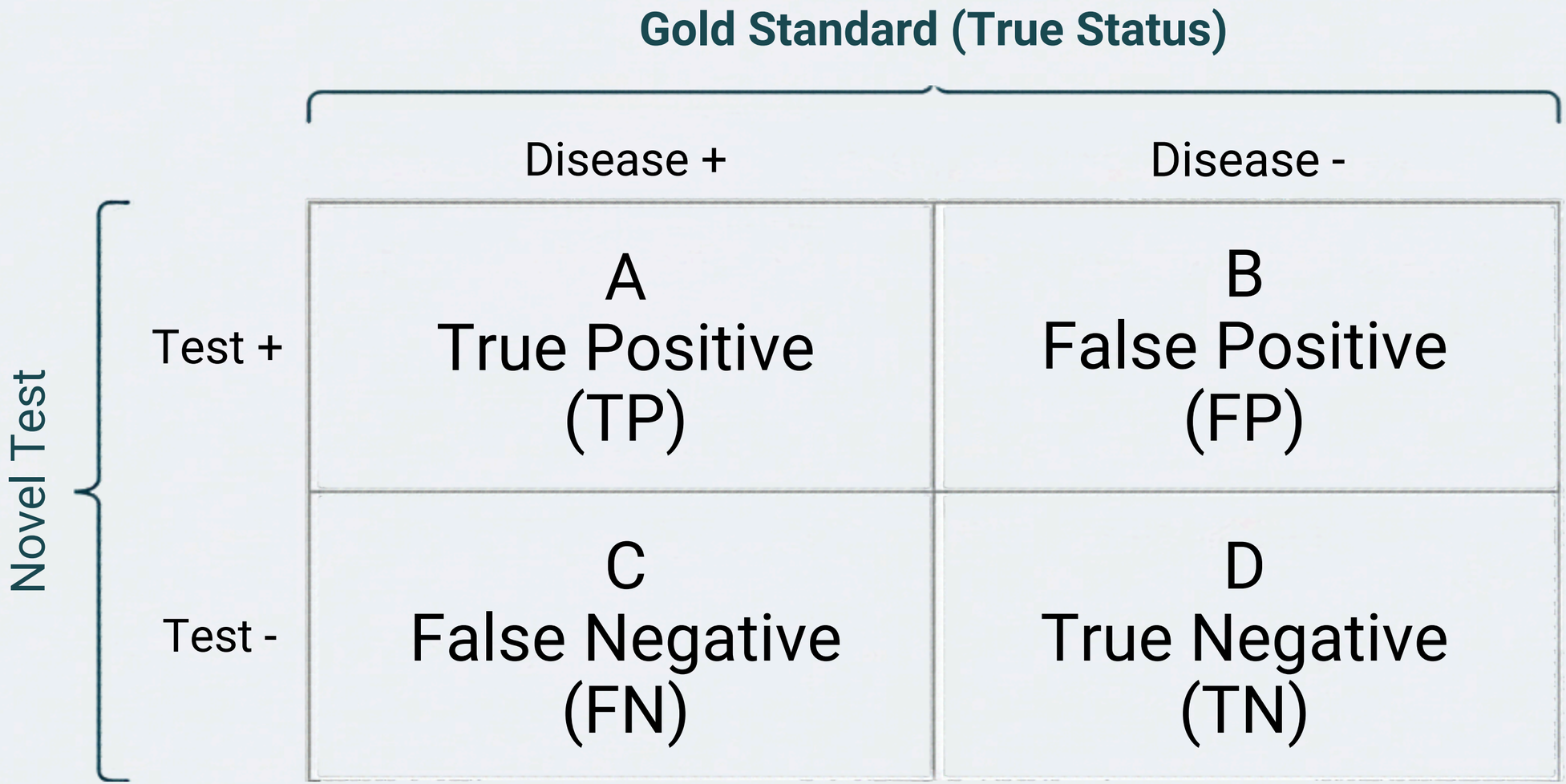
Receiver Operating Characteristic curves (ROC)

