Insurance Testing

Tumor Markers For Prostatic Cancer (Is there a screening test for Prostatic Cancer?)

Hugo C. Pribor, MD, PhD, FCAP

THE AUTHOR: Hugo C. Pribor, MD, PhD, is a diplomate of the American Board of Pathology and Anatomic and Clinical Pathology and is a member of Associated Pathologists, P.C., a twenty-five member group of pathologists serving Tennessee and Southern Kentucky. He is a Clinical Professor of Pathology at Vanderbilt University School of Medicine in Nashville, and serves as Medical Director of SmithKline Beecham Clinical Laboratories and its insurance testing laboratory in Nashville. He is an internationally recognized authority in clinical pathology, particularly computer applications and expert systems in laboratory medicine. His clinical pathology system software and physician's clinical laboratory support system is distributed by Lea & Febiger (Philadelphia) worldwide. His handbook of interpretation of laboratory profiles will be published by Lea & Febiger in the early to mid 1990s. He has authored over 125 articles, was chapter author in several text books and published two monographs. He is listed in various standard references including American Men of Science, The Dictionary of International Biography, National Encyclopedia of American Biography, and in Who's Who in the world. Several years ago (1968) when he was an active ocean racing sailor he was listed in Who's Who in Yachting.

Abstract

Prostatic-Specific Antigen (PSA) is a low-molecular weight glycoprotein, that is uniquely associated with prostatic tissue. It has considerable diagnostic specificity for prostatic disease. Concentrations of PSA in serum correlate well with the stage of disease, and response to treatment in patients with prostatic cancer. It is, therefore, a good *tumor marker* for prostatic cancer. However, it has been reported to be elevated in benign prostatic hypertrophy, after prostatic massage, after biopsy procedures and other benign conditions, therefore, this test has not been recommended as a screening test for prostatic cancer. It has a positive predictive value of only 0.41%, that is one out of every 241 positive tests would be a true positive test. In symptomatic males over the age of 55 there is good evidence suggesting the importance of using this test along with other procedures in the diagnostic workup of such patients.

Introduction

I am happy to introduce this new column devoted to insurance testing. Testing of applicants in some form and the assignment of risk factors as applied to an insurance applicant has been the backbone of the insurance industry. For years there has been some sort of laboratory testing on most insurance applicants, even if it is only a dipstick for protein in the urine.

The advent of AIDS and its affect on mortality in young people and the availability of new more reliable and economical laboratory testing have encouraged insurance companies to make greater use of laboratory testing in evaluating an insurance applicant, particularly one for a substantial policy. This has been a mixed blessing. The insurance professionals now have to tackle the problem of false positive and false negative results. He/she needs to understand to some extent the concepts of sensitivity and specificity of laboratory tests, as well as understanding the predictive value of a positive or negative test to detect or exclude a disease. (Appendix A. or see Reference #14)

It is my purpose in providing this column to review various tests used or proposed for use in insurance testing. I will try to provide you, the insurance professional, with unbiased, authoritative and up-to-date information about a test with pertinent literature references. Often the decision to use a test and when not to use it, is not obvious. There may be conflicting views. A test may be very useful in certain instances in diagnostic medicine or in follow-up care and yet of little discriminating value in testing an insurance applicant. Sometimes the use of a test may give you misleading information; for example, a low predictive value (high false positive rate) will imply the presence of disease in an applicant without disease.

In this column I will try to provide you all of the necessary information to allow you to make a valid decision of whether to use a test or not, and when to use it. When the discussion is in my area of expertise, I will write the column. When it is not, I will get a guest author with specialized expertise.

This column will primarily consider laboratory testing, however, not exclusively so. If there is an area of testing outside the laboratory that you are interested in, I will attempt to find a knowledgeable expert to discuss it in this column. We will attempt to discuss only information relative to insurance testing. We will give references when available for other information about the test useful in diagnosis and therapeutic medicine. For example, a recent Medline search of the National Library of Congress Medical Literature file identified 400 articles regarding prostatic-specific antigen. Three-hundred of these articles were published in the last two years and there were five review articles. Almost all of these articles referred to the clinical usefulness of this test as a "tumor marker" for prostate carcinoma and its relationship to different stages of this disease. This information would be inappropriate for this column. For the interested insurance professional, however,

the physicians and scientists of SmithKline Beecham Clinical Laboratories have written an excellent review discussing the clinical usefulness of this test[1].

