TUMOR MARKERS: ISSUES FROM AN INSURANCE PERSPECTIVE

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Trends in Cancer Mortality

Two important trends in cancer mortality are being reported world-wide. First, changing mortality due to certain cancers is being observed. In a study of trends in 15 industrialized countries, increases in cancer mortality were reported for lung, breast and prostate cancers in most age groups, while a substantial decline in stomach cancer mortality was noted. Intestinal cancer mortality varied by age and region of the world. Such patterns should always be interpreted in the context of other changes that may have been taking place during the time of the study. For example, significant improvements in the accessibility and quality of health care may have occurred over the years, or changes in cancer mortality may be due largely to better statistics or earlier diagnosis due to cancer screening.

The second trend is much more significant: proportionate mortality due to cancer -- relative mortality caused by malignant diseases compared to mortality from all other causes -- is increasing dramatically. In the last sixty years, the proportion of deaths due to cancer has increased progressively in many developed countries, from one in eight to one in four and, in middle-aged women, to more than one in two deaths. This pattern is related to enhanced prevention of non-malignant disease, better treatment for specific diseases other than cancer, and changes in demographics. The latter factor is particularly important. More and more people are living to older ages. In the United States, for example, within the next 10 or 20 years almost half of all deaths will occur after age 80 if present trends continue. Since the causes of death at these older ages differ from those in younger populations, overall proportionate mortality becomes more and more weighted by diseases affecting the elderly unless age-specific data are analyzed.

Tumor Markers in Clinical Medicine

Tumor markers are substances that can be measured in tissue or body fluids to identify the presence of cancer. The existence of some of these markers has been known for decades or, in a few instances, more than a century. The first marker discovered, the Bence-Jones protein, was identified in 1846 in patients with multiple myeloma. Urinary amylase was described several years later in pancreatic cancer. Human chorionic gonadotropin (HCG) and serum acid phosphatase were identified in the 1930s, followed by the discovery of alkaline phosphatase, vanillylmandelic acid (VMA), and lactic dehydrogenase (LDH). But it was not until the isolation of carcinoembryonic antigen (CEA) in 1965 that tumor marker measurements became an important part of oncology and laboratory medicine.

Tumor markers may be bound to tissues or circulate freely in body fluids. Those that are tissue bound, such as estrogen and progesterone receptors in breast cancer, can only be obtained via biopsy. Circulating tumor markers are found in body fluids such as blood or urine. These are the markers that are commonly used in clinical medicine: prostate-specific antigen, carcinoembryonic antigen, alpha-fetoprotein, etc. Only circulating tumor markers will be discussed in this review.

Circulating tumor markers may be either organ-specific or general. Organ-specific tumor markers are primarily associated with certain types of cancer. They are categorized as hormones, oncofetal antigens (proteins or antigens that are present during fetal development, occur in low concentrations in adults, and become elevated in some malignancies), enzymes, mucins and other glycoproteins, and specific proteins. Many of these markers are commonly used in clinical practice at the present time. General tumor markers are in theory associated with a wide variety of cancers. None of the general markers are currently used by the medical community except in research protocols, because studies to date have involved very few patients and have not been reproduced by other researchers.

Some of the more common tumor markers are listed in Table 1.

Tumor markers are used in clinical medicine for cancer diagnosis and management. They may also be used for screening purposes in selected high-risk populations.

Diagnosis

Tumor markers sometimes aid in confirmation and staging of cancer. This use is limited because most current markers are not specific for only one type of cancer.
Management

This is the most significant and accepted use of tumor markers. Information is provided regarding prognosis, response to treatment, and detection of residual disease.5

1. Prognosis before treatment. Example: Pre-operative CEA levels correlate with survival rates in colorectal cancer.

2. Likely response to treatment. Example: HCG levels in testicular cancer predict the success or failure of a drug regimen.

3. Detection of residual disease. Example: In ovarian cancer, residual disease is likely if CA 125 levels remain elevated after treatment.

