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CLINICAL APPLICATIONS OF TUMOR MARKERS

Susan E. Bates, MD

DR. SCHWARTZ: This morning we discussed the past, the present and the future. This afternoon, we're going to get into what someone said is the nitty-gritty of tumor markers; how they're being used in the real world. The first presentation is entitled "The Clinical Applications of Tumor Markers" which will be delivered by Dr. Susan Bates. Those of you who read *Annals of Internal Medicine* may have noticed her review article on tumor markers, which appeared a number of months ago. I consider it among the best that has ever been written, even though I've written a few myself. I would recommend it to you all. Dr. Bates is at the National Cancer Institute, and she has long-standing interest in tumor markers which originated with her research studies of transforming growth factor alpha as a tumor marker, and has also studied multidrug resistance of P glycoprotein. I would like to introduce Dr. Susan Bates.

DR. BATES: Thank you for this opportunity to share some of my biases and to convince you of a few of them. I do come at this from a different perspective from most people, not really being in the tumor marker business, but instead being an oncologist who does basic science. As I was listening this morning I was thinking that actually we're not putting the question correctly for you all, because you in the science industry have a different question from that of clinical oncology. You don't really need a tumor marker with exquisite sensitivity, and a long, long lead time. It seems to me that the insurance industry may prefer a tumor marker that has a short lead time, but that is exquisitely specific. It seems to me that you must be somewhat less worried about sensitivity. You can think about how your viewpoint of this might contrast with the clinical viewpoint, where you really want to know when the tiniest amount of cancer is present, so that you can institute therapy aimed toward cure.

(SLIDE)
Clinical Value of Serum Tumor Markers*

Marker	Clinical Setting
Proven Value	
AFP	Screening, diagnosis, prognosis, monitoring therapeutic response, detecting relapse
HCG	Diagnosis, prognosis, monitoring therapeutic response, detecting relapse
LDH	Monitoring therapeutic response, detecting relapse
CEA	Detecting relapse
PAP	Monitoring therapeutic response
PSA	Prognosis, monitoring therapeutic response, detecting relapse
CA125	Diagnosis, monitoring therapeutic response, detecting relapse
Probable value	
CA15-3	Monitoring therapeutic response
CA19-9	Diagnosis, prognosis, monitoring therapeutic response, detecting relapse
NSE	Monitoring therapeutic response
Possible value	
MCA	
MAM-6	
MSA	
TAG72.4	
CA50	

* AFP=alpha-fetoprotein; HCG=human chorionic gonadotropin; LDH=lactate dehydrogenase; CEA=carcinoembryonic antigen; PAP=prostatic acid phosphatase; PSA=prostate-specific antigen; NSE=neuron-specific enolase; MCA=mucinous-like carcinoma-associated antigen; MSA=mammary serum antigen; TAG=tumor-associated glycoprotein; MAM-6=epithelial membrane antigen. (*Ann Intern Med* 1991, 115: 623)

This is a classification of tumor markers. Tumor markers come from a variety of sources. As was mentioned earlier, a lot of them serve as antigens, the true function of which is unknown. Some of them are enzymes, which are secreted by the cancer in increased quantities as it's deregulated away from the normal state. Others are hormones that are produced both by the normal cell and

by its malignant counterpart. Others are proteins which are typically found in the fetus or placenta, but then are, again, deregulated as the cancer becomes abnormal and is no longer under normal genetic regulatory controls.

(SLIDE)
Tumor Marker Value

Screening
Diagnosis
- How good is the test?
- What is the likelihood of the disease?

Predicting Prognosis
Monitoring Therapy
Detection of Relapse
- How good is the therapy?

This slide shows the potential roles for tumor markers: screening, diagnosis, prognosis, monitoring therapy, and detecting recurrence of cancer after the person has had supposedly curative treatment. The roles which a marker plays in clinical oncology is influenced by its sensitivity and specificity.