I look forward to your suggestions and advice. The decision on what topics to be discussed will be based on questions I receive from you. Please write suggestions to me or write Dr. John Elder, the JIM editor. I plan to include in future columns a discussion on diagnostic usefulness of gamma glutamyl transferase (GGT). I have also enlisted a guest author to discuss the significance of an indeterminate Western blot or Hivagen test.

Tumor Markers

We in laboratory medicine have been looking for a screening test that could accurately detect the presence of cancer in a patient early in the course of the disease. In my career in laboratory medicine, starting in the mid 50s, there have been tests proposed in the medical research community to perform this function. Unfortunately, a test or group of such tests to date has not been discovered. In recent years, a group of tests has been developed and designated Tumor Markers. These tests have been associated with one or more cancers and have been useful in suggesting the extent of the tumor, and detecting the recurrence of the tumor after the surgical removal of the tumor. One of the earliest tumor markers was the carcinoembryonic antigen (CEA) determination. This test has a false positive elevation in a significant number of persons. Nevertheless it has been extremely useful in monitoring patients with proven colon/rectal cancer. Because of the occurrence of false positive elevations of these tumor markers in patients with no disease, or with nonmalignant disease, and the unnecessary emotional and diagnostic problems related with the detection of a falsely elevated tumor marker, the medical community in general has discouraged the use of these tests as screening tests for the detection of various cancers.

Prostatic Acid Phosphatase

Serum acid phosphatase has been known to be associated with cancer of the prostate for over 40 years. In the late 1970s there was widespread attention to a new role for serum acid phosphatase determinations in the detection of prostatic cancer. In an editorial in the New England Journal of Medicine, Gittes,[2] citing data from an accompanying article by Foti and his co-workers[3] observed, "The clear implication of the accompanying report is that mass screening on the basis of a blood test alone can reverse this gloomy experience" (i.e., of fatal delays in diagnosis). Since then, refinements of radio-immunoassay technique, with consequent improvement in its sensitivity and specificity have been reported.[4,5,6,7] Encouraging data such as that quoted and that anticipated from other groups developing improved assays for serum prostatic acid phosphatase, heralded the era of routine screening for prostatic cancer in the near future.[8] Medical World News, in front cover headlines, announced, "New Prostate Ca Test Recommended as Screen"; the ensuing article envisioned blood screening tests as "part of any comprehensive health exam for any adult male."[9] A commercial laboratory in an advertisement in the New York Times alerted readers to the availability of a "new blood test called the Male-PAP test."[10]

After this, additional studies suggested reservations concerning mass screening through blood tests alone. Disappointing clinical experiences in a nationwide trial led the National Prostatic Cancer Project to recommend against the use of PAP as a primary screening tool.[11] Watson & Tang[12] in 1980 reviewed the data and discussed "The predictive value of prostatic acid phosphatase as a screening test for prostatic cancer" they noted, "It is important to understand that the sensitivity and specificity of a test do not alone determine its ability to predict the presence (or absence) of disease in a population to be screened." They referred to the classic work of Galen & Gambino[13] referring to predictive value of medical diagnosis. If a test is positive in 95 percent of patients known to have a disease, it DOES NOT FOLLOW that in a mass screening program, 95 percent of those with a positive blood test actually have the disease. There was an excellent review of probability theory to evaluate laboratory tests in insurance medicine in this journal recently by Iacovino.[14] In appendix A, we discuss in more detail diagnostic sensitivity, specificity, positive and negative predictive value, and how this information can be used to determine diagnostic efficiency. Using the values for sensitivity and specificity of Foti et al[3], which may differ substantially from those obtained from a broad survey of a population, and assuming the prevalence of prostatic cancer is 35 per 100,000, Watson[12] calculated the positive predictive value of the Prostatic Acid Phosphatase is 0.41. In other words only one out of every 244 subjects (100/0.41) with a positive test would, in probability, have carcinoma of the prostate. He noted further that the probability is smaller still if we exclude from consideration all the patients who have a palpable prostatic nodule and we assess the positive predictive value of this test at the sensitivity for Stage I carcinoma - 33%. In this same issue of The New England Journal of Medicine, Guinan et al[15] reviewed the accuracy of the rectal examination in the diagnosis of prostatic carcinoma in a screening of 300 men and concluded that the digital rectal examination is the most efficient screening test for the diagnosis of prostatic cancer.