Table 1
Categories of Circulating Tumor Markers

<table>
<thead>
<tr>
<th>Category</th>
<th>Cancer(s) Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Organ-specific Tumor Markers</td>
<td></td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
</tr>
<tr>
<td>Human Chorionic Gonadotropin (HCG)</td>
<td>Placenta, Testis</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Oncofetal Antigens</td>
<td>Colon, Breast, Lung</td>
</tr>
<tr>
<td>Antigen (CEA)</td>
<td>Liver, Testis</td>
</tr>
<tr>
<td>Alpha-Fetoprotein (AFP)</td>
<td></td>
</tr>
<tr>
<td>Enzymes</td>
<td></td>
</tr>
<tr>
<td>Prostate-Specific Antigen (PSA)</td>
<td>Prostate</td>
</tr>
<tr>
<td>Prostatic Acid Phosphatase (PAP)</td>
<td>Prostate</td>
</tr>
<tr>
<td>Neuron-Specific Enolase</td>
<td>Neuroblastoma, Lung</td>
</tr>
<tr>
<td>Mucins and Other Glycoproteins</td>
<td></td>
</tr>
<tr>
<td>CA 125</td>
<td>Ovary, Breast, Colon</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreas, Stomach, Liver</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>Breast, Ovary, Colon</td>
</tr>
<tr>
<td>Specific Proteins</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>II. General Tumor Markers</td>
<td></td>
</tr>
<tr>
<td>Cancer Pro-Coagulant</td>
<td>Multiple Types</td>
</tr>
<tr>
<td>Tumor-Associated Antigen (TAA)</td>
<td>Multiple Types</td>
</tr>
<tr>
<td>Anti-Malignin Antibody</td>
<td>Multiple Types</td>
</tr>
</tbody>
</table>

Screening

Most tumor markers developed to date have not been useful, cost-effective or approved for population screening because the underlying likelihood of disease is too low. The few instances of successful screening programs have involved populations at very high risk of cancer. In China, for example, individuals with chronic viral hepatitis are screened for hepatocellular carcinoma with serum alpha-fetoprotein levels. The effectiveness of this program has been documented by a decrease in tumor size and an increase in resectability and survival over the past 20 years.8

Tumor Markers in Insurance

The increasing proportion of mortality due to cancer in the general population has attracted the attention of insurers. There is interest in knowing if cancer is becoming a more common cause of mortality among insured lives, if this trend is likely to continue, which ages are at particular risk, and what steps can be taken to limit exposure. It is this last point that causes the greatest uncertainty: how can insurers respond to increasing cancer mortality if medical underwriters lack the necessary tools to detect increased risk of death from cancer? Whereas it is possible to screen for heart disease with an electrocardiogram or for diabetes with a blood sugar test, underwriters concerned with the possibility of cancer have to rely on nonspecific findings such as weight loss, anemia, or unexplained fatigue, findings that generally occur only with advanced disease.

Increasing cancer mortality is particularly important to companies who are insuring greater numbers of individuals aged 55 or older, prime ages for the development of cancer. Many of these individuals chose not to purchase insurance in the preceding decades when the ability to obtain coverage at low rates was almost certain. By the time they recognize the importance of insurance, the mortality rate for their age group may have become very high, or their health may have deteriorated. For companies interested in this market, identification of those at greatest risk for early cancer mortality may be one way to increase the affordability of coverage for these individuals.

Finally, expertise in risk selection has been a traditional strength of many insurers and a significant contributor to profitability. Although the role of underwriting diminished over the last ten to fifteen years in some markets as premium volume and investment return became more important sources of revenue, this trend is now reversing due to decreased profit margins and poorer investment results. Companies that maintained
strong underwriting departments during the last decade are now positioned to take advantage of the renewed importance of underwriting. New underwriting tools that would enable a company to identify those at greatest risk of cancer would have appeal because of their expected beneficial effect on mortality results.

With this introduction, the issues associated with use of tumor markers in an insurance context will be discussed.

**Underwriting Issues**

**Application Forms**

Current application forms have only a general question regarding "prior diagnostic tests." Will this type of questioning be sufficient when tumor marker testing becomes commonplace in the medical community, or will specific questions be needed? Will applicants fail to mention abnormal results if they were told by their physicians that the tests were false positives?

**Pre-Notice and Informed Consent**

Informed consent refers to a person's agreement to allow some activity to happen, based on a disclosure of the facts needed to make an intelligent decision. In an insurance testing context, these facts are conveyed to the applicant via pre-notification that certain laboratory tests will be performed.

Concern for informed consent has increased because of greater awareness of individual responsibility for health and the importance of confidentiality. AIDS has served to highlight this issue for insurers. For example, it is common practice to inform applicants if an HIV test will be performed. This allows the insurer to provide educational materials concerning HIV infection and facilitates post-test notification in the event of a positive test. It also gives applicants the option to refuse to have the test.

Insurers who consider ordering tumor marker tests in the future will need to decide how much information should be given to applicants. As a practical matter, many people would want to know if any of the tests being performed were specific for cancer simply because cancer instills fear into everyone and people want to prepare themselves for the remote possibility of such a diagnosis. A few applicants might even refuse the test because they don't want to learn about unfavorable results.