# The Foundational 2x2 Matrix



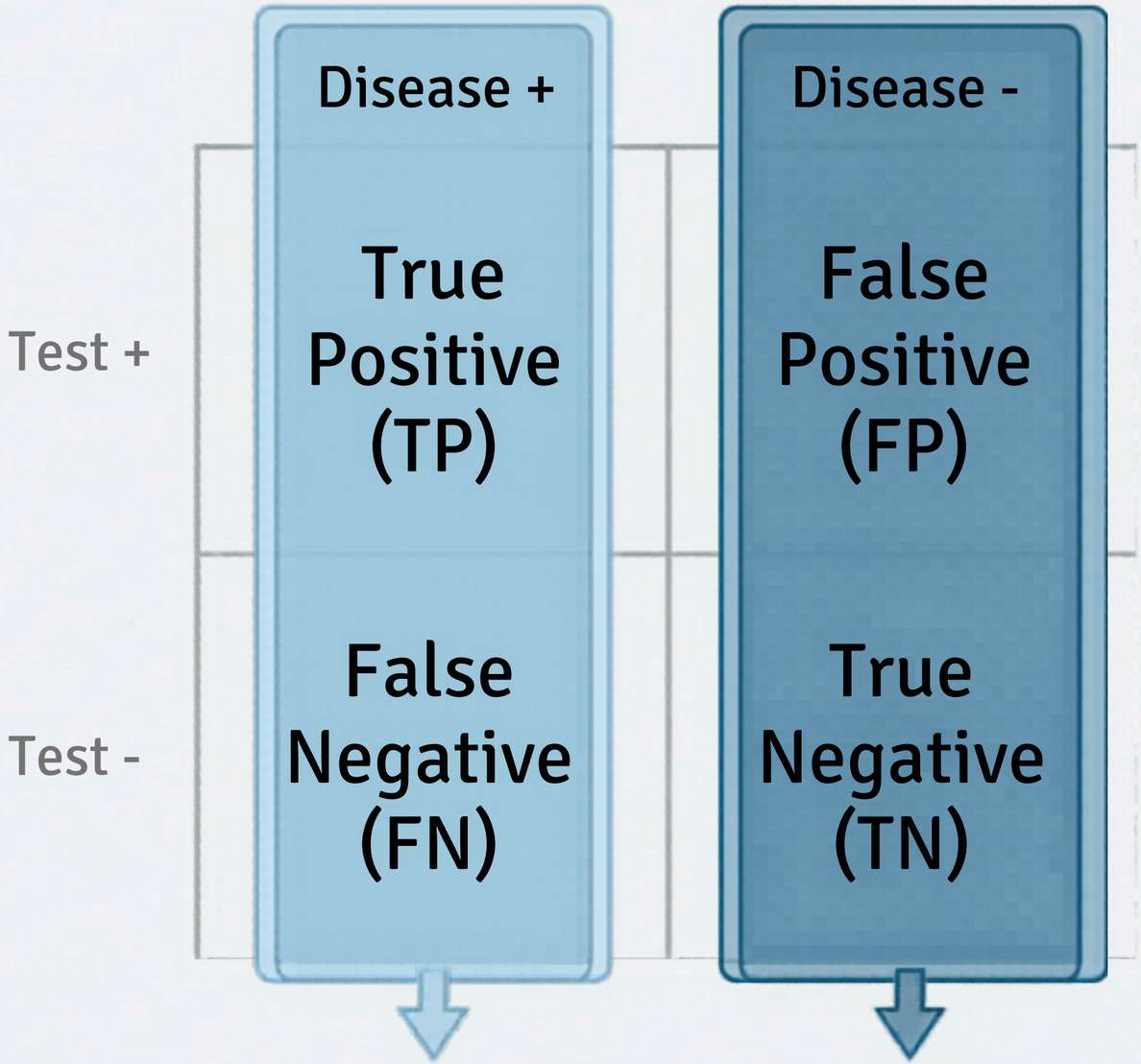

$$\text{Prevalence} = \frac{\text{Disease}}{\text{Total population}} = \frac{A+C}{A+B+C+D}$$

# The Foundational 2x2 Matrix




Prevalence = Disease / Total populatino = A+C / A+B +C +D

# Intrinsic Properties: Sensitivity and Specificity




## Sensitivity

Proportion of individuals with the disease who correctly test positive (True Positive Rate).

$$\text{Sensitivity} = \frac{TP}{(TP + FN)}$$

Mnemonic: **SnNout** (High sensitivity rules OUT disease).

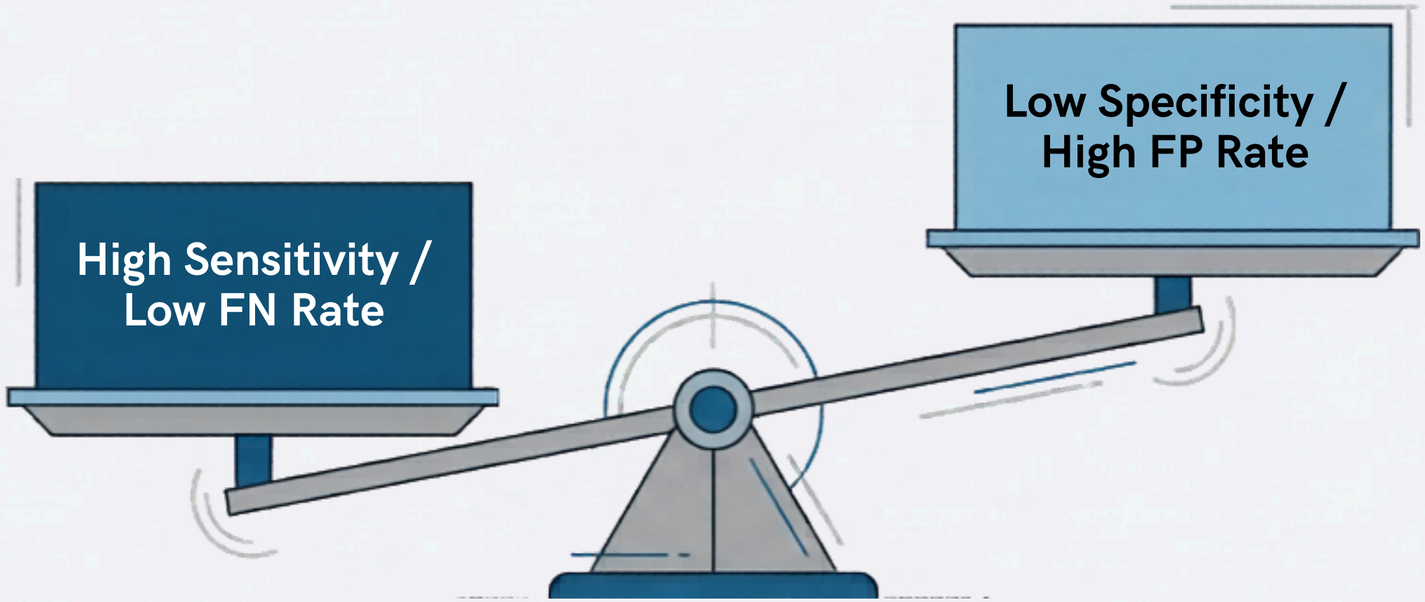
## Specificity

Proportion of individuals without the disease who correctly test negative (True Negative Rate).

$$\text{Specificity} = \frac{TN}{(TN + FP)}$$

Mnemonic: **SpPin** (High specificity rules IN disease).

# The Cost of Error: False Positives and Negatives




## False Negative Rate

Proportion of truly diseased individuals who incorrectly test negative.

$$\text{FN Rate} = 1 - \text{Sensitivity} = \frac{FN}{FN + TP}$$

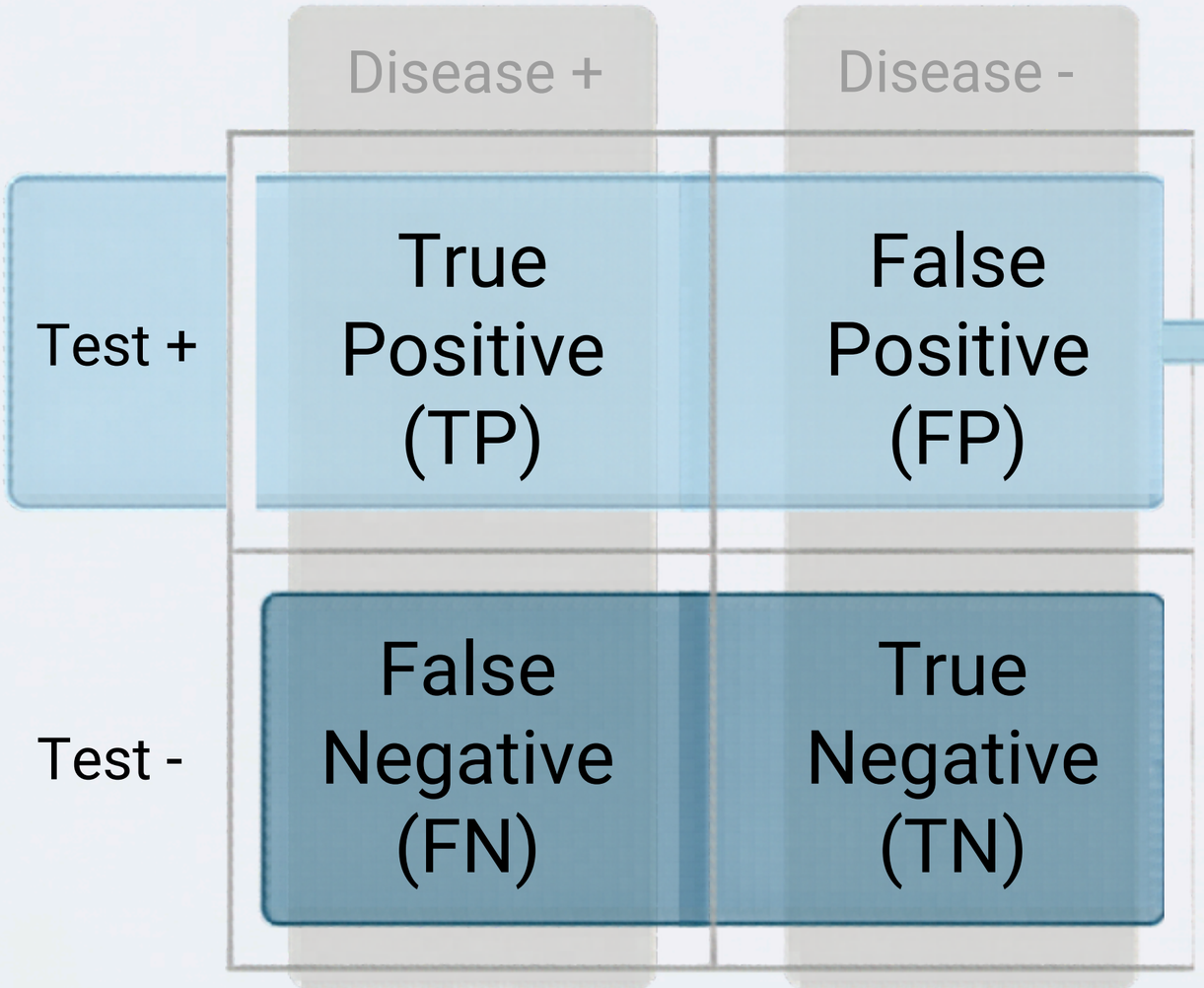
## False Positive Rate

Proportion of truly healthy individuals who incorrectly test positive.

$$\text{FP Rate} = 1 - \text{Specificity} = \frac{FP}{FP + TN}$$

**Clinical Cost:** Improving sensitivity often increases false positives, whereas improving specificity may increase false negatives.

# Clinical Context: Predictive Values




## Positive Predictive Value (PPV)

Answers the patient's core question: If I test positive, what is the probability I actually have the disease?

$$PPV = \frac{TP}{(TP + FP)}$$

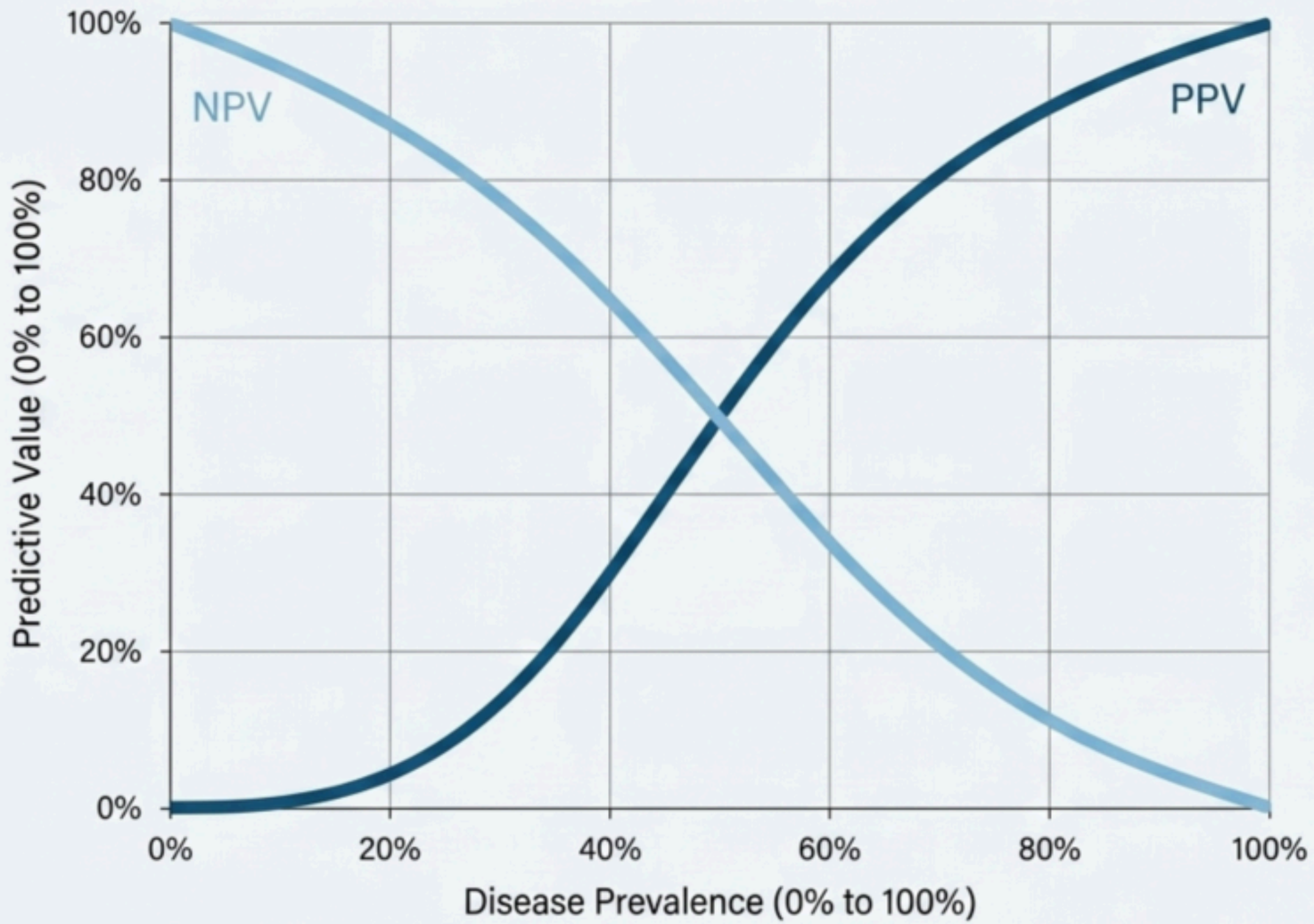
## Negative Predictive Value (NPV)

Answers the patient's core question: If I test negative, what is the probability I am truly healthy?

$$NPV = \frac{TN}{(TN + FN)}$$

# The Prevalence Paradox

PPV/NPV depend on prevalence




## The Paradox

Intrinsic properties (Sensitivity / Specificity) remain mathematically stable across entirely different populations.

However, clinical metrics (PPV / NPV) are inextricably tied to the background disease prevalence.

**As Prevalence Increases**
→ PPV dramatically increases; NPV decreases.

**As Prevalence Decreases**
→ PPV plummets; NPV increases.

# Example

Sensitivity and specificity of a HIV rapid test was 100% and 98% respectively. The prevalence of HIV infection among IV drug users was 10%. What is the percentage of positive predictive value of the test?

A. 1

B. 10

C. 67

D. 83

E. 99

# Solution: step by step: 2x2 table

| | | Standard test | | |
|---|---|---|---|---|
| | | Present | Absent | |
| New test | Positive | | | (A+B) |
| | Negative | | | (C+D) |
| Totals | | A+C | B+D | (A+B+C+D) |

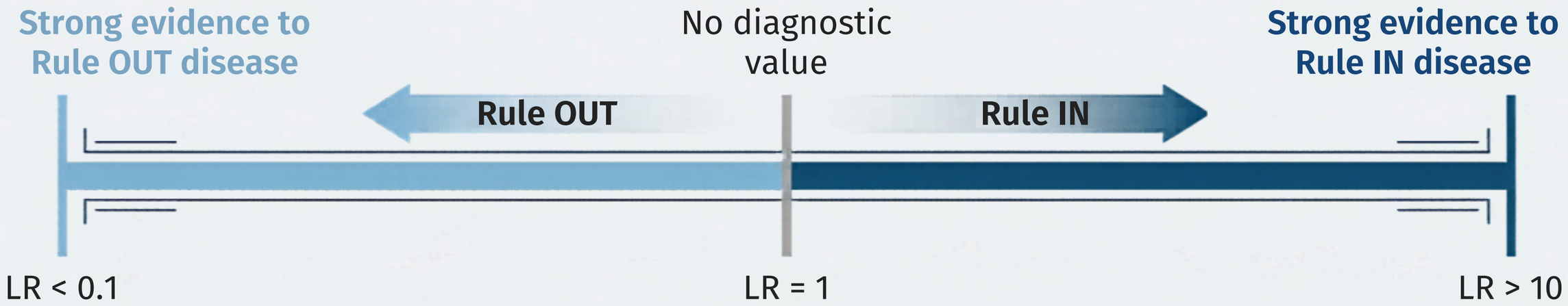
# Solution: step by step: Prevalence

| | | Standard test | | |
|---|---|---|---|---|
| | | Present | Absent | |
| New test | Positive | | | |
| | Negative | | | |
| Totals | | 10 | 90 | 100 |

# Sense/Spec/PPV/NPV

| | | Standard test | | |
|---|---|---|---|---|
| | | Present | Absent | |
| New test | Positive | **10** | **2** | **12** |
| | Negative | 0 | 88 | |
| Totals | | 10 | 90 | 100 |

# Likelihood Ratios: The Strength of Evidence




## LR+

How much more likely is a positive test result in a diseased patient compared to a healthy patient?

$$LR+ = \frac{(a/a+c)}{b/(b+d)} = \frac{\text{Sensitivity}}{(1 - \text{Specificity})}$$

## LR-

How much less likely is a negative result in patients with disease

$$LR- = \frac{(c/a+c)}{d/(b+d)} = \frac{(1 - \text{Sensitivity})}{\text{Specificity}}$$

| Metrics | Abv. | Formula |
|---|---|---|
| **Sensitivity** | sn | a/(a+c) |
| **Specificity** | sp | d/(b+d) |
| **Positive predictive value** | ppv | a/(a+b) |
| **Negative predictive value** | npv | d/(c+d) |
| **Prevalence** | pv | a+c/a+b+c+d |
| **Pre-test odds** | | Prevalence/1-prevalence |
| **Positive likelihood ratio** | LR+ | (a/a+c)/ b/(b+d) |
| **Negative likelihood ratio** | LR- | (c/a+c)/ d/(b+d) |

# Unveiling Post-COVID-19 syndrome: incidence, biomarkers, and clinical phenotypes in a Thai population

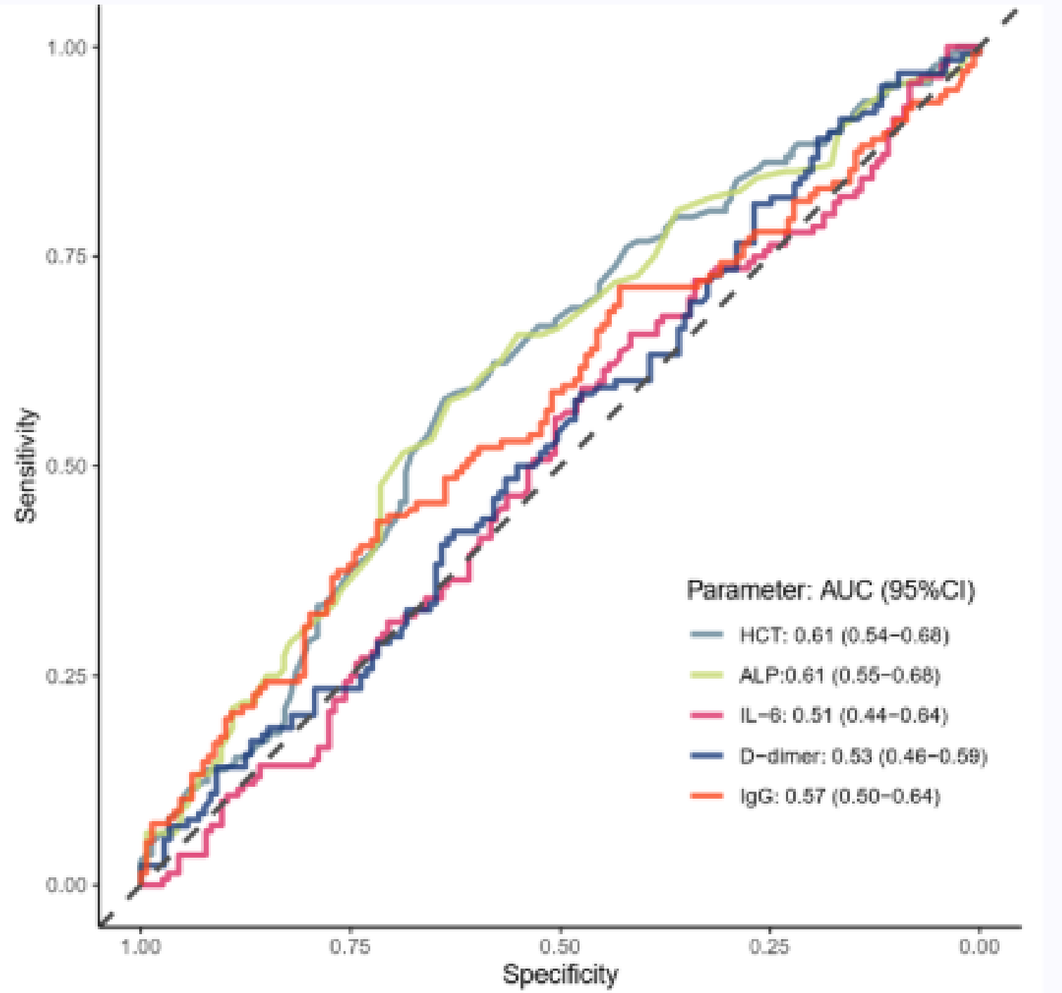
Sorawat Sangkaew[1,2*], Hathaitip Tumviriyakul[1], Chutima Cheranakhorn[3], Nopporn Songumpai[3], Nawamin Pinpathomrat[4], Bunya Seeyankem[4], Kameelah Yasharad[5], Palanthorn Loomcharoen[6], Wisitsak Pakdee[7], Chanunya Changawej[8], Dararat Dumrongkullachart[8], Amornrat Limheng[9] and Ilaria Dorigatti[10]

**Table 2** Association between biomarkers and post-COVID syndrome examined through univariate (crude) and multiple (adjusted) logistic regression analyses

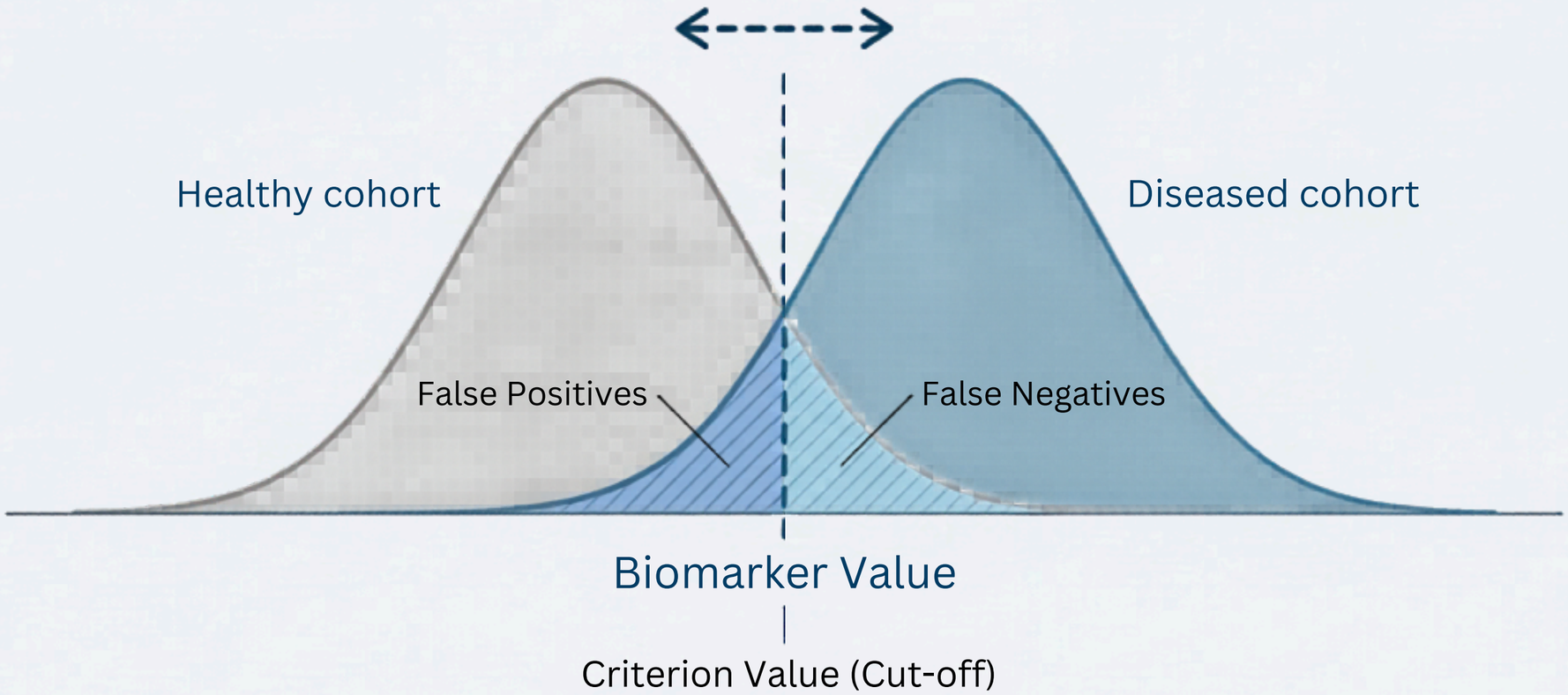
| Biomarkers | Crude ORs (95% CI) | *p*-value | Adjusted ORs (95% CI) | *p*-value | AUROC (95% CI) |
|---|---|---|---|---|---|
| **Demographic and Clinical Characteristics** | | | | | |
| Age (year) | 1.01 (0.99–1.02) | 0.350 | 1 (0.99–1.02) | 0.607 | |
| Female | 3.20 (1.93–5.40) | **< 0.001** | 3.51 (2.06–6.12) | **< 0.001** | |
| BMI (kg/m$^2$) | 0.97 (0.92–1.02) | 0.200 | 0.97 (0.92–1.03) | 0.326 | |
| Number of underlying diseases | 3 (1.64–5.64) | **< 0.001** | 2.98 (1.55–5.93) | **0.001** | |
| Vaccine doses | 0.65 (0.49–0.84) | **< 0.001** | 0.66 (0.49–0.86) | **0.003** | |
| **Laboratory** | | | | | |
| HCT | **0.91 (0.85–0.96)** | **0.001** | 0.98 (0.91–1.06) | 0.605 | 0.61 (0.55–0.68) |
| WBC | 1.03 (0.91–1.17) | 0.663 | 1.03 (0.9–1.18) | 0.705 | 0.51 (0.44–0.57) |
| PLT | 1 (1–1) | 0.909 | 1 (1–1) | 0.741 | 0.53 (0.46–0.53) |
| NLR | 0.95 (0.72–1.23) | 0.691 | 0.93 (0.7–1.24) | 0.611 | 0.55 (0.49–0.62) |
| PLR | 1 (0.99–1) | 0.260 | 1 (0.99–1) | 0.194 | 0.52 (0.45–0.58) |
| AST | 1 (0.97–1.03) | 0.803 | 1.01 (0.98–1.04) | 0.652 | 0.48 (0.42–0.55) |
| ALT | 1 (0.99–1.01) | 0.805 | 1.01 (1–1.03) | 0.286 | 0.47 (0.40–0.54) |
| AST/ALT ratio | 1.18 (0.72–1.95) | 0.501 | 0.85 (0.49–1.46) | 0.557 | 0.53 (0.46–0.59) |
| ALP | **1.02 (1.01–1.03)** | **0.005** | **1.02 (1–1.03)** | **0.016** | 0.61 (0.55–0.68) |
| Albumin | 0.55 (0.25–1.18) | 0.128 | 1.26 (0.5–3.2) | 0.628 | 0.56 (0.50–0.63) |
| CRP | 1.02 (0.97–1.08) | 0.404 | 1.03 (0.98–1.09) | 0.303 | 0.52 (0.47–0.60) |
| D-dimers | 1 (1–1) | 0.364 | 1 (1–1) | 0.677 | 0.53 (0.46–0.60) |
| IL-6 | 1 (0.98–1.01) | 0.418 | 0.99 (0.98–1.01) | 0.340 | 0.51 (0.44–0.57) |
| log (IgG) | **0.78 (0.62–0.96)** | **0.024** | 0.84 (0.64–1.09) | 0.203 | 0.57 (0.50–0.64) |