Prostatic-Specific Antigen

In 1979 prostate-specific antigen (PSA) was isolated. This glycoprotein is specific for prostate epithelial cells. Being a normal antigen of the prostate, low levels of PSA are found in all men in the normal population. The levels are generally higher in subjects with benign prostatic hypertrophy (BPH). Of patients with BPH, 20% have PSA levels over the upper reference range level (4ng/L). Other prostatic disorders such as acute prostatitis and other nonmalignant perturbations can sometimes have elevated PSA levels. Due to the significant overlap of PSA levels among patients with BPH and low stage prostatic cancer its utility as a screening assay is limited, as is its use in preoperative staging. However, since patients with radical prostatectomy should have no circulating levels of PSA, it becomes an excellent marker for judging persistent or recurrent disease. Most patients with advanced stage disease have very elevated PSA making it an ideal marker for managing patients with metastatic disease.

The presence of this new marker for prostatic cancer is exciting to all of us. As additional studies are performed we note continued information indicating its superiority to prostatic specific antigen as a tumor marker. Stamey et al in 1987[16] compared the clinical usefulness of the serum markers PSA and PAP in 2200 serum samples from 699 patients, 378 of whom had prostatic cancer. PSA was elevated in 122 of 127 patients with newly diagnosed, untreated prostatic cancer, including 7 of 12 patients with unsuspected early disease and all of 115 with more advanced disease. The PSA level increased with advancing clinical stage and proportional to the estimated volume of the tumor. But PSA was increased in 86% of the patients with BPH. Stamey et al in 1989[17] noted that PSA was strongly correlated with volume of prostate cancer. He states further that bivariant and multivariant analyses indicate that cancer volume is the primary determinate of serum prostate specific antigen levels. Prostate specific antigen was elevated 3.5 ng/ml for every cc of cancer, a level of at least 10 times that observed for benign prostatic hyperplasia.

Is PSA Usable as a Screening Test for Prostate Cancer?

In most of the studies reviewed in the literature there seems to be unanimous agreement that PSA is a much better tumor marker than PAP for following the effect of therapy on cancer of the prostate. However most papers specifically point out that the present knowledge suggests that this test, because of false positive results in benign prostatic hypertrophy and other benign conditions, cannot be used as a screening test for cancer of the prostate.

Barek[19] in a recent study of 437 subjects determined a better sensitivity of 84.4% and specificity of 92.9% for the PSA test. Using the same prevalence figures as before (35/100,000), the positive predictive value of the PSA test is 0.4145% or that is only one out of every 241 (100/0.4145) with a positive test would in probability have carcinoma of the prostate.

It is well recognized that the prevalence of this disease significantly increases in males as they age. Therefore if we assume a 10 times increase in prevalence of prostate cancer in men over 50, the positive predictive value is 0.43% or one true positive in 233 positive results. If we assume however a 100 times increase in prevalence of prostate cancer in men over 55 the positive predictive value goes up to 0.64% or one true positive for every 157 positive test results. At this level the test begins to look more promising as a screening test.

Some authors defined their own upper limits of normal for the PSA assay. These studies with various upper limits of normal have revealed that 20 to 86% of patients with benign prostatic hypertrophy, and 41 to 98% with various stages of prostate cancer have elevated PSA levels.[20,21] Hudson et al[22] in their study of 168 patients with presumed benign prostatic hyperplasia 21% had a PSA level greater than 4 ng/ml, however only 3 of those patient (2%) had PSA levels of more than 10 ng/ml. In their review of the literature they note that the great majority of patients with pathologically confirmed benign prostatic hyperplasia have PSA levels less then 10 ng/ml. In their study of patients believed to have clinically organ-confined prostatic cancer, 66% had preoperative PSA levels of greater than 4.0 ng/ml compared to 72% of those with extracapsular extension on rectal examination or documented metastatic disease. The observation that PSA levels of greater than 10 ng/ml are associated more frequently with prostate carcinoma than benign prostatic hyperplasia DOES NOT necessarily mean that PSA is an accurate screening test for prostate cancer.[22] Nevertheless PSA levels of greater than /10 ng./ml are worrisome for prostate carcinoma. A PSA level of greater than 10 ng./ml should not be considered diagnostic of prostate cancer, since patients with a large, obstructing adenoma or prostatitis also may have PSA values above this level. However, this group certainly warrants additional studies to exclude or confirm the diagnosis of prostate cancer.