The extent of pre-notice may depend on the type of tumor marker tests developed in the future. If a marker identified early cancers that were usually curable, applicants would probably receive this information with concern but relief that a cure was likely. However, if the tumor marker primarily identified advanced malignancies where death was imminent and unavoidable, the reaction would more likely be anger and denial. More detailed pre-notice would be necessary in this latter instance.*

Is it adequate to provide general pre-notice, much as would be done prior to obtaining a urine specimen, blood glucose test, or electrocardiogram? If this approach was chosen, it would be a simple matter merely to add the specific tumor marker(s) to the list of tests being done, or to inform applicants that "tests for cancer may be performed." Or should more detailed information be given via a specific form that would be read and signed? This latter approach has the advantage of preparing the applicant for the unlikely possibility that the test might be abnormal, but it complicates and prolongs the process.

**Post-Test Notification**

Applicants would be informed of abnormal tumor marker results via post-test notification. Many elements of this process would be similar to established procedures for other tests. For example, it would be preferable to send unfavorable results to an attending physician rather than the applicant whenever possible since most people lack the medical knowledge to interpret this type of information. Further consideration of insurance may be possible after a medical evaluation has been completed.

Certain cases would be problematic. One is the occasional applicant who would prefer not to know about an abnormal tumor marker, a situation analogous to the individual who does not want to be informed of an abnormal HIV antibody test.

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* Issues raised by "lead time" may need to be addressed in the future. Lead time refers to the amount of time that passes between when a tumor marker becomes abnormal and when the cancer would normally have been detected by traditional clinical means. It is also used to describe how much time there is between the discovery of an abnormal test and the point at which cure is no longer possible. From a clinical perspective, tumor markers are considered useful only if they convey long lead times. It remains to be seen if this would be an essential criterion if insurers order tumor markers in the future. If accurate tumor markers existed that were associated with short lead times -- brief intervals between a positive test and the discovery of cancer or incurable cancer -- it's likely that insurers would find such tests of interest even though their clinical value was limited.
A much more common dilemma is the situation where the insurer decides to issue a policy even though a tumor marker test was clearly abnormal according to guidelines published by the laboratory. Consider the post-test notification problems that would occur with the prostate-specific antigen test if this approach were adopted.

Normal PSA values are 0-4 ng/ml, 4-10 ng/ml is interpreted as a mild to moderate elevation, and levels greater than 10 ng/ml are very suggestive of prostate cancer. Suppose an insurer chooses to issue a policy -- at standard rates, with additional premium charges or with some policy modifications -- whenever the PSA is 4-10 ng/ml. The rationale may be that most of these men probably have benign prostatic hypertrophy or some other non-malignant process, or those who do have cancer are unlikely to have advanced disease.

What does the insurer tell applicants in these situations? Simply accepting the case without notifying them of the test abnormality doesn't seem to be a viable alternative. The best option may be to establish a practice of strongly encouraging these individuals to consult their attending physicians. This approach satisfies ethical, business and legal concerns.

- **Ethical concerns** — Cancer may be present. The attending physician should be consulted to determine if further evaluation is needed.

- **Business concerns** — An insurer who follows this course of action displays an interest in the well-being of its policyholders. As a practical matter, if cancer is present, notification will in all likelihood lead to earlier diagnosis and more favorable morbidity and mortality.

- **Legal concerns** — Failure to notify applicants of abnormal tumor marker tests raises the possibility of legal action in the future. This is true if cancer is present (failure to notify), is not present (failure to convey information that would be perceived by many people as important), or develops in the future. This last scenario is of particular interest. Since it can never be determined exactly when cancer starts, it could be argued that a malignancy that is discovered at a later date was already present at the time of application, and that diagnosis and treatment was delayed because the applicant was never told about the tumor marker abnormality.

There is one final theoretical concern. Suppose an applicant fails to admit that a tumor marker abnormality was detected by his/her attending physician. If the insurer orders this same marker and chooses to ignore a borderline elevation, does this eliminate the defense against misrepresentation? This same situation arises if the applicant fails to mention a prior cancer history and the insurer ignores a borderline elevation of a tumor marker associated with that type of cancer. Such scenarios will be rare in the foreseeable future but may assume greater importance if screening with tumor markers becomes common in the medical community.

**Borderline Abnormalities**

Some applicants with abnormal tumor marker results would be postponed until after a medical workup has been completed. Evaluating this workup to determine insurability would be the responsibility of underwriters and medical directors. The process would be similar to what is used for other tests, although the consequences of an incorrect decision might be more severe since cancer is a very serious impairment.