(SLIDE)
Bayes' Theorem and Definitions of Terms

$$\text{Sensitivity (S)} = \frac{\text{number of patients with cancer who have a positive test}}{\text{number of patients with cancer}}$$

$$\text{Specificity (Sp)} = \frac{\text{number of patients without cancer who have a negative test}}{\text{number of patients without cancer}}$$

Prevalence (P) = incidence of disease in the population studied

$$\text{Positive predictive value} = \frac{(S) \times (P)}{(S)(P) + (1 - Sp)(1-P)}$$

Bayes' Theorem expresses the utility of a tumor marker. Sensitivity: Among people who have cancer, how many have a positive test? Specificity: Among people who don't have cancer, how many have a negative test? Prevalence: What is the frequency of disease in the population being studied? Positive predictive value: How accurate is the positive test?

(SLIDE)
Influence of Specificity on PV_{pos}

$$\frac{(S)(P)}{(S)(P) + (1-Sp)(1-P)}$$

Assume:

Prevalence, P = 0.1 (1 in 10 patients has disease)

Sensitivity, S = 0.7 (70% tests positive in pts with disease)

Then, for a given Specificity (Sp), the positive predictive value is:

Sp	PV_{pos}
98%	.80
95%	.61
90%	.43
80%	.28
70%	.20
60%	.16

This morning you saw a table showing the influence of prevalence on the positive predictive value. This is the influence of specificity on the positive predictive value. If you assume a prevalence of 1 in 10, or 10%, and a sensitivity of 70%, you can calculate the positive predictive value for various apecificities as shown here. The specificity will directly relate to how good the test will be. As the specificity drops, and you have more false positives, the predictive value of that positive test will also decrease. Using an increasing cutoff level to decide what your positive test is will result in a decreasing sensitivity and an increasing specificity. Some people plot this as a receiver operating characteristic curve, which shows directly that at a given cutoff for any test, you will have a decrease in specificity with an increase in sensitivity, and vice versa. This is true for any tumor marker. In a good test you want few false positives, less than 10%, at a relatively high sensitivity.

(SLIDE)
Predictive Value as a Function of Disease Prevalence (For a Laboratory Test with 95 Percent Sensitivity and 95 Percent Specificity)

Prevalence of Disease Percent	Predictive Value Percent
1	16.1
2	27.9
5	50.0
10	67.9
15	77.0
20	82.6
25	86.4
50	95.0

This is the same table you saw this morning, and it shows that the higher the prevalence of disease, the more likely is a positive test to indicate cancer.

The prevalence is key to interpreting some studies in the literature For example, one study concluded that CA19-9 had good diagnostic accuracy to detect patients with cancer, especially of GI origin. (*Tumor* 1986; 72:621.) The positive predictive value was 75%, the best positive predictive value of any test I've seen. Then you begin to look, how did they determine their predictive value? The author gathered 50 patients with GI cancer, 50 patients with benign disease, and 50 with non-GI benign disease, and thus defined the prevalence as 33% in this population. So, if you choose to study your tumor marker in a population with a high prevalence of cancer, then you can make a tumor marker look as good as you want it to. This is really an unfair use of the predictive value, because the investigator defined the prevalence in this study.

Those are issues that have to do with how good the test is, but of equal importance is how good the therapy is. For the clinician, both of these stand equally. If there is not good therapy for the disease, you can argue a case not to have a tumor marker for it. For hepatocellular carcinoma (HCC) this is critical, because, if your tumor marker can't detect an HCC which can be resected, then you've got no therapy for the disease whatsoever. So the question is not, "Can we detect hepatocellular carcinoma?," but, "Can we detect resectable hepatocellular carcinoma?" The same is true for cancers in which medical therapy is to be used. If you look at patients who have metastatic prostate cancer, PSA would be of no value whatsoever, if there were no decent medical therapy for prostate cancer. But, if you can find a drug or a hormonal treatment to which tumors respond, you can show a dramatic decrease in PSA. So the value of the marker really depends on the quality of the test and the quality of the therapy.