Mutlivariable logistic regression was adjusted for age, sex, comorbidity, and the number of received vaccine doses

## Discriminative performance (ROC curve)



# Setting the Bar: Shifting the Cut-off Point



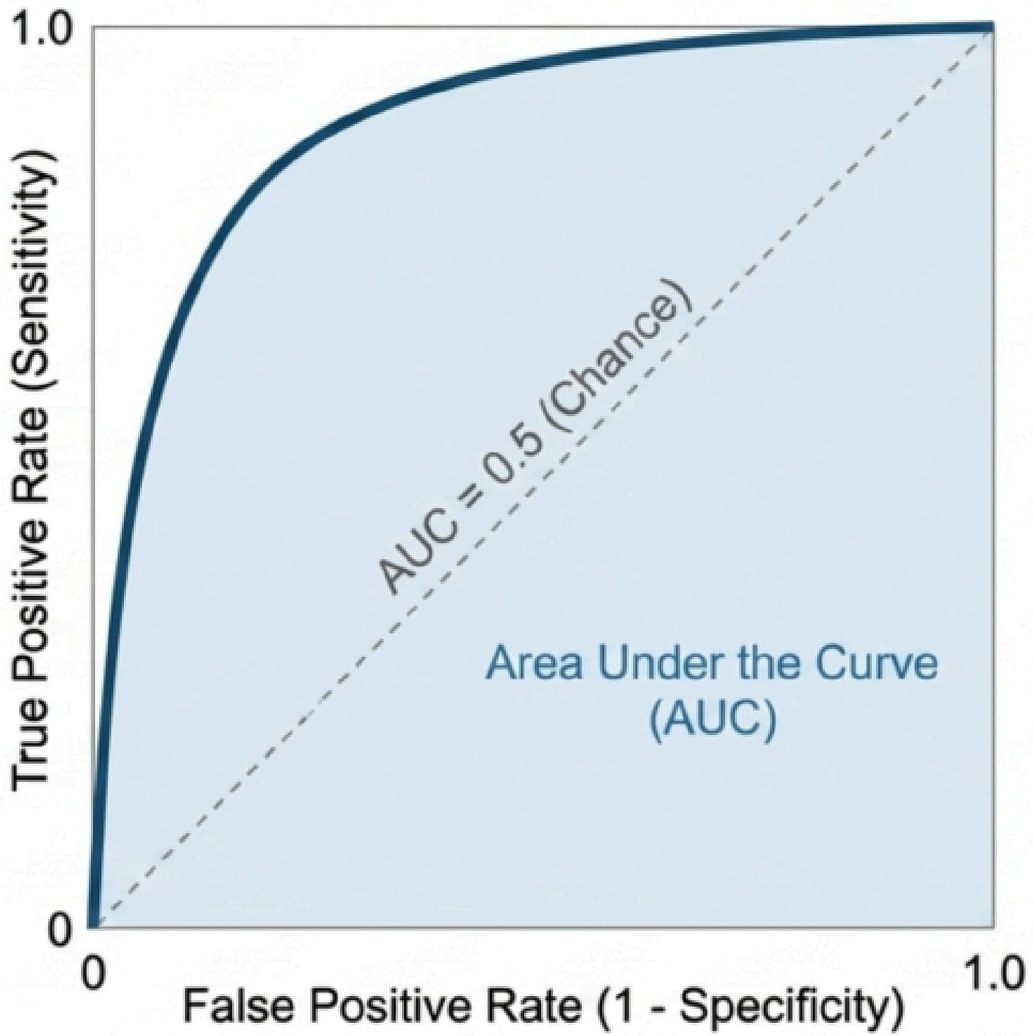

## Lowering the cut-off (Moving Left)

Increases Sensitivity (catches more true cases), but increases false positives.

## Raising the cut-off (Moving Right)

Increases Specificity (generates fewer false alarms), but increases false negatives.

# ROC Curves: Gauging Overall Performance




## Function of the ROC

Evaluates a test's diagnostic accuracy across all possible cut-off thresholds simultaneously.

## Area Under the Curve (AUC)

A quantifiable measure of a test's ultimate discriminative power.

| | |
|---|---|
| 1 | Perfect Test: AUC = 1.0 (Curve anchors into the top-left corner). |
| 2 | Useless Test: AUC = 0.5 (Diagonal line; no better than a coin flip). |

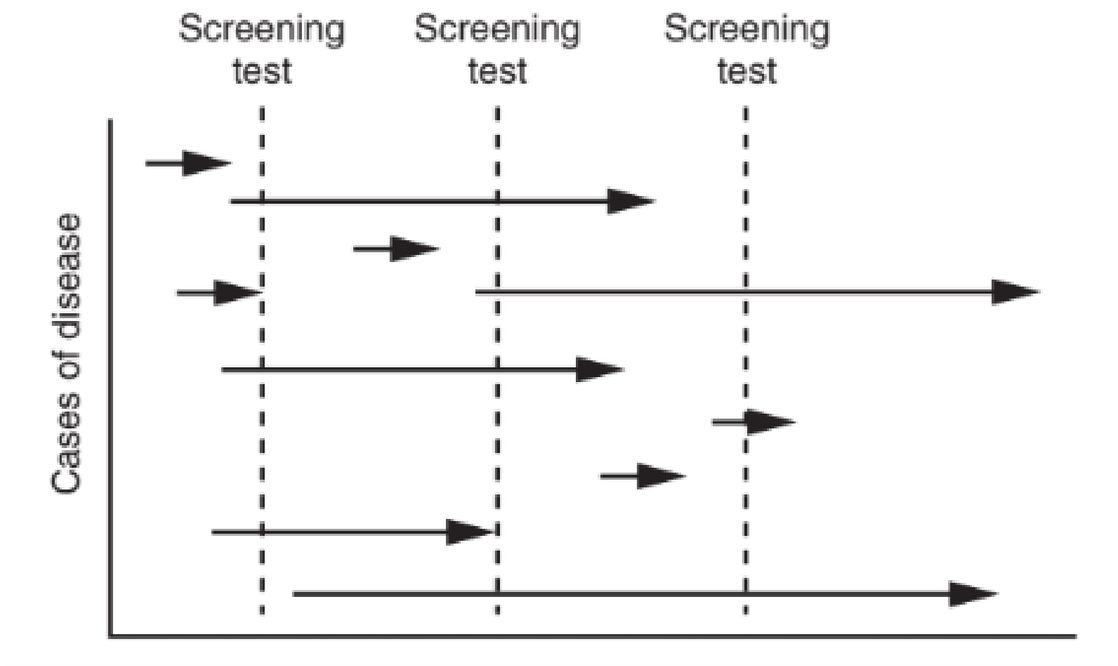
# Population Screening and Survival Biases