In some instances, it would be difficult to determine what action to take on applications with borderline tumor marker abnormalities. For example, consider the practical underwriting problems that occur if an insurer decides to order a PSA test on all male applicants aged 60-79. Using data from a recent study of PSA in asymptomatic males, the following results could be anticipated if 1000 tests were performed.

<table>
<thead>
<tr>
<th>PSA Value (ng/ml)</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 4.0</td>
<td>883</td>
</tr>
<tr>
<td>4.0-9.9</td>
<td>92</td>
</tr>
<tr>
<td>10.0 or higher</td>
<td>25</td>
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</tbody>
</table>

Markedly abnormal results (10.0 ng/ml or higher) are not an underwriting problem since the likelihood of cancer is high. The real concern lies with the 92 applicants with PSA values of 4.0-9.9 ng/ml. Using a positive predictive value of 24% and an estimation that 41% of the cancers have spread beyond the prostate, 13 people would have localized cancer (Stages A or B), 9 would have cancer that has already extended beyond the prostate (Stages C or D), and 70 would not have cancer. But it would be impossible for the underwriter to assign these 92 applicants to the correct group with the available information. What are the options?

- **Standard?** 22 applicants have prostate cancer (13 localized, 9 extensive).
• Rate, postpone or decline? This would necessitate an adverse underwriting decision in more than 9% (92 per 1000) of applications from males aged 60-79.

• Change the test parameters? Raising the cutpoint for an abnormal test to 6 or 8 ng/ml decreases the magnitude of the problem but will not eliminate all of the uncertainties.

Actuarial Issues

Current underwriting techniques cannot distinguish those people with early malignancies. Actuaries recognize this situation and include the estimated mortality from these cases when pricing the product. What type of pricing adjustments would be needed if many of these applicants with early cancers were identified during the underwriting process?

More favorable mortality would be likely in some cases. People who would have died prematurely from cancer would now be cured or have years added to their lives. The actuarial problem occurs when trying to assess the degree of mortality improvement. Would medical advances in tumor marker technology translate into an improvement in overall mortality? How many of these individuals would have died of other impairments before or after the cancers became clinically apparent?

Statistics reveal the complexity of this situation. Autopsy studies have demonstrated that the incidence of prostate cancer increases from 30% in men in their forties to almost 100% in those over the age of 90 years. However, the cumulative lifetime risk for death due to prostate cancer is only 2.5%. Yet, screening PSA tests would be abnormal in many of the men who would die with prostate cancer, not of it, including many of those in the earliest stages of cancer.

Laboratory Issues

As with all tests, there are quality assurance concerns associated with the collection and delivery of tumor markers and their preparation by the laboratory. The product brochures accompanying most tumor marker kits suggest that specimens be centrifuged immediately to remove the serum from the red blood cells. Serum may then be maintained at 4 degrees centigrade for up to 24 hours but frozen if longer periods of time pass before analysis. It would be difficult, if not impossible, to meet this standard for specimens collected from insurance applicants: hours often pass before centrifugation and days may pass while the specimen is en route to the laboratory.

There are indications that the recommended protocols may not always be absolutely necessary if reasonable care is taken in transporting specimens. Most tumor markers are glycoproteins (combinations of carbohydrate and protein) which are generally very stable molecules. For example, CEA remains stable for periods of time beyond what is recommended in the product literature and there are data indicating that PSA is unaffected when left at room temperature for 4-5 days. Nonetheless, anecdotal reports suggest that tumor marker specimens lose their viability when exposed for several days to the temperature extremes found in desert or tropical regions, a situation that is fairly common in some areas of the world where insurance specimens are mailed to laboratories. This is an area where additional research is needed.

Another concern is variation in test kits. Medical underwriters may find themselves reviewing two very different tumor marker results, one test performed by an insurance laboratory and the other by a clinical laboratory. This task will be complicated by the fact that the results may or may not be comparable if different manufacturer’s kits were used.

Proprietary tests represent a unique dilemma. Innovation is important if improvements in test accuracy are to be achieved. Yet, use of proprietary tests that have not been confirmed by recognized experts in cancer research would raise new concerns. As a practical matter, how would an insurer interpret an abnormal tumor marker if the result could not be confirmed by other established diagnostic tests, especially if there was no reason to suspect cancer from the information provided by the application form, examination or attending physician’s report?