Brawer & Lange[23] noted that the specificity of PSA for prostate cancer has been considered too low for the use of this marker alone in screening. They state: "However, data is emerging to suggest that this may warrant further examination." For example, a screening study of 1,023 men by digital rectal examination and transrectal ultrasonography Cooner et al[24] found carcinoma in 4.5% of patients with PSA levels of 4.1 - 10 ng/ml and 61.5% of those with levels of 10.1 ng/ml. Among 152 positive biopsies, PSA values were <4.0 ng/ml in 21%, between 4.1 and 10.0 ng/ml in 32% and >10.1 ng/ml in 97%.

They[23] further state that if the true prevalence of prostate cancer in men over 55 is 30% (much greater than my hypothetical estimate of a 100 fold increase in prevalence), and if the sensitivity of PSA levels of >10 ng/ml for patients with apparently localized prostate cancer that might be detected in a screening clinic is 20%, and if the specificity of PSA is 95% (i.e., only 5% of men over 55 without cancer will have levels of >10ng/ml), then the positive predictive value for a PSA value of >10 ng/ml is 63%. They further state that under these circumstances, "this figure is certainly sufficient to warrant using PSA as a screening tool."

The article by Brawer & Lange[23] is the only reference I could find suggesting the use of PSA as a screening test. It should be noted, however, that they refer to its use using values over 10 ng/ml in patients over 55 years of age coming to a urology clinic. If a patient comes to a urology clinic it can be assumed he has clinical symptoms requiring medical attention. I think we would all agree that as part of this patient's workup, laboratory work should be done including a PSA determination. I assume this is being done along with a digital rectal examination of the prostate. Finally these authors state "if the true prevalence of prostate cancer in men over 55 is 30%" — this is 1000 times the generally stated prevalence of prostatic cancer in the male population in general. While we note the incidence of carcinoma of the prostate is significantly increased in the male population over 55 years of age — earlier in this presentation I calculated the predictive value at 100x increase for males over 55 to be 0.65 % or one positive in 158 positive test results would be a true positive. Assuming we increase the upper reference limit to 10 ng/dl this would increase the sensitivity of this test. There are no studies in the medical literature to my knowledge to date that quantitate this sensitivity for asymptomatic males over 55 years of age.

I think we can all agree that if the prevalence rate is 30% for men over 55 coming to urology clinic for evaluation — the ue of the PSA as a screening test in this instances is justified. This data, however, to my mind doesn't necessarily cost justify the routine use of this test in asymptomatic males over the age of 55. Hopefully there will be studies in the future to evaluate the usefulness of this test using these reference ranges in men over the age of 55.

Summary

There is no good screening in laboratory tests today for the diagnosis of prostatic cancer. From the literature it would appear that the digital examination of the prostate is still the best screening test for prostatic cancer. The medical literature support the PSA test as a new significantly better tumor marker for prostatic cancer. Based on PSA predictive value, it cannot be recommended to be used as a routine screening test in asymptomatic males. There is however evidence in the medical literature to suggest that in males over the age of 55 this test should be determined along with the other procedures in a workup of a patient with urological symptoms.

If it is used as a screening test, the reviewer must be aware of the high incidence of false positive results. A positive test result should be followed up with a complete workup before a presumption diagnosis of prostatic cancer is assumed.

APPENDIX A

The Predictive Value of Laboratory Tests

In order to have some understanding of the usefulness of any procedure, it is necessary to have an understanding of sensitivity, specificity and predictive value of the test. The diagnostic performance of a laboratory test can be defined by its diagnostic sensitivity, diagnostic specificity, predictive value.

DIAGNOSTIC SENSITIVITY is a measure of the frequency of a positive test when a particular disease is present. For example, the sensitivity of an acid phosphatase in patients with advanced prostate cancer is 91% that is, 91 out of 100 patients with prostate cancer at this stage would be expected to have a positive test result, while 9 out of 100 patients would be expected to have a false negative result. The higher the sensitivity the more likely a negative test is to correlate with the absence of the disease in question. Thus, one clinical use of a test with a high sensitivity is to help exclude an unlikely disease if the test result is negative.

DIAGNOSTIC SPECIFICITY is a measure of frequency of a negative test in the absence of a particular disease. For example, the specificity of an acid phosphatase person without prostate cancer is said to be 92%. That is 92 out of 100 persons without prostate cancer would be expected to have a true negative test result while 8 out of 100 persons without the disease would be expected to have a false positive result. The higher the specificity the more likely a positive test is to indicate the presence of the disease. Thus, one clinical use of a test with high specificity is to help confirm a likely disease if the test result is positive.

A PERFECT LABORATORY TEST would have 100% sensitivity and 100% specificity, and an abnormal result would unfailingly identify those with the disease in question. Such tests, except those used in a purely descriptive situation, do not exist.

When a test is applied to a population, some patients having the disorder will have negative tests (false negatives) and some not afflicted with the disorder will have positive tests (false positives). The probabilities of these outcomes can be calculated for any defined population and expressed as predictive values.

THE POSITIVE PREDICTIVE VALUE of a test result is the percentage of all positive results that are true positives, or it is the frequency of the disease in question in all patients with positive test results.

THE NEGATIVE PREDICTIVE VALUE OF A NEGATIVE result is the percentage of all negative results that are true negatives, or is is the frequency of patients not having the disease in question in all patients with negative test results. In most clinical applications, we are interested primarily in the predictive value of a positive result. The predictive value of a positive test identifies the percentage of patients who will be presumptive positive for a particular disease and who, after detailed diagnostic work-ups, turn out to have the disease.[25]

In order to calculate predictive value, the PREVALENCE of the disease in the population studied is particularly important. If a test is positive in 95% of patients known to have a given disease, it does not necessarily follow that in a mass screening program, 95% of those with a positive blood test actually have the disease. The positive predictive value incorporates integral relations between three key values: test sensitivity, test specificity, and the prevalence of the disease in the population. Thus it serves to measure the ability of a positive test to predict the presence of disease. If certain important limitations are recognized, the applications of these calculations to the PSA test can provide answers to important questions concerning the usefulness of this test as a screening tool.

The importance of prevalence in understanding the positive predictive value of a test may be better understood if you consider the positive predictive value of the pregnancy test first on a population of women in the childbearing age as compared to using the test with a group of NFL football players. Obviously, a positive test in the football players would have the highest probability of being a false positive. Even though when the same test is run in the same circumstances on females positive results would more than likely be significant as positive.

Below is the formula for predictive value and calculations of positive predictive value based on data in the medical literature.

PREDICTIVE VALUE

$$PVpos = \frac{(Se) \times (P)}{(Se) \times (P) + (1\text{-}Sp) \times (1\text{-}P)}$$

Se = sensitivity of the test
Sp = specificity of the test
P = prevalence of the disease