The prevalence of the disease affects the use of the tumor marker in screening or in diagnosis, and the available therapy affects its use in prognosis, monitoring therapy or in detection of relapse. The question we have in screening is, "Can the cancer test find the disease in an unselected population at a stage which is early enough to make a difference? Further, will the cost and suffering induced by the inherent false positive rate be outweighed by the benefit?" The principal problem with screening for any cancer is that the tumor markers are not secreted in an early stage of the cancer.

(SLIDE)
Marker Elevation in Early Stage Cancer

Malignancy	Stage	Marker	Sensitivity
Colon cancer	A	CEA	28%
Breast cancer	I/II	CEA	15%
Breast cancer	I/II	CA15-3	21%
Gastric cancer	localized	CEA	14-29%
Testicular cancer	I	AFP & HCG	18%
Prostate cancer	A	PAP	24%
Prostate cancer	A	PSA	50-70%

This is a list of early stages of various cancers and the marker that has been evaluated. You can see that for CEA in Stage A colon cancer, the sensitivity is only 28%. For early stage breast cancer, 15%. For gastric cancer it's very low. Testicular cancer, in which AFP and HCG make a superb marker combination, the sensitive is 18%. For prostate cancer, it appears that in Stage A there is a higher incidence of PSA, yeilding hope that screening may be of value in this cancer.

(SLIDE)
Value of CEA in Screening for Cancer

2372 registered voters over the age of 40 in Brusselton, Australia

CEA-related cancers	9 of 73 (13%) with raised CEA
	25 of 2299 (1%) with normal CEA levels
	9 of 24 (26%) with cancer had high CEA

Sensitivity = 26%
Specificity = 95%
Prevalence = .014

$$PV_{pos} = \frac{(.26)(.014)}{(.26)(.014)+(1-.95)(1-.014)} = .068$$

Each positive test would be correct 6.8% of the time; 74% of cancers would be missed.

(*Aust NZ J Med* 1976; 6:279.)

That CEA cannot be used in screening was laid to rest really quite a long time ago. But just to run through this one study with you, as an example, here are 2000 registered voters in Australia. They found CEA related cancers in 13% of those who had a raised CEA. They also found 25 cancers in patients who had normal CEA levels. Nine of 34 patients with cancer had a high CEA. If you calculate the sensitivity and the specificity, and the resulting positive predictive value would show that there was a 6.8% positive predictive value, so that each positive test would be correct 6.8% of the time, and would be wrong, therefore, 93% of the time. You would also be missing 3/4ths of all the cancers.

In Dr. Catalona's study using PSA as a screening test for prostate cancer, 1,653 healthy men were evaluated and a control group of 300 symptomatic men were also evaluated. (*N Engl J Med* 1991; 324: 1156.) Two PSA values were drawn. If the results were over 4, then they were categorized into a group under 10 and a group over 10. If the repeat level was under 10 and the examination was normal, there was no biopsy. If the level was under 10 and an exam was abnormal, there was a biopsy. And, all patients with levels over 10 received a biopsy.

While there are flaws in this study, it was found that 137 PSAs were elevated out of the 1653 healthy men screened. Of those, 107 were below 10, and 30 were over 10. Of the 30 over 10, most of them (27) had abnormal exams, and 18 of those 27 had cancer. Of the 107 who had levels less than 10, the majority had abnormal exams; 19 of those had cancer. So that about 27% (37/137) of those with an elevated PSA actually had cancer.

The specificity, then, in this study was 94% (1516/1616), and the prevalence was 2% (37/1655).

(SLIDE)
PSA as a Screening Tool: Men Over 50
Bayes Theorem

$$PPV = \frac{(.79)\ (.022)}{(.79)(.022) + (1-.94)(1-.022)} = .224$$

Conclusion:

1/4 tests would indicate cancer.
3/4 tests would be wrong.

(*N Engl J Med* 1991; 324:1156.)

Putting these numbers into Bayes theorem, you can calculate a positive predictive value of about 22%, using 79% sensitivity, based on the control group, (because they didn't determine the actual prevalence of cancer in the screened population). Thus, 1 in 4 tests would indicate cancer and 3 out of 4 positive tests would be wrong. Since rectal examinations were not done in persons with PSAs <4ng/ml, the false negative rate cannot be determined. We know that 43% of pateints with organ-confined prostate cancer have PSA values below 4 ng/ml. So, it really becomes a question of looking at the numbers, as to whether that becomes cost-effective or not. For the clinician wanting to know whether cancer is present, 1 accurate test in 4 isn't good enough. But in the insurance industry, maybe that is good enough.

If you were to re-evaluate this question from the industry perspective and established the cutoff at 50 nanograms per ml, I think you could define a subgroup in which people clearly had cancer, in which you had a specificity of 100%. But the question would have to be formulated to fit that result and not the clinician's question.

(SLIDE)
Screening for Ovarian Cancer with CA125

Screening in the general population (20 to 40 cases of ovarian cancer/100,000 persons)

Sensitivity = 80%
Specificity = 99% in a healthy population
Prevalence = 30/100,000 = 0.0003

$$\text{Positive predictive value} = \frac{(0.80)\,(0.0003)}{(0.80)(0.0003) + (1 - 0.99)(1 - 0.0003)} = 0.023\ (2.3\%)$$

Screening in American women with pelvic masses

Sensitivity = 80%
Specificity = 78%
Prevalence = 18/182 = 0.0989

$$\text{Positive predictive value} = \frac{(0.80)\,(0.0989)}{(0.80)(0.0989) + (1 - 0.78)(1 - 0.0989)} = 0.285\ (28.5\%)$$

Screening in Scandinavian women with pelvic masses

Sensitivity = 87%
Specificity = 88%
Prevalence = 91/184 = 0.5

$$\text{Positive predictive value} = \frac{(0.87)\,(0.5)}{(0.87)(0.5) + (1 - 0.88)(1 - 0.5)} = 0.88\ (88\%)$$

See: *Obstet Gynecol* 1987; 69:606.
Hum Reprod 1989; 4:1.
Obstet Gynecol 1988; 71:751.
Eur J Cancer Clin Oncol 1989; 25:1187.

The problem with screening for ovarian cancer is that CA125, although a good tumor marker with a 99% specificity in a healthy population has a lower specificity in patients who have symptoms. If you were to screen just healthy women, the problem for the predictive value is that there are only 20-40 cases of ovarian cancer per 100,000 persons. So predictive value is low because of very low prevalence in the normal population. If you screen women with pelvic masses, then you would have the same sensitivity, becuase that is a measure of elevation in persons with cancer, But the specificity goes down because of all the abnormal gynecologic problems that result in elevated CA125. The prevalence is up in a symptomatic population. In one study the prevalence was almost 10%. Now, the positive predictive value is 1 in 4. In Scandinavia, the very same study was done, again evaluating patients with operable pelvic masses, but now the prevalence of cancer was 50%. And the positive predictive value was much higher.

This, then, really becomes a diagnostic test.

(SLIDE)
Screening for Ovarian Cancer with CA125

915 Roman Catholic nuns
Average age 54.7

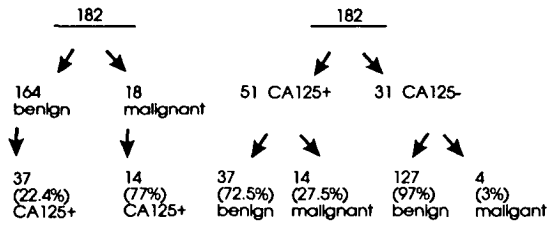
CA125 ≥35 U/ml in 36 cases (4%)
No cases of ovarian cancer
4 died of non-ovarian malignancies; CA125 ≤35 U/ml

Obstet Gynecol 1987; 69:606.

In the general population, a positive predictive value of 2.3% was calculated. Only 2.3% of positive tests actually would indicate cancer. That is, in fact, what was seen in this study of almost 1000 women, average age being 54. Thirty-six cases had an elevated CA125, but not a single case of ovarian cancer was found. Four had other kinds of malignancies.

(SLIDE)
CA125 in Ovarian Cancer

182 Patients with Pelvic Masses



Obstet Gynecol 1988; 71:751.

This slide shows the study of 182 patients with pelvic masses. 164 were benign, and a quarter of those had positive CA125. Eighteen were malignant, and 3/4ths of those patients had a positive CA125.

If you look at the opposite side of the coin, how many people would you miss? You would be missing one-fourth of patients with cancer, or 3% of those with a negative CA125. Now, I wouldn't want to be the physician who didn't operate on the pelvic mass because that probably wasn't a cancer. I think that 3% (one quarter of those with cancer) is not acceptable in terms of deciding whether or not a person has a cancer. If it's positive, it doesn't mean you have cancer and if it's negative, it doesn't mean you don't have cancer. It only can mean that if it's elevated, you probably have cancer, but, in any case, you have to have the final diagnostic test.

(SLIDE)
Benign Disorders Associated with Elevation of Serum CA125 (>35 U/ml)

		CA125 >35 U/ml (%)
Benign ovarian tumors		
Serous	7/57	(12.3)
Mucinous	3/35	(8.6)
Benign cystic teratoma	5/74	(6.8)
Fibroma	1/7	(14.3)
All benign tumors	31/299	(10.4)
Other benign disorders of the female reproductive tract		
Acute salpingitis	19/47	(40.4)
Chronic salpingitis	2/24	(8.3)
Uterine myoma	12/122	(9.8)
Endometriosis		
Stage I & II	32/277	(11.5)
Stage III & IV	58/115	(50.4)
Disorders of the digestive tract		
All cirrhosis	98/146	(67.1)
Cirrhosis + ascites	24/24	(100.0)
Chronic active hepatitis	3/33	(9.1)
Acute pancreatitis	20/62	(32.2)
Chronic pancreatitis	1/54	(1.9)
Other benign disorders		
Renal failure	7/48	(14.6)
Diabetes	0/10	(0.0)

Hum Reprod 1989; 4:1.

This is a list of the benign disorders that can be associated with an elevated CA125. Included are benign ovarian tumors, esophagitis, endometriosis, disorders of the digestive tract, pancreatitis, and renal failure.

(SLIDE)
Screening Patients with Testicular Masses

69 patients with testicular mass

14 had nonseminomatous germ cell testicular cancer

11 of 14 had marker elevation

21% false negative rate

No false positives

Thus, AFP & HCG determination in patients with testicular masses is reliable only if elevated.
Marker determination cannot preclude biopsy.

(*Ann Intern Med* 1979; 90:373.)

In addition to ovarian cancer, people have thought we could screen for testicular cancer. CA125 is a very good tumor marker for ovarian cancer, but it failed to be a screening test in the broad population, as I've shown you. Similar results were found in screening patients with testicular masses. Here are 69 patients; 14 have cancer, 11 of 14 had a marker elevation, so that 20% had false negatives. So, here you can never preclude a biopsy based on the negative tumor marker level.

(SLIDE)
Screening for Subclinical Hepatocellular Carcinoma

Disease prevalence varies dramatically –
High risk populations have been identified

Population of 3.5 million in China	23.7 / 100,000
Subgroup with liver disease	304 / 100,000
Hepatitis B_s Antigen + Alaskan natives	646 / 100,000
Cirrhosis of liver, any cause, U.K.	6851/ 100,000

Predictive value of positive test:

$$\frac{(.65)(.00023)}{(.65)(.00023) + (1 - .98)(1 - .00023)} = .00744 = 0.74\%$$

$$\frac{(.65)(.00304)}{(.65)(.00304) + (1 - .98)(1 - .00400)} = .091 = 9.1\%$$

Zhao-you. Subclinical hepatocella carcinoma 1985.
Hepatology 1991; 14:68.
JAMA 1985; 154:3052
Lancet 1985; 1:1357.

With a PV_{pos} = 0.74%, there would be 142 patients without disease for each one with the disease. With PV_{pos} = 9.1%, there would be 9 patients without disease for each one with the disease.

Hepatocellular carcinoma is an area in which the predictive value of positive tests can be increased by choosing a high risk population. Choosing patients with cirrhosis of the liver or with hepatitis B surface antigen positive chronic hepatitis, can increase your positive predictive value up to 10-15%. However, specificity declines in the group with liver disease, because of ain increase in false positive AFP elevations. The actual predictive value will be lower than 9.1%. (*Hepatology* 1991; 14:68.)

(SLIDE)
Diagnosis

HCG	choriocarcinoma
AFP	hepatocellular carcinoma
PSA	prostate cancer
CA125	ovarian cancer

Screening high risk populations overlaps with use of tumor markers in diagnosis. Again, as in screening, a marker must be detectable in early stage or occult cancer to be valuable. Really, in only one cancer can you absolutely use the marker for diagnosis and that's in choriocarcinoma, where you can use the HCG. In hepatocellular carcinoma, high levels, over 100, 200, 400 nanograms per ml, are very suggestive of cancer. In prostate cancer, I've shown you that if you pick a high enough cutoff, 50 or 60 nanograms per ml, it likely indicates cancer, and in CA125 levels in patients with pelvic masses, you can likely indicate cancer. But only in choriocarcinoma could you consider diagnosing the cancer based on the tumor marker level.

(SLIDE)
Analysis of 309 Cases of Hydatidiform Mole (University of Milan, 1976-1985)

	n	(%)
Total Patients	309	
Spontaneous remission	287	(92.9)
Gestational trophoblastic tumor	22	(7.1)
Indications for Treatment		
Raised β-HCG	15	(68.2)
β-HCG plateau	5	(22.7)
β-HCG + at 20 weeks	1	(4.5)
β-HCG + at 16 months	1	(4.5)

All patients achieved a biochemical cure following treatment.

Tumori 1988; 74:93.

This simply shows one study in which 309 cases of hydatidiform mole were examined. The patients were thought to be in remission, and the beta-HCG level was the single determining factor for whether or not they received cytotoxic chemotherapy. All patients had either a raised beta-HCG, a rising one, a plateau, or a failure to completely normalize. All patients then went on to receive cytotoxic chemotherapy and a complete remission.

(SLIDE)
Prognosis

Tumor Volume	vs.	Tumor Biology
CEA PSA		CEA
HCG AFP		HCG
LDH CA19-9		LDH

Prognosis is the next area in which you would like a tumor marker to serve a role, and, in fact, high levels do confer a poor prognosis, generally speaking. Whether this is due to tumor volume or tumor biology has not been entirely elucidated. Most of the tumor markers confer a poor prognosis because of increased tumor volume. That applies to CEA, PSA, HCG, AFP, LDH and CA19-9. For tumor biology, since CEA is thought to be an adhesion molecule that might confer an increased ability to metastasize, it may be that for a given amount of cancer having a higher CEA is worse. Likewise, in testicular cancer, in non-seminomatous testicular cancer, for a given tumor volume having a higher HCG is worse than not. Also for choriocarcinoma, increased intensity of chemotherapy can be recommended. Likewise, LDH has been thought to denote a poor tumor biology in some lymphomas.

(SLIDE)
Certainty of Allocation to Worse Prognosis (Survival <9 mo) Based on Pretherapeutic Carcinoembryonic Antigen (CEA) Level *

All patients with pre-therapeutic level	Allocation to worse prognosis (survival <9 mo) Right	Wrong	Sensitivity	Specificity
CEA >2.5 ng/ml	43%	57%	69%	36%
CEA >5 ng/ml	61%	39%	61%	67%
CEA >10 ng/ml	51%	49%	30%	78%

Cancer 1988; 62:1348-1354.

* While marker levels may correlate with prognosios, this does not always indicate that the marker can be used to determine prognosis.

This study evaluated the capability of CEA small cell carcinoma of the lung, to show whether patients would

have a poor or better prognosis. Mean CEA levels were significantly different in the two prognostic categories. Hwever, in using CEA to allocate patients to a given category, they were right or wrong in their allocation to the prognostic group an equal amount of time. So, they may as well have been guessing.

(SLIDE)
Monitoring Therapy

AFP	CA125
HCG	CA15-3
LDH	CA19-9
PAP	NSE
PSA	CEA

Monitoring therapy is the next major category, and really the most important category for the use of markers clinically, for the oncologist. Any tumor marker can be used to monitor therapy if you understand its limitations and understand in what instances it might be falsely positive. But it doesn't have to be as sensitive or as specific to monitor someone's therapy if they've already got a diagnosis of cancer, as it does in the process of screening or in diagnosis. So all of these have been shown to be of some value in monitoring treatment.

(SLIDE)
Detection of Relapse

AFP	PSA
HCG	CA125
LDH	CA19-9
CEA	

Likewise, for detection of relapse. This is a little more tricky, because in these patients you're assuming a complete remission, and you want to have a long lead time between the time your tumor marker is elevated and the time that you detect their clinical relapse, so that you can institute a treatment like bone marrow transplantation or a repeat surgery, or other potentially curative therapy. Here you have AFP, HCG, LDH, CEA, PSA, CA125 and CA19-9. All of these have at least some role in detecting relapse after a potentially curative treatment.

(SLIDE)
Half-Lives of Tumor Markers

AFP	5 days
HCG	12 - 20 hours
CEA	3 weeks
PSA	2.2 - 3 days
CA125	4.8 days

Part of what determines how good a tumor marker is going to be in monitoring therapy is half-life. If its half-life is 12-20 hours or 2-3 days, then it will typically be easier to follow that marker and determine how effective your therapy is than if it's half-life was 3 weeks and subject to more variability.

(SLIDE)
Interval Between Marker Elevation and Clinical Diagnosis of Relapse

	Malignancy	Lead Time Mos.
CEA	Colon	3-8
AFP/-HCG	Nonseminomatous Testis	6
PSA	Prostate	1-23
CA19-9	Pancreas	1-7
CA125	Ovary	2-8

The lead time suggested this morning as being important in having a useful tumor marker is also critical. What's been reported for CEA after curative surgery for cancer of the colon, is a lead time of 3-8 months. For alpha-fetoprotein and beta-HCG in non-seminomatous testicular cancer, a lead time of around 6 months. PSA varies from 1 to 23 months. Pancreatic cancer, a lead time of 1-7 months. CA125 of the ovary, a lead time of 2-8 months, and CA15-3 of the breast, and CEA, not on this list for breast cancer, after curative surgery, a lead time again of 2-3 months. In most of these cases, that's not enough time to institute a repeat attempt at curative therapy. It's often not enough time to institute an experimental therapy. So the clinician would like to have a test that was more sensitive than the ones that are represented here.

So again, how good is the test and how good is the therapy? Those are the things that have to be kept in mind in evaluating how effective a marker is going to be in monitoring cancer treatment.

(SLIDE)
AFP & β-HCG in Testicular Cancer

Following orchiectomy, levels should fall in accordance with serum half-life unless there is residual tumor:

β-HCG	12-20 hrs
AFP	5 days

Following chemotherapy, levels decline more slowly. Nomograms indicating success:

- Day 22:Day 1, HCG ratio ≤1:200
- One log decrease/cycle
- Calculated half-life = biologic half-life

Ann Intern Med 1984; 100:183.
J Natl Cancer Inst 1988; 80:1373.
Oncodev Biol Med 1981; 2:129.

Alpