

DIAGNOSTIC VALUE OF LABORATORY TESTS

The diagnostic usefulness of a laboratory test lies in the test's ability to support or revise a tentative clinical diagnosis. Methods available to assess test diagnostic utility include test specificity and sensitivity that are used to determine the predictive value of a test, likelihood ratios and odds, and relative operating characteristic (ROC) curves. Some definitions follow.

ACCURACY

How close the test result is to a "true value" using a stringent reference test.

PRECISION

Measures reproducibility of the test result e.g., duplicate results. May be expressed as standard deviation (SD) or the derived coefficient of variation (CV = SD/Mean).

REFERENCE RANGE

The term traditionally means the range of values that includes 95% of the test results observed in a healthy reference population. This range excludes the highest 2.5% and the lowest 2.5% of the results. The term replaced "normal values" or "normal range". The reference population tested may be limited to male or female or specific age groups.

When the distribution of results is Gaussian, the 95% reference range closely approximates the mean \pm 2 standard deviations. Many test results have a non-Gaussian distribution but the central 95% range is still generally used as the reference range using non-parametric methods for defining the lower 2.5 percentile and upper 97.5 percentile cut-off points. The cut-off point for the reference range affects the test's diagnostic sensitivity and specificity.

WITHIN-PATIENT TEST REPRODUCIBILITY

Deciding whether a change in a patient's test result represents a "real" change, rather than random fluctuation, depends on the magnitude of two sources of variation: 1) the normal intra-individual, biological variability and 2) the methodologic imprecision for the test in question. Statistically, assuming both sources of variation show Gaussian distributions, the 95% confidence limit for difference between two repeat measurements is $2.77 \times \text{SD}$. In this case, the SD is computed by taking the square root of the sum of the methodological (analytical) variance (SD^2) plus the within-person (intra-individual) variance (SD^2), e.g., for albumin the 95% confidence for a change in analyte value is $[(0.1)^2 + (0.11)^2]^{1/2} \times 2.77 = 0.4$.

The table shows approximate methodological SDs and short term, intra-individual, biological SDs for several routinely monitored laboratory tests, as well as the 95% confidence limits for two repeated measurements. While methodological SDs are well known in both the normal and abnormal range, most of the intra-individual variation data has been accumulated from middle aged, healthy adults. The exact magnitude of this source of variability no doubt differs with gender, age, and time interval between repeat sampling and most importantly with disease. Therefore, the listed 95% confidence intervals should be used only as general guidelines for whether a test result change is "real" or merely statistical variation. Methodological, within person variability, and computed 95% confidence limits for a change in a test result assuming no change in the patient:

<u>Analyte</u>	<u>Sample (Mean)</u>	<u>Methodological SD(CV)</u>	<u>Within-person SD(CV)</u>	<u>95% Confidence Limit for a Change in Analyte Value</u>
Albumin	3.9	0.10 (2.6)	0.11 (2.8)	\pm 0.4 g/L
Calcium	9.8	0.25 (2.6)	0.11 (1.1)	\pm 0.8 mg/dL
Cholesterol	214	6.60 (3.1)	9.20 (4.3)	\pm 31.4 mg/dL
Creatinine	1.1	0.05 (5.0)	0.045 (4.1)	\pm 0.2 mg/dL
Glucose	99.5	2.37 (2.4)	4.14 (4.2)	\pm 13.2 mg/dL
HDL Cholesterol	50.3	2.30 (4.6)	2.70 (5.4)	\pm 9.8 mg/dL
Magnesium	1.6	0.07 (4.4)	0.055 (3.4)	\pm 0.2 mg/dL
Phosphorus	3.4	0.09 (2.8)	0.26 (7.6)	\pm 0.8 mg/dL
Potassium	4.3	0.05 (1.3)	0.23 (5.4)	\pm 0.7 mmol/L
Sodium	139.9	1.40 (1.0)	0.79 (0.6)	\pm 4.4 mmol/L
Triglycerides	133	10.40 (7.8)	27.50 (20.7)	\pm 81.4 mg/dL
Total Protein	6.9	0.16 (2.4)	0.17 (2.5)	\pm 0.7 mg/dL
Urea Nitrogen	15	0.72 (4.8)	1.42 (9.5)	\pm 4.4 mg/dL
Uric Acid	6.3	0.17 (2.7)	0.46 (7.3)	\pm 1.4 mg/dL

TEST INFORMATION

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DIAGNOSTIC SENSITIVITY AND SPECIFICITY OF TESTS

Four entities are used for tabulation: test positive, test negative, disease positive, and disease negative. True positives represent those subjects who have a positive test result and who have the disease in question. True negatives represent those subjects who have a negative test result and do not have the disease. False positives are those without the disease but with a positive test result. False negatives are those with the disease but with a negative test result. The point (value) chosen to separate a "positive" laboratory result from a "negative" laboratory result influences the resulting sensitivity and specificity (Galen and Gambino).

SENSITIVITY

The proportion of subjects with a negative diagnostic test in a population without the disease, expressed as a percentage.

Sensitivity % = (true positives)/(true positives + false negatives) x 100.

SPECIFICITY

The proportion of subjects with a negative diagnostic test in a population without the disease, expressed as a percentage.

Specificity % = (true negatives)/(true negatives + false positives) x 100. Whether or not the person has the disease in question must be answered by another means to validate specificity and sensitivity for any one test.

PREDICTIVE VALUES

In order to find the predictive value of a test, the sensitivity, specificity, and prevalence of the disease in a population should be known. The value is useful in screening for disease. The figure used for prevalence has a major impact on the predictive value result.

PREVALENCE

Prevalence of a disease is often reported as the number of subjects with the disease in a general population of 100,000. (Incidence of a disease is the number of subjects found to have a disease within a defined time period, such as a year, in a population of 100,000). When disease prevalence is high, the efficacy is related to the sensitivity.

ROC CURVE

This is a plot of the true positive rate (sensitivity) on the Y-axis and the false positive rate (1-specificity) on the X-axis as the reference limit is changed over its possible range. As the diagnostic usefulness of the test improves, the ROC curve moves upwards and to the left. Using ROC curves, tests may be compared in a standardized fashion (Beck).

LIKELIHOOD RATIO (LR)

For a positive test result, this is the sensitivity (true positive) divided by the false positives (1-specificity) (Radack). LR may be used to calculate post laboratory test odds for diagnosis versus a predetermined clinical estimate or odds for a particular disease based on clinical and published experiences (Wasson).

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Reviewed 2/99, 9/01, 5/04, 6/07; Revised 5/06;6/08 Last Approved: J Eckfeldt 6/08