Realistic expectations of laboratory testing

JOHN J. FERNANDES, DO

The ordering, reviewing, and interpreting of laboratory tests require recognition and familiarity with the concepts of normal values, sensitivity, specificity, predictive values, and prevalence. The significance of these test properties in clinical decision-making is explained.

(Key words: Laboratory tests, sensitivity, specificity, predictive value, prevalence)

The diagnostic usefulness of a laboratory test rests with that test's ability to exclude or confirm a diagnostic hypothesis, to monitor the course of disease, or to detect clinically unsuspected disease. Tests so used can be technically reliable; that is, they are accurate and precise analytically, but of little clinical value if improperly used.

Clinical interpretation requires an understanding of the diagnostic sensitivity, specificity, and predictive value of a laboratory test. These properties, when appropriately applied with the concept of prevalence, will guide clinical screening or profiling, enhance pattern recognition in exclusion and confirmation testing, and confirm an hypothesis.

Normal values

The normal range of laboratory results as cur-

From the Department of Pathology and Laboratory Medicine, Philadelphia College of Osteopathic Medicine, Philadelphia, Pa, where Dr Fernandes was formerly chairman.

Reprint requests to John J. Fernandes, DO, professor of pathology, Department of Pathology, Olympia Fields Osteopathic Hospital and Medical Center, 20201 Crawford Ave, Olympia Fields, IL 60461.

rently reported—not reference or referent values—identifies a range of values representing a statistical distribution from the mean, encompassing 95% of the values of the test population. This distribution forms the standard bell curve with calculated deviations from the mean (Fig 1). These Gaussian statistics are based on Gauss' law of errors, and applies only to repeated measurements on the same subject, not to a series of measurements on different subjects. These results tell us nothing about morbidity or mortality, and they are unrelated to the prevalence of a disease. Gauss' law of errors implies that a plot measurement made on the same individual would fit a normal distribution, a Gaussian distribution. This implication does not take into account health or disease, and reports to clinicians only values that are only most commonly encountered in various groups. Clinicians dealing with one individual patient are not concerned with frequency distribution in populations, but with individual patients and their diagnostic needs.

When "normal range" is defined as the central 95% of a series of measurements from a group of healthy people, this definition means that 5% of these healthy people are called "abnormal." In addition, it also means that if we are healthy, we have a 5% chance of being labeled "abnormal." The more testing done on a patient, the more likely it is that the results of at least one test will be abnormal (Table 1). As we increase the number of tests, the likelihood of the patient's being labeled "abnormal" increases proportionately.¹ Thus, in chemical profiling or screening, when a healthy person undergoes 20 independent tests, the like-

Figure 1. Standard bell curve with calculated deviations from the mean. This represents the normal range for most laboratory tests, with results defined as falling within ± 2 standard deviations (SD) from the mean (95%) of all results.

likelihood of that person's being labeled "abnormal" is greater than 50%. But in addition, when 20 tests are done as a screen, as on a routine hospital admission screen, there is only a 36% chance that the results of all 20 tests will be normal.

Routine screening and routine hospital admission laboratory testing have created a situation in which, based on chance alone (Gaussian distribution), some results would be reported as "abnormal" in an otherwise healthy patient. In published studies, these abnormal test results that do not reflect disease have been calculated to be as high as a third of biochemical screening.²

Sensitivity and specificity

The sensitivity of a laboratory test is the incidence of true-positive results obtained when the tests apply to a group known to have the disease. It is the probability that a test result will be abnormal, true-positive in disease. Specificity of a laboratory test is the incidence of true-negative results when the test is applied

to a group known to be free of the disease. It is the probability that a test result is normal in the absence of disease. Sensitivity is equal in percentage to positive results obtained in subjects with disease, and specificity is the percentage of normal results obtained in healthy subjects.

Because some overlap always exists between health and disease, it follows that no test is 100% specific or 100% sensitive (Fig 2). The cutoff point, or upper limit of normal value chosen for a laboratory test to distinguish between health and disease, defines sensitivity and specificity. If the cutoff point is placed at A, everyone with disease is termed "abnormal," and sensitivity is 100% (Fig 3). However, in this circumstance, given normal overlap between health and disease, a significant segment of the healthy group is termed "abnormal" (false-positive results).

If the cutoff point is placed at B, everyone without disease is termed "normal," and specificity is 100% (Fig 4). Again, given normal overlap between health and disease, a substantial segment of the patients with disease will have normal (false-negative) results. When the cutoff point is moved, sensitivity and specificity become reciprocal; that is, as sensitivity is increased, specificity decreases, and vice versa. When a single limit is used, either absolute

Table 1
Chance of Abnormal Result in Relation to Number of Tests a Patient Has

No. of independent tests	Probability of abnormal result, %
1	5
2	10
5	23
10	40
20	64
50	92
90	99

Figure 2. The overlap that exists between health and disease in laboratory results is expressed as a value between points A and B. Patients falling in this zone may have their condition misdiagnosed.

Figure 3. With cutoff point placed at A, everyone with disease is termed "abnormal"; sensitivity is 100%. However, in normal overlap, a substantial segment of the group without disease falls in "abnormal" range.

Figure 4. With the cutoff point placed at B, everyone without disease is termed "normal"; and specificity is 100%.

sensitivity or absolute specificity can be achieved, never both.

Sensitivity and specificity can be altered by combination testing.³ Using three hypothetical tests, A, B, and C with listed sensitivity and specificity, we can increase specificity and decrease sensitivity with serial testing (A, B, and C), and increase sensitivity and decrease specificity with parallel testing (A, B, or C). (See Table 2.) Sick patients are more likely to have one of three results abnormal than to have all three abnormal and, therefore, sensitivity increases in parallel testing. Also, a patient without disease is more likely to have a single abnormal laboratory test than multiple abnormalities; therefore, specificity increases with serial testing. Parallel testing decreases false-negative results, and serial testing decreases false-positive results.

Prevalence and predictive value

Prevalence is the likelihood of disease being present before any testing is done. When expressed as a rate, prevalence equals the number of patients per 100,000 who have disease at the time of analysis. The incidence rate, however, expresses the number of patients per 100,000 in whom the disease develops in a 1-year period. The predictive value of a positive test is the percentage of positive results that are true-positive when a test is applied to a population containing both healthy and ill subjects; it is the probability that a positive test will be correct.

The relationship of the properties of sensitivity and specificity with predictive value and prevalence are expanded in Table 3. As the prevalence of a disease increases, with sensitivity and specificity held constant, the predictive value of a test increases (Fig 5). Also, false-negative rates increase, and false-positive rates decrease.³ The combination of these effects can be seen in Table 4. Here, a test having 90% sensitivity and 90% specificity is used to detect disease in two different circumstances in adults.

In the first circumstance, there is a high prevalence rate of 50%, as in coronary artery disease; and, in the second example, the prevalence rate is 1%, as in some infrequently oc-

Figure 5. Predictive value of test increases as prevalence of a disease increases, with sensitivity and specificity held constant.

curing primary malignancies such as primary hepatoma. If 200 people are tested and the prevalence is 50%, 100 of them are healthy and 100 have the disease. Because the test is 90% sensitive and 90% specific, there will be 90 true-positive, 10 false-negative, 90 true-negative, and 10 false-positive results. Therefore, 100 positive results and 100 negative results are obtained. Of the 100 positive results, 90 are true-positive; thus, the likelihood that a positive result is truly positive is 90%. This percentage would represent the predictive value of a positive test. Therefore, when a physician orders this test in the clinical environment, where the likelihood of the disease is 50%, a positive result means that there is a 90% chance the disease is present.

When the prevalence is 1%, as in the second example, the results are quite different. If 10,000 people are tested and the prevalence is 1%, 100 have the disease, and 9,900 do not, there will be 90 positive, 10 false-negative, 8,910 true-negative, and 990 false-positive results. The likelihood that any positive result is truly positive is approximately 8%. Therefore, a positive result in this circumstance would more than likely suggest health rather than disease. In this circumstance, when disease is suspected clinically, positive results are likely to be positive; however, in asymptoma-

tic patients, positive results are more likely to be false-positive.

Contrarily, negative results are more likely to be truly negative in asymptomatic patients than in those in whom disease is suspected. This likelihood, over time, may explain some of the difficulties physicians encounter with biochemical profile testing. Many false results occur simply because the tests are used to search for a low-prevalence disease.

Laboratory tests with a low predictive value may fall outside the normal range and provide little clinical information, although they often show up on panels. The serum chloride and the lactic dehydrogenase (LDH) assays are examples of this phenomenon. Electrolyte panels routinely include chloride and, although chloride is a major cellular anion, the chloride assay provides little useful clinical information in the routine setting. Elevated serum chloride values are nonspecific, because they may represent a diversity of clinical situations, such as dehydration, renal tubular acidosis, diabetes insipidus, and reactions to medications.

Similarly, decreased chloride values are equally nonspecific and are seen with processes that lose hydrochloric acid. Ravel,⁴ in a study of 649 consecutive patients, found a significant discrepancy between chloride and sodium, and only 1.5% of cases. Hyperchloremia no more implies chloride excess than hypernatremia implies sodium excess; and hypochloremia, like hyponatremia, does not reflect the state

Table 2
Sensitivity and Specificity
of Combination Testing

Test(s)	Sensitivity, %	Specificity, %
A	90	90
B	92	93
C	95	95
Serial testing (A + B + C)	75	100
Parallel testing (A or B or C)	100	75

Table 3
Relationship of the Properties of Sensitivity and Specificity
to Predictive Value and Prevalence

Variable	Patients with positive test result	Patients with negative test result	Total
Patients with disease	TP	FN	TP + FN
Patients without disease	FP	TN	FP + TN
Total	TP + FP	FN + TN	TP + FN + FP + TN
Sensitivity $= \frac{TP}{TP + FN} \times 100$			
Specificity $= \frac{TN}{FP + TN} \times 100$			
Predictive value of positive test $= \frac{TP}{TP + FP} \times 100$			
TP = True-positive results, patients with disease correctly classified by test			
FP = False-positive results, patients without disease misclassified by test			
TN = True-negative results, patients without disease correctly classified by test			
FN = False-negative results, patients with disease misclassified by test.			
<hr/> Source: Adapted from Galen RS, Brennan L: <i>Clinical Chemistry: Laboratory Diagnosis and Patient Monitoring. A Diagnostic Medicine Book</i> . Oradell, NJ, Medical Economics, 1981.			

of iron depletion.⁵ The positive predictive value of serum chloride is low.

An abnormal LDH level in the absence of a known clinical process or other laboratory abnormality, is of little diagnostic value. Elevated LDH levels are seen in neoplastic disease, hypoxia, hemolytic anemias, myocardial infarction, liver dysfunction, and in general categories like pulmonary and renal diseases. The presence of elevated LDH values more frequently creates confusion because of the assay's nonspecificity. In a study at the Cleveland Clinic,⁶ screening tests of 2006 patients revealed 22 elevations of LDH. Further analysis with isoenzymes revealed three of the elevations to be due to cardiac ischemia, liver dysfunction, or hemolysis; 13 elevations were non-diagnostic, and the remainder were considered

to be falsely positive. How often, in the pursuit of clinical excellence, do these falsely abnormal findings contribute to the cost of medical care?

The erythrocyte sedimentation rate (ESR), as a screening test in an asymptomatic population, will be the only clue to serious illness in 0.06% of patients.⁷ Even in elderly nursing home residents with multisystem disease, the predictive value of a moderately elevated ESR is less than 12%.⁸ However, if the ESR is greater than 100 mm/h, the predictive value increases. Although the predictive value of this test for any given disease is low, when all patients with infection, malignancy, renal disease, and inflammatory disease are taken together, the predictive value of the ESR greater than 100 mm/h is about 90%.⁹

Table 4
Effects of Disease Prevalence on Positive Predictive Value

Variable	No. with positive test result	No. with negative test result	Total
Disease prevalence = 50%			
No. of patients with disease	90	10	100
No. of patients without disease	10	90	100
Total	100	100	200
Positive predictive value = 90%			
Disease prevalence = 1%			
No. of patients with disease	90	10	100
No. of patients without disease	990	8,910	9,900
Total	1,080	8,920	10,000
Positive predictive value = 8.3%			

The predictive value model can be applied to other areas of medicine, such as interpretation of electrocardiograms and x-ray studies as well as history and physical examinations. A thorough history and physical examination of a given population will increase the prevalence of a disease, thereby increasing the predictive value of any test or procedure used on that population. Finally, the predictive value model, when applied to the medical literature, can enhance the reader's ability to properly interpret scientific data.

Comments

The relative importance of sensitivity, specificity, predictive value, and prevalence of disease for profiling and for exclusion or confirmation of an hypothesis is described. High sensitivity is a major profiling requirement. High specificity and positive predictive value should be sufficient to reduce the number of false-positive results to a reasonable level. As a general rule, high sensitivity is a major requirement for definite exclusion, and high specificity and positive predictive value are major necessities for definite confirmation. When it becomes necessary in clinical decision-making to

exclude a dangerous disease, sensitivity should be close to 100%. Similarly, when it is necessary to confirm a diagnosis that requires dangerous therapy, specificity and positive predictive value are crucial indicators.

1. Murphy EA: *The Logic of Medicine*. Baltimore, Md, Johns Hopkins Press, 1976.
2. Bradwell AR, Carmalt MHB, Whitehead TP: Explaining the unexpected abnormal results of biochemical profile investigations. *Lancet* 1974;2:1071.
3. Galen RS, Gambino SR: *Beyond Normality: The Predictive Value and Efficiency of Medical Diagnosis*. New York, NY, John Wiley & Sons, Inc, 1975.
4. Ravel R: *Clinical Laboratory Medicine: Clinical Applications of Laboratory Data*, ed 5. Chicago, Ill, Year Book Medical Publishers, 1989.
5. Hall WD: Serum chloride, in Walker HK, Hall WD, Hurst JW (eds): *Clinical Methods: The History, Physical and Laboratory Examinations*. Stonebarn, Mass, Butterworth, 1976.
6. Van Lente F, Castellani W, Chou D, et al: Application of the expert consultation system to accelerated laboratory testing and interpretation. *Clin Chem* 1986;32:1719.
7. Sox HC Jr, Liang MH: The erythrocyte sedimentation rate: Guidelines for rational use. *Ann Intern Med* 1986;104:515.
8. Tinetti ME, Schmidt A, Baum J: Use of the erythrocyte sedimentation rate in chronically ill elderly patients with a decline in health status. *Ann J Med* 1986;80:844.
9. Fischer RM, Page MI: Clinical significance of extreme elevation of the erythrocyte sedimentation rate. *Arch Intern Med* 1986;146:1581.

B
1080-1168

Coming soon from
BASEL Pharmaceuticals
Division of CIBA-GEIGY Corporation

HabitrolTM

nicotine

TRANSDERMAL
THERAPEUTIC SYSTEM

**BASEL
Pharmaceuticals**
Division of CIBA-GEIGY Corporation

IN LOWER RESPIRATORY INFECTIONS

Your patients deserve
first-time success*...

Brief Summary of Prescribing Information

AUGMENTIN amoxicillin/clavulanate potassium

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Lower Respiratory Infections caused by β -lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Otitis Media caused by β -lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Sinusitis caused by β -lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Skin and Skin Structure Infections caused by β -lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β -lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β -lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β -lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication. **WARNINGS:** SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID REACTIONS) HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN IN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENTLY FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur usually involving *Pseudomonas* or *Candida*, the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with *Azthiase* (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential. **Pregnancy (Category B):** Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreases the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthritis, myalgia, and frequently fever, erythema multiforme, rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic. hepatocellular or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one *Augmentin* 250 tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* 500 tablet every eight hours.

Since both the *Augmentin* 250 and 500 tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* 250 tablets are not equivalent to one *Augmentin* 500 tablet. Therefore, two *Augmentin* 250 tablets should not be substituted for one *Augmentin* 500 tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* 125 and 250 chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

BRS-AG-1 9417095

SB
SmithKline Beecham
Pharmaceuticals

Philadelphia, PA 19101

Prescribe
1 AUGMENTIN[®]
amoxicillin/clavulanate potassium

**First-line
for all the right reasons**

*Clinical success rate for bronchitis and pneumonia was 98%. Data on file, Medical Department, SmithKline Beecham Pharmaceuticals.
© SmithKline Beecham, 1991