| Lead-time Bias | Length-time Bias | Compliance Bias |
| --- | --- | --- |
| Earlier detection makes survival mathematically look longer, even if the actual date of death remains unchanged. | Screening naturally catches slower-growing, less aggressive disease variants with inherently better prognoses, ignoring fast-acting fatal cases. | Health-conscious volunteers who seek out screening tend to have better lifestyle outcomes regardless of the actual medical intervention. |

# Characteristics of Effective Screening Programs

| | |
|---|---|
| **Important public health burden** | • The disease should represent a substantial health burden. |
| **Detectable asymptomatic phase** | • A detectable preclinical stage should exist. |
| **Reliable screening test** | • Screening tests should demonstrate adequate sensitivity and specificity |
| **Effective early treatment** | • Early treatment should provide better outcomes than delayed intervention |
| **Acceptable screening process** | • Screening must be acceptable and feasible for the target population. |
| **Favorable benefit-to-harm ratio** | • Population-level benefits should exceed harms and costs |

# Length-time Bias




Diseases with **a long preclinical phase** remain detectable for **a longer period**, making them more likely to be identified during routine screening

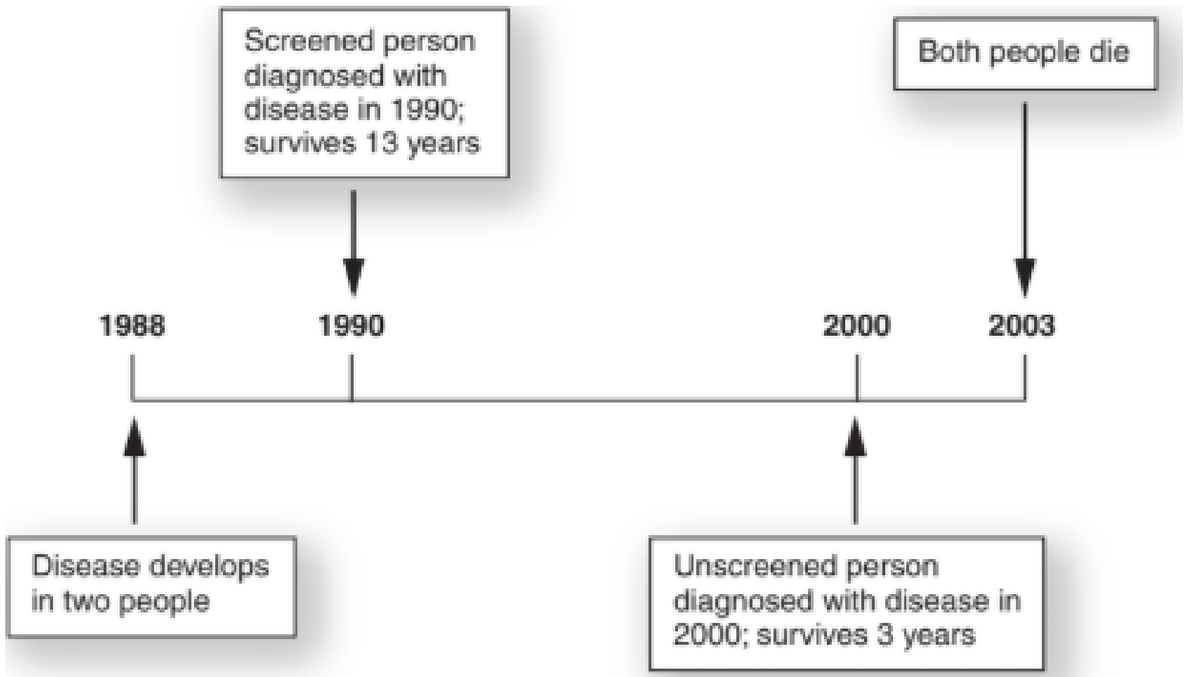
Breast Cancer Screening

- Slow-growing tumors remain asymptomatic for years → more likely detected on mammography
- Aggressive tumors progress rapidly and present symptomatically before the next screening round

Therefore:

- Screen-detected cancers tend to look “less severe”
- Survival among screened patients appears longer

# Lead-time Bias




**Earlier detection** through screening increases the **observed survival time** without actually delaying death.

| Without Screening | With Screening |
|---|---|
| Diagnosis at symptom onset | Diagnosis before symptoms |
| Survival after diagnosis: 2 years | Survival after diagnosis: 5 years |
| Same age at death | Same age at death |

# Summary: The Diagnostic Toolkit

### Intrinsic vs. Clinical

Sensitivity and Specificity are fixed properties; PPV and NPV are entirely dependent on prevalence.

### Evaluation

ROC Curves and AUC assess a test's overall performance across all potential cut-offs.

### Decision Making

Likelihood Ratios provide the most stable, actionable evidence for shifting clinical probabilities.

### Population Health

Screening programs must strictly account for lead-time, length-time, and volunteer compliance biases.

**A diagnostic test is only as good as the clinician's ability to critically interpret it in context.**