Lack of proficiency testing is a final issue. Numerous programs have been established worldwide to certify that laboratories are reporting accurate test results. This process is known as proficiency testing. An expert reference laboratory sends samples — some normal and some abnormal — to participating laboratories, who perform the specified tests and report back to the reference laboratory. The results are used to document that these laboratories have high quality standards and are able to run the tests accurately.

There is currently very little proficiency testing that specifically addresses a laboratory’s ability to perform tumor marker tests. Where programs have been set up, the conclusions have been disappointing: when a single specimen was sent to different laboratories or re-sent to a single laboratory, the results varied widely among laboratories and even within the same laboratory.
great deal of work remains before the level of confidence in tumor marker testing approaches that of other common laboratory tests.

Evaluating New Tumor Markers

At a time when new serum tumor markers are being described "almost monthly" in the research community, how can an insurer decide if the latest test is or isn't useful for underwriting purposes? Before addressing the specifics of this question, it is helpful to reflect on two historical examples where everything didn't go as expected. These tests share a common denominator: both were initially touted as breakthroughs in early cancer detection. If insurers had chosen to use either of these tests to screen applicants, they may have been subjected to criticism for employing unproven and inaccurate risk selection practices.

The first example involved an earlier test for prostate cancer, prostatic acid phosphatase (PAP). There was tremendous enthusiasm for this test in the early 1970s. This was accompanied by talk of it becoming the "male PAP smear," i.e., it would be ordered on a regular basis in much the same way as the Papanicolaou smear was used to screen women for cervical cancer. Only later was it realized that this test was not appropriate for screening purposes. It lacked adequate sensitivity and specificity.

Carcinoembryonic antigen (CEA) is the second example. Following its discovery in 1965, it was hoped that CEA would be a sensitive and specific marker for the presence of cancer, particularly gastrointestinal cancer. The test was greeted with great fanfare by researchers and the media alike. After the passage of many years, the publication of several thousand journal articles, and two major medical conferences in 1977 and 1980, it was conclusively determined that CEA was a poor cancer screening test.

The following discussion includes some of the major points to consider when evaluating the potential use of tumor marker tests in the underwriting process. Additional background information concerning technology evaluation from an insurer's perspective is available in an editorial that specifically addresses this subject.

Potential for Antiselection

The limited ability to underwrite cancer has proven adequate in the past since the potential for antiselection was low. People generally didn't know about early cancer and therefore couldn't use this information to their advantage when purchasing insurance.

Insurers considering use of tumor markers would be on much firmer ground with consumers, regulators and the medical community if antiselection becomes a realistic concern. For example, the rationale for HIV antibody screening was apparent: the associated morbidity and mortality were very high and the poor claims experience that would result if insurance applicants concealed this information would be unfairly borne by other policyholders. It is likely that this same argument will arise in discussions regarding tumor markers. If tumor marker screening becomes common in the medical community, the risk of antiselection may increase to the point where use of these tests by insurers is widely viewed as a necessary defensive practice. Such a response is especially likely for products that provide living benefits, such as dread disease cover. But for the foreseeable future (with the possible exception of PSA), using tumor markers to screen for cancer in the absence of a realistic potential for antiselection will probably raise this question: "Why are insurers ordering these tests when the mortality due to cancer is already included in their pricing?"

Acceptance by the Medical Community

Medical tests used by insurers to classify risks should be generally accepted by the medical community. This practice is particularly applicable to tests such as tumor markers where attending physicians will be consulted immediately if an abnormality is detected.

The significance of medical acceptance is again exemplified by industry experience with HIV testing. This was a very emotionally-charged issue. Yet, the need for insurers to screen for HIV infection was recognized by both regulators and consumers because such testing was endorsed by the medical community.

Acceptance of a tumor marker by the medical community can take many forms.

Official Acceptance as a Screening Test

An official medical society may endorse a tumor marker for general screening purposes. Such official recognition would be ideal for insurers interested in using the test: physicians would be familiar with the tumor marker and agree that it is a reasonable test for screening purposes. At the present time, the only tumor marker test recommended for population screening in the United States is the prostate-specific antigen test. This endorsement was made by the American Cancer Society, the American Urological Association and the American College of Radiology. These societies recommend annual PSA screening for all men over age 50.
Unofficial Acceptance as a Screening Test

It may become standard practice within a significant segment of the medical community to use a tumor marker to screen for cancer even though the test is not recognized for this purpose by an official medical body. Insurers using a test within this category would find that many physicians would agree that it is a reasonable cancer screening tool. At a minimum, most physicians would be familiar with the test.

