The following information was prepared and distributed as a handout at the ACLI Medical Section's June 12, 1993, Tumor Marker Committee meeting in Boca Raton, Florida. The information was subsequently published in the September/October 1993 issue of Lincoln National Reinsurance Medical Resource (R) and is reprinted here with permission from Lincoln National Life Reinsurance Company. (Copyright 1993 Lincoln National Life Reinsurance Company. All rights reserved.)

1. The National Center for Health Statistics reports an "alarming increase" in the incidence of prostate cancer since 1980. The detection of prostate cancer increases by about 3 percent per year. Mortality from prostate cancer increased 1 percent per year (or 16 percent in total) from 1973 to 1989.

2. Adenocarcinoma of the prostate gland is now the most common male cancer. Thirty percent of all men over 50 — or about 9 million people — have prostate cancer. The good news, if any, is that only 2 percent (or 165,000) of these men with cancer are diagnosed as having clinical disease every year. That means that most prostate cancer is latent and relatively insignificant.

Even so, 35,000 patients will die from metastatic prostate cancer this year. Nearly a quarter of men with latent prostate cancer will eventually develop clinically evident disease, and 30 percent of these will die of it.

3. For men, prostate cancer is second only to deaths from lung cancer. Twenty percent of all male cancer deaths are due to prostate cancer.

4. Prostate cancer almost always affects men over age 50 rather than younger men. There are 28 million men in America above age 50. Prostate cancer increases faster with age than any other major cancer. And this fact, coupled with the aging of our population, means that the incidence of prostate cancer will continue to increase substantially.

5. The incidence of prostate cancer doubles each decade. Ten percent of men in their 50s have the disease. This figure jumps to 20 percent for those in their 60s and 40 percent for men in their 70s. Seventy percent of men in their 80s have the disease. Prevalence of prostate cancer increases 40-fold from ages 50 to 85. One percent of all prostate cancer occurs before age 50. Sixteen percent occurs among men ages 50-64.

6. Three special characteristics of prostate cancer are high prevalence, slow growth and size of the occult lesion (tumor volume is a strong predictor of clinical outcome). A fourth distinguishing characteristic probably deserves identification, which is the extraordinary uncertainty and controversy that exists as to how best to treat those with apparent, localized Stage A or B disease.

Of those 165,000 Americans who are diagnosed this year as having prostate cancer, 60 percent will be judged initially to have localized (organ-confined) disease. Half of these men will later be found to have more extensive Stage C or D, and thus incurable, disease.

7. Prostate cancer has a long doubling time, meaning it is slow-growing. As judged by prostate-specific antigen (PSA) levels, the doubling time of Stage A and Stage B lesions is two years. A long doubling time presents the opportunity to detect prostate cancer while it is still localized and, thus, treatable and curable.

On the other hand, a long doubling time might prompt the elderly individual with a limited life...
expectancy to decide that potential side effects of radiation or prostatectomy outweigh the possible benefits of curative therapy. Indeed, there are reports, including one published in the May 26, 1993 issue of The Journal of the American Medical Association, suggesting that, for many men with localized carcinoma, the choice of "watchful waiting" is a reasonable alternative to invasive treatment.

8. The five-year survival for prostate cancer (all stages, all ages) is 76 percent. Whereas Stage B disease carries a better prognosis than Stage C disease, as one would expect, it's helpful to keep in mind that there is significant extra mortality for Stage B disease beyond five years. Also, those with Stage C disease may well experience disease-free survival for 15 years or longer.

9. Tumor volume correlates highly with metastatic potential and, thus, with clinical significance. As a general statement, a tumor must have a volume of at least 0.5 ml to be significant. Eighty percent of prostate cancer is less than 0.5 ml. The majority of men with prostate cancer have microscopic disease that has a low probability of ever causing clinical problems.

10. PSA correlates with tumor volume, each gram of prostate cancer "leaking" PSA into the blood stream and raising serum PSA by 3.5 ng/ml. Unfortunately, this correlation is imperfect. Hyperplastic prostate tissue, i.e., the type of tissue men with benign prostatic hyperplasia (BPH) have, also raises PSA levels, although to a lesser extent (0.3 ng/ml/gm). Epithelial hyperplasia leaks more PSA than stromal hyperplasia. Prostatitis is common, and it, too, elevates PSA. Then there is the fact that high-grade (poorly differentiated) cancers produce less - and sometimes no - PSA.

11. Grading of tumors reflects the pathologist's effort to predict tumor behavior. Tumor grade, as determined by microscopic (histologic) analysis of the lesion, correlates well with progression potential just as tumor volume does. The Gleason grading system is most often used. Gleason scores of 2-4 reflect low-grade lesions. Scores of 5-7 reflect moderate differentiation; 8-10 denotes poorly differentiated lesions.

12. There are two staging systems: the conventional ("ABCD") system and the tumor, nodes, metastasis ("TNM") system. As a footnote, men with an elevated PSA but a normal digital rectal exam (DRE) are classified "BO" by the former system and "T1c" by the latter.

13. An estimated 90 percent of all primary-care physicians now routinely use PSA to screen their male patients – up from 60 percent just last year.

14. The normal range for PSA is 0-4 ng/ml. Approximately 8 percent of all males over age 50 have "low titer" PSAs between 4.1 and 9.9; 2 percent have a PSA 10.0 ng/ml or higher.

15. Because PSA correlates with prostate cancer and benign prostatic hypertrophy (BPH), both of which increase with age, the percentage of those men with elevated PSAs increases with age. Here is a comparative analysis of age groups 50-54 and 70-74.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Above 4.0</th>
<th>Above 10.0</th>
<th>Above 20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 50-54</td>
<td>3.3%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>70-74</td>
<td>24.5</td>
<td>6.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

16. When groups of men are studied, PSA correlates with the stage of prostate cancer. However, for any individual, the PSA level is a relatively poor predictor of pathologic stage.

17. A study by Dr. William Catalona showed that about a quarter (26 percent) of the 8 percent of men with PSAs between 4 and 10 have biopsy-proven prostate cancer; about a quarter of these (27 percent) have prostate cancer that has extended beyond the gland, meaning Stage C or D disease. By multiplying 8.0 percent by 0.26 and then 0.27, one calculates that approximately one-half of 1 percent (or one in every 200 men over age 50) have a PSA between 4 and 10 and advanced prostate cancer.

18. Catalona's study also revealed that nearly 60 percent of the 2 percent with PSA of 10.0 or higher had prostate cancer, and that 52 percent of these men had Stage C or D disease.

19. Items 17 and 18 demonstrate that of the 1.18 percent of males over age 50 who have a PSA above 4.0 and advanced disease, about half of these men (0.56 percent) have low titer (4.1-9.9) PSAs.

20. Twenty-five percent to 45 percent of those with localized prostate cancer have a PSA that falls within the normal range (4.0 or less).
Twenty percent to 50 percent of men with benign prostatic hypertrophy generally have modest PSA elevations. Occasionally, BPH can cause markedly elevated PSA titers. Sustained PSA levels of 100 or more were documented in men who almost certainly did not have prostate cancer.

Many are concerned that increased use of PSA and other screening methodologies will simply increase the number of those people with clinically insignificant disease, thus subjecting men to unnecessary surgical morbidity and mortality. Radical surgery causes incontinence about 30 percent of the time and sexual impotence in 90 percent of cases. Heart and other complications can occur as well. The fear is that in older men—those over age 65—the benefits of treatment of disease assumed to be localized are not much greater than the resultant harms.

Screening opponents point out that we do not have survival data acquired in randomized, controlled studies over a long period of time,* and so we cannot confidently advocate screening asymptomatic populations for prostate cancer. Because of this lack of supporting data, there is little or no support for screening in countries like Canada, Sweden and France.

A couple of statistical phenomena add to uncertainty of the value of population PSA screening. One is called "length-time bias," where screening tends to identify those with the slowest-growing, most indolent, and, so, least clinically significant lesions. The other is "lead-time bias," where detection of those with prostate cancer at an earlier point in the natural history of their disease merely gives the appearance of extending longevity, when in reality the course of disease is inescapable.

The almost certain enormous cost of screening is of great concern. A recent Wall Street Journal article stated that the total estimated cost of mass PSA screening is $28 billion a year in this country alone. Aside from the test itself, related costs include biopsies, ultrasound tests, repeat biopsies, treatment and complications from treatment.

Screening proponents counter concerns of overdiagnosis by saying that the ability of PSA, DRE and TRUS to detect low-volume or latent cancer is limited by the low sensitivities of these tests. PSA and DRE screening detect only a small fraction of truly occult (microscopically focal and well-differentiated) prostate cancer. This seems plausible, given the high prevalence of clinically insignificant disease known to exist at mature ages—and the fact that most of these people are not being diagnosed as having prostate cancer.

Some people believe that because the ability of these tests to detect cancer begins at tumor volumes of about 0.5 ml, all detected cancers should be considered clinically important. Even if we assume that most cancers detected via screening are clinically significant, i.e., life-threatening, there is still doubt as to whether early, aggressive therapy will lead to improved survival. If not, then screening may not be cost-justifiable clinically, whereas it would be from the insurer’s viewpoint.

Catalona believes the key in screening is detecting people with prostate cancer before their PSA reaches 10.0. These are men who may still have localized disease—but disease that could certainly progress to incurable stages within three years.

Despite uncertainties about screening, the American Cancer Society advocates a routine, yearly DRE for all males ages 40 and over, coupled with a yearly PSA beginning at age 50 (age 40 for African-Americans or those with a positive family history of prostate cancer).

The Mayo Clinic uses the following screening algorithm:

<table>
<thead>
<tr>
<th>DRE</th>
<th>PSA</th>
<th>TRUS</th>
<th>PSAD**</th>
<th>Biopsy (bx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>normal</td>
<td></td>
<td></td>
<td>Return for annual exams</td>
</tr>
<tr>
<td>normal</td>
<td>4-10</td>
<td>+</td>
<td></td>
<td>TRUS guided bx</td>
</tr>
<tr>
<td>normal</td>
<td>10 up</td>
<td>+</td>
<td></td>
<td>Sextant bx</td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td>+</td>
<td></td>
<td>TRUS guided bx</td>
</tr>
</tbody>
</table>

** "PSA Density" is derived by dividing a person’s PSA by the estimated volume of that person’s prostate gland as determined by TRUS measurements; if the [PSAD] quotient is above 0.15, it is then considered abnormal or positive.

* Long-term studies have been initiated. The National Prostate Cancer Detection Project of the American Cancer Society is a prospective study to determine the feasibility of early prostate cancer detection by DRE, TRUS (transrectal ultrasound) and PSA. The National Cancer Institute is funding a 15-year prospective, randomized clinical trial to determine the value of prostate cancer screening. Called the PLCO Trial (prostate, lung, colorectal and ovarian cancer), the study will...
30. Were it not for the overlap of benign and malignant populations at PSA levels of 4-10, the PSA test would be an undebatably valuable screening test. Unfortunately, PSA cannot distinguish between those with BPH and those with stages A and B cancer. One study showed a mean PSA of 5.92 for the BPH population and 5.61 for those with clinically localized prostate cancer.

31. Two factors help distinguish those men with cancer who have normal or borderline abnormal PSA titers. One is the PSA density (see Item 29). The M.C. Benson study showed that those with a PSA of 4-10 who had a normal DRE and TRUS but whose PSAD was above 0.15 had a 15 percent chance that a biopsy would reveal cancer. Men with stages A and B cancer had an average PSAD of 0.581 vs. 0.044 for the BPH group.

The second determinant is the rate of change of PSA over time. As shown in H.B. Carter’s study, increases of 0.75 ng/ml or more per year have a 90 percent specificity for prostate cancer. This applies, even if the latest PSA is still below 4.0 ng/ml, making this determination a unique clue to the possible existence of early but clinically significant disease.

32. PSA presents insurers with a big dilemma. With PSA screening of males over age 50 rapidly becoming a standard of medical practice in this country, many men will discover in the next few years that their PSA is considerably elevated and that they are at high risk of having life-threatening prostate cancer.

Worst fears may be realized; the initial elevated PSA may lead to confirmation that they do, indeed, have advanced prostate cancer. Stripped of their insurability, most of these men will see no option but to dismiss whatever desires they might have to apply for additional life insurance. On the other hand, some will buy more life insurance. How? By antiselecting. By concealing their abnormal PSA and any other significant medical history that exists.

33. What antiselection potential does PSA present? Any scenario presented here will be faulted. Readers are encouraged to take the following information and derive what they believe to be a reasonable estimate of what insurers might expect:

- Twenty-eight million men in the USA are age 50 and older (much of the life insurance sold in this country is sold to this subset of our population).
- Annual PSA screening for men age 50 and older is fast becoming a standard of medical practice.
- Ten percent of those men screened will discover that their PSA is abnormal.
- More than 1 percent of those men who are screened will be discovered to have advanced, incurable prostate cancer. An even larger number will have localized disease that most insurers regard as uninsurable for at least a few years following curative treatment.

Based on the above, most insurers will presumably calculate a potential antiselection hit that could reach into the hundreds of millions of dollars.

34. To which insurers will the antiselectors apply? Those who wish to apply for a sizeable amount of insurance will, presumably, avoid companies that have initiated a PSA screening program and take their business to those that have no such program.

35. Can insurers rely on the attending physician’s statement (APS) to protect them from antiselection? In other words, will those who elect to antiselect mention the doctor who did the prior testing and/or who made the diagnosis of prostate cancer? Most will not. Directed questions on Part 2 of the application are also unlikely to be protective.

36. Will the two-year contestability period offer protection? Even those who discover they have advanced-stage cancer will probably live for several more years, meaning that the contestability period will rarely protect the insurer.

37. Given the clinicians’ rush to use the test in this country, increased use of PSA by insurers comes as no surprise. The number of insurers that routinely do age/amount PSA screening is growing rapidly. Well over 100 companies now screen with PSA, including some of the larger companies. Most confine their testing to males ages 50 and over. Threshold amounts are highly variable.

38. Relatively speaking, PSA is an expensive test, costing at least $10, if not more. The price of reagents is high, even when the test is done in large quantity.

39. Part of the PSA dilemma for insurers is that the need for this costly test comes at the very time that insurers are looking for ways to control – or even reduce – underwriting expenses. Some are hoping that they can someday move away from blood testing allo-
gether. The thought of becoming dependent on PSA testing is unsettling to almost everyone.

40. Another aspect of the PSA dilemma deals with the FDA and timing. For starters, the FDA has approved PSA, but not as a screening test. Even so, it's likely that the FDA will approve PSA for this purpose, given that virtually all of America is now using PSA.

41. No one, including the American Cancer Society, advocates the use of PSA as a stand-alone screening test. PSA should be used with the DRE. Actually, this should not pose a problem for insurers, in that the PSA test done by the insurer legitimately can be regarded as step one of a two-step procedure. Insurers can inform the proposed insured what his PSA was and then strongly encourage that he see his doctor for a DRE. If the PSA is abnormal, especially if it's high enough to cause an adverse underwriting action, the insurer's medical director can try to communicate with the proposed insured's attending physician.

42. Some in our industry fear that the insurer's use of PSA now could be the "straw that breaks the camel's back." We had the urine HIV situation, which alienated the FDA. So did saliva HIV testing. TAA created negative publicity. Any problems that result from wide-scale PSA testing in our industry (and there are certain to be some) could have a more damaging effect than one might otherwise expect, given a more tranquil environment.

43. What kinds of problems might we anticipate? One is counseling and the effectiveness (or lack of such) of our efforts to communicate with the proposed insured both before and after the PSA test is done. Before the test, insurers must let the proposed insured know that he is to have a test for prostate cancer and warn him as to what will happen if results are abnormal. After the test, insurers should communicate not only abnormal results, but also normal results. If done well, post-test disclosure of normal and abnormal results can build strong and positive relationships with the client and his agent. If done poorly, or not at all, potential problems abound.

44. Can the insurer's dilemma with PSA be resolved through future advancements in technology? Possibly. There is talk of developing a far more specific PSA test for prostate cancer. The May/June 1993 issue of the American Cancer Society's CA journal focused on the costs and benefits of prostate-cancer screening. The author concludes that recent studies suggest that PSA elevations produced by BPH may be fractionated and differentiated from elevations produced by cancer. If this research results in identifying PSA isomers specific for prostate cancer, then the entire game and playing field of this whole issue will change dramatically.