References

1. *Prostatic-specific Antigen* - A new test announcement, 661086N Smith-Kline Bio-Science, Insurance Testing Center, 5 Park Plaza, Nashville, TN 37203 800-752-5467 Att. Vickie Wilson.
2. Gittes R. Acid phosphatase reappraised. *N Engl J Med.* 1977;297:1398-9.
3. Foti AG, Cooper JF, Herschman H, Malvaex RR. Detection of prostatic cancer by solid-phase radioimmunoassay of serum prostatic acid phosphatase. *N Engl J Med.* 1977;297:1357-61.
4. Bruce AW, Mahan DE, Morales A, Clark AF, Belville WD. An objective look at acid phosphatase determinations: a comparison of biochemical and immunological methods. *Br J Urol.* 1979;51:213-7.
5. Vihko P, Sajanti E, Janne U, Peltonen L, Vihko R. Serum prostatic specific acid phosphatase development and validation of a specific radioimmunoassay. *Clin Chem.* 1978;24:1915-9.
6. Choe BK, Pontes EJ, Morrison MK, Rose NR. Human prostatic acid phosphatases II. A double-antibody radioimmunoassay. *Arch Androl.* 1978;1:227-33.
7. Mahan DE, Doctor BP. A radioimmune assay for human prostatic acid phosphatase levels in prostatic disease. *Clin Biochem.* 1979;12:10-7.
8. Murphy GP, Karr J, Chu TM. Prostatic acid phosphatase: where are we? *CA.* 1978;28:258-64.
9. Anonymous. New test for prostate cancer advised as routine. *Med World News.* 1978;19(13):13-4.
10. Metpath Laboratory (Teterboro, NJ) *New York Times*, Sunday ed. 21, January 1979.
11. Wajsman Z, Chu TM, Saroff M, Slack N, Murphy GP. Two new direct and specific methods of acid phosphatase determinations: national field trial. *Urology.* 1979;13:8-11.
12. Watson RA, Tang DB. The predictive value of prostatic acid phosphatase as a screening test for prostatic cancer. *N Engl J Med.* 1980;303:9:497-9.
13. Galen RS, Gambino SR. *Beyond normality: the predictive value and efficiency of medical diagnoses.* New York: John Wiley, 1975.
14. Iacovino John R. Use of Probability Theory to evaluate cost effectiveness of laboratory tests in insurance medicine. *J Ins Med.* 1989;21/3:200-202.
15. Guinan P, Bush I, Ray V, Vieth R, Rao R, Bhatti R. The accuracy of the rectal examination in the diagnosis of prostate carcinoma. *N Engl J Med.* 1980;303:9:499-503.
16. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med.* 1987;317(15):909-16.
17. Stamey TA, Kabalin JN, McNeal JE, Johnstone IM, Freiha F, Redwine EA, Yang N. Prostate-specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II Radical prostatectomy treated patients. *J Urol.* 1989;141(5):1076-83.
18. Chan DW, Bruzek DJ, Desterling JE, Rock RC, Walsh PC. Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and polyclonal immunoassay compared. *Clin Chem.* 1987;33/10:1916-20.
19. Barak M, Mecz Y, Lurie A, Gruener N. Evaluation of prostatic-specific antigen as a marker for adenocarcinoma of the prostate. *J Lab Clin Med.* 1989;113(5):598-603.
20. Myrtle JF, Klimley PG, Ivor JP, Bruni JF. Clinical utility of prostate specific antigen (PSA) in the management of prostate cancer. *Adv Cancer Diagnostics.* p7,1988.
21. Osterling JE, Chan DW, Epstein JI, Kimball AW, Bruzek DJ, Rock RC, Brendler CB, Walsh PC. Prostate specific antigen in the preoperative and pre-operative and postoperative evaluation of localized prostatic cancer treated with radical prostatectomy. *J Urol.* 1988;139:786.
22. Hudson MA, Bahnson RR, Catalona WJ. Clinical use of prostate specific antigen in patients with prostate cancer. *J Urology.* 1989;142:1011-1017.
23. Brawer MK, Lange PH. PSA in the screening, staging and follow-up of early-stage prostate cancer. A review of recent developments. *World J Urol.* 1989;7:7-11.
24. Cooner WH, Mosley BR, Rutherford CL, Beard JH, Pond HS, Bass RB, Terry WJ. Clinical application of transrectal ultrasonography and prostatic specific antigen in the search for prostate cancer. *J Urol.* 1988;139:758-761.
25. Teitz NW Editor, *Text book of clinical chemistry*, WB Saunders Co., 1986;397-398.

Errata

Printing errors occurred in two articles in the last issue of JIM (Vol. 21. No 3):

1. "Use of Probability Theory to Evaluate Cost Effectiveness of Laboratory Tests in Insurance Medicine," by John R. Iacovino, MD, pages 200-202.

   The reference numbers were omitted from the text; and in Table 1 (page 202) the numbers in the second horizontal line of figures were moved one vertical column to the right and the last number omitted. The Table should have been:

Table 1.
Summary of Test Results (1000 tested individuals)

	True Pos.	True Neg.	False Pos.	False Neg.
Original group tested (1000)	71	783	117	29
Result of positive tests reflex (188)	140	22	6	20
Final outcome of original group tested (1000)	140	805	6	49
Net change from reflex testing	+69	+22	–111	+20

2. "Fructosamine — Clinical Usefulness and Determination of Reference Ranges," by Carl W. Ludvigsen Jr., MD, PhD, JD, Gwen Sprague, MT, Kaye M. Smith, MS, pages 203-207.

   The bottom line of the right column on page 203 was omitted; The last two sentences of that paragraph should have read:

   In contrast, fructosamines arise from a post-translational modification involving a nonenzymatic mechanism and should not be confused with glycoproteins. The reaction of glucose and protein to form fructosamine is presented above in schematic form (Figure 1).

Correct reprints of either or both articles will by provided by the Editor on request.