Official Acceptance But Not as a Screening Test

A tumor marker may be endorsed by the medical community as an aid to diagnosis or treatment but not recognized as a cancer screening test. Examples include use of CA 125 with ovarian cancer and HCG for choriocarcinoma. Insurers screening with a test in this category would find that most physicians would be familiar with the test but there would be objections to its use as a screen.

Acceptance for Research Purposes

Tests in this category are used primarily in research protocols and are unknown to most practicing physicians. Insurers screening with this type of tumor marker could encounter opposition from the medical community since attending physicians would not know how to interpret the results. As noted during the Forum on Tumor Markers in 1992, "Even if the (tumor marker) abnormality is found as part of an insurance application, an individual must be treated for what may be a devastating or life-threatening disease. ... we must insure that we have not destroyed this individual from a psychological point of view by reporting an abnormal value that cannot be interpreted."13

When does a tumor marker progress from a research tool to a test that is generally accepted by the medical community? According to one expert in this field, it is reasonable to "adopt the FDA philosophy in reviewing a test; that there must be good data from at least three institutions before some conclusion can be reached about its validity. ... Without the additional support for it (or against it, for that matter), it therefore must await a good, properly-controlled trial by people who are, hopefully, not biased, and people who are willing to have their data evaluated by outside groups."13

Positive Predictive Value

The statistical criteria used to characterize an acceptable tumor marker screening test will evolve as new tests are discovered that are suitable for use in an asymptomatic population. The only generally accepted criteria at this time apply to diagnostic rather than screening tests. These were first advocated by Berlin in 197528 and later reaffirmed by Schwartz,19 and recommend that a reasonable diagnostic test should have a sensitivity of .75 and specificity of .95. However, these criteria fall short of what is needed for screening tumor marker tests since they do not include prevalence of disease in the population being tested. As noted in Appendix B, disease prevalence, in addition to sensitivity and specificity, is critical in determining the predictive value of a test.

Disease Severity

The target disease for a test should have a significant impact upon mortality so that a truly positive result requires a rating or declination. Although tumor markers would at first glance appear to satisfy this criterion, certain tests, including the prostate-specific antigen, will be problematic. As noted earlier, many elderly men have prostate cancer but only a minority will die from this cause.

Rate of Return

A new test must be cost-effective: the financial benefits of the test must significantly outweigh its costs. In assessing this parameter, there are a number of items to consider in addition to direct laboratory costs.

First, is it possible to obtain equivalent information from another less expensive test or source that already exists? If it is, this would prevent the needless adoption of a new technology simply because it is new. Secondly, are there hidden administrative costs? Tumor marker tests are complex. There are false positives, varying degrees of abnormal, and extenuating medical and historical circumstances. Medical directors and underwriters would need to spend more time underwriting these cases and corresponding with applicants and attending physicians. Finally, intangible costs must be weighed as well. False positive results are bad for customer relations and lead to the loss of good business. Even true positive tests (abnormal tests in applicants with cancer) can be a dilemma if many or most of the applicants will die from some other cause.

Sensitivity to Regulatory Issues

Regulatory groups are displaying greater interest in controlling laboratory testing. In the United States, the Food and Drug Administration (FDA) is taking a more aggressive stance in evaluating medical devices, diagnostic tests, equipment, and laboratory reagents in an
effort to protect the public. Tumor markers are included in their most stringent regulatory class, requiring large clinical trials similar to those used during the evaluation of new drugs, prior to allowing them on the market. As an example of this increased emphasis on safety and effectiveness, the FDA took the unusual step in 1991 of issuing a "cease and desist" order against a large biotechnology company who was marketing two tumor markers (CA 15-3 and CA 19-9) without FDA approval. More recently, the FDA issued a draft Compliance Policy Guide in an attempt to tightly regulate laboratory testing procedures. This trend serves as an indication of the likely resistance that insurers would face if they decided to use tumor marker tests that hadn't been studied to the extent mandated by regulatory authorities.

Conclusion

Proportionate cancer mortality has increased in the latter half of this century. Insurers have recognized this pattern and a few are investigating use of tumor markers to screen for cancer in applicants.

While the idea of improving mortality results via tumor marker screening may seem appealing to insurance companies, there will be significant issues that must be addressed. Among the most important are pre-notice and informed consent, post-test notification, borderline abnormalities, ability of the tests to predict excess morbidity and mortality, lack of proficiency testing, potential for antiselection, acceptance by regulatory authorities and the medical community, and effects on the image of the insurance industry.

Because of the nature of these issues, companies considering tumor marker screening are advised to proceed cautiously.
APPENDIX A: PROPORTIONATE CANCER MORTALITY

(Figures 1-4 and Tables 3 and 4 were modified from a report by Sutherl, et al. entitled "Proportionate Mortality Trends: 1950 through 1986," with permission of the American Medical Association.)

Trends in cancer mortality are most apparent when viewed over long periods of time. In a study dealing with proportionate mortality trends in the United States from 1950 through 1986, the six leading causes of death were analyzed: heart disease, cancer, cerebrovascular diseases, injuries, chronic obstructive lung disease (COPD), and pneumonia and influenza. Mortality from perinatal conditions was also studied since these disorders had been among the six leading conditions prior to 1970.

This study identified the following patterns in proportionate mortality:

<table>
<thead>
<tr>
<th>Increasing</th>
<th>Decreasing</th>
<th>Stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Cerebrovascular</td>
<td>Heart diseases</td>
</tr>
<tr>
<td>COPD</td>
<td>Injuries</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Perinatal</td>
<td>Influenza</td>
</tr>
</tbody>
</table>

During the last four decades, heart disease as a proportion of total mortality has stayed approximately the same, although age-specific and age-adjusted mortality rates from ischemic heart diseases have declined steadily since 1968 (Fig 1). This pattern can be explained by the fact that more people live to age 85 years, more die after age 85 (17% of total mortality in 1986 compared to 8% in 1950), and almost 50% of total deaths among those 85 or older are due to heart disease. Thus, when deaths from all age groups are combined, heart disease continues to account for approximately 37% of total mortality in the United States.

Cancer mortality accounts for an increasing proportion of deaths even though little has changed in overall age-adjusted cancer mortality rates (Fig 2). Cancer is now the leading cause of death in those aged 35 to 64 years and, if present trends continue, it could overtake heart disease among those aged 65 to 74 years. Much of this increase in proportionate cancer mortality can be attributed to the threefold increase in mortality due to respiratory cancer. Among those age 85 years and older, however, cancer accounts for only 10.5% of total deaths.

Heart disease and cancer accounted for the largest proportion of total mortality from 1950 to 1986. The proportionate mortality relationships between these two disease are shown in Fig 3a-g. There are increases in the percent of deaths due to cancer at all ages and decreases in proportionate heart disease mortality in all age groups except for those aged 85 years and older. Among those aged 85 years or older -- the fastest growing segment of the population in the U.S. and many other countries -- heart disease accounted for just under 50% of all deaths compared to approximately 11% for cancer.
The other five conditions in this study contributed much less to total mortality but cumulatively explain some of the proportionate changes in heart disease and cancer (Fig 4). Cerebrovascular mortality, the third leading cause of death, decreased dramatically due to increased and more effective treatment of hypertension. Injuries decreased as a cause of proportionate mortality but still rank fourth on the overall list and number one among individuals aged 1 through 34. Chronic obstructive pulmonary disease (COPD), now the fifth leading cause of death, continues to increase because of earlier smoking patterns. Sixth on the list are pneumonia and influenza (identified in Fig 4 as "P&I"), stable but particularly important causes of death in the elderly. And mortality due to perinatal conditions has dropped from fifth to fourteenth place because of improvements in infant mortality.
This study noted that proportionate mortality can be divided into four major age groups. Although overly simplified, such a listing highlights the importance of examining age-specific mortality rates and trends when considering underwriting requirements.

### Table 4

<table>
<thead>
<tr>
<th>Age</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 1 year</td>
<td>Perinatal conditions</td>
</tr>
<tr>
<td>1 through 34 years</td>
<td>Injuries</td>
</tr>
<tr>
<td>35 through 64 years</td>
<td>Cancer</td>
</tr>
<tr>
<td>65 and older</td>
<td>Heart diseases</td>
</tr>
</tbody>
</table>
New tumor markers are constantly being identified. Most never progress beyond the developmental stages because subsequent studies fail to confirm the accuracy or validity of the test. Of those that do survive to reach the clinical world, stringent standards must be met before the test is widely accepted. These standards involve an acceptable test sensitivity, specificity and predictive value.

The following discussion concerns prostate-specific antigen (PSA). This brief overview serves both as a review of basic statistical principles and as an indication of the detailed analysis that would be needed in order to assess the potential value of a tumor marker for risk classification purposes.

In this theoretical example, 100,000 men will be screened for prostate cancer with the PSA test. It will be assumed that 10% (.10) of them have prostate cancer. The entire group is thus categorized into 10,000 men (100,000x.10) with cancer and 90,000 (100,000-10,000) without cancer.

**Sensitivity**

When discussing tumor markers, test sensitivity refers to the ability of a test to detect cancer in those who have the disease. Mathematically, it is determined by the dividing the number of people with cancer who have a positive test by the total number of people with cancer.

\[
\text{Sensitivity} = \frac{\text{Number of people with cancer with a positive test}}{\text{Total number of people with cancer}}
\]

For example, if the PSA is abnormal in 6,500 of the 10,000 men with prostate cancer, the test sensitivity is .65 (6,500/10,000). This means that the test can detect 65% of those with cancer but misses the others.

**Specificity**

The specificity of a tumor marker is its ability to identify those who do not have cancer. It is determined by dividing the number of people without cancer who have a negative test by the total number of people without cancer.

\[
\text{Specificity} = \frac{\text{Number of people without cancer with a negative test}}{\text{Total number of people without cancer}}
\]

If the PSA is normal in 72,000 of the 90,000 men who do not have prostate cancer, the specificity is .80 (72,000/90,000). In 18,000 men (90,000-72,000), the PSA is abnormal but cancer is not present.

**Positive Predictive Value**

Men with a positive PSA test can be divided into two groups: (1) true positives- the PSA is abnormal and prostate cancer is present, and (2) false positives- the PSA is abnormal but prostate cancer is not present. The relationship between true and false positives is expressed by the positive predictive value.

\[
\text{Positive predictive value} = \frac{\text{True positives}}{\text{True positives} + \text{false positives}}
\]

The positive predictive value is of great importance for all screening tests, particularly those designed to detect cancer. It provides an estimate of how often a positive test truly identifies the presence of cancer. In the example above, the PSA would be elevated in 6,500 men with prostate cancer (true positives) and 18,000 men without prostate cancer (false positives). The positive predictive value is .27 [6,500/(6,500+18,000)]. This means that only 27% of positive PSA tests indicate prostate cancer. The other 73% would not have cancer even though the test was positive. The problem is that these two groups cannot be differentiated without clinical examination, often involving prostatic ultrasound and biopsy.

**Cutpoints**

Choosing acceptable cutpoints is an important decision when using tumor marker tests to screen for cancer. This is because test sensitivity, specificity and positive predictive value vary dramatically depending on the definition of a normal or abnormal test. For example, PSA values greater than 4.0 ng/ml (nanograms per milliliter) are generally considered abnormal. This is the cutpoint used in the calculations above. Using this cutpoint, only 27% of those with an abnormal test actually have prostate cancer; a positive predictive value that is far too low for screening purposes.
To remedy this situation, the definition for "abnormal" is often raised to 10 ng/ml. When using 10 rather than 4, 4,100 of the 10,000 men with cancer are detected, yielding a new test sensitivity of .41 (4,100/10,000). When using 4,100 rather than 4,100 of the 90,000 normal men are correctly identified as not having cancer, giving a new specificity of .98 (88,200/90,000). This means that 1,800 men (90,000-88,200) have a positive test but do not have cancer. The positive predictive value increases to .69 (4,100/(4,100+1,800)). Changing the definition of an abnormal test has increased specificity and positive predictive value but decreased sensitivity. More people with prostate cancer are missed but those with a positive test are more likely to have cancer.

Prevalence

Prevalence refers to the number of people who have cancer. Estimating prevalence in the population to be screened is crucial when evaluating the potential worth of a tumor marker test since the positive predictive value varies greatly depending on prevalence.

In the earlier illustrations, the assumption was that 10% of those being screened had prostate cancer. Using a cutpoint of 10 ng/ml, sensitivity of .41, and specificity of .98, the following positive predictive values would theoretically occur when using PSA to screen asymptomatic males with varying prevalences of cancer:

<table>
<thead>
<tr>
<th>Age</th>
<th>Disease Prevalence</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>1^21</td>
<td>17</td>
</tr>
<tr>
<td>50-59</td>
<td>10</td>
<td>69</td>
</tr>
<tr>
<td>80-89</td>
<td>80^22</td>
<td>99</td>
</tr>
</tbody>
</table>

It is apparent that there are problems at the extremes of prevalence. In the very young, only 17% of those with a PSA greater than 10 ng/ml will have cancer. Screening this group identifies far more people without cancer than with it. And in very elderly men, 99% of those with a PSA greater than 10 ng/ml will have cancer. This seems very advantageous at first glance. Yet, identifying all of these men poses a real dilemma since the natural history of this disease is for the great majority of these cancers to remain undetected and clinically unimportant for decades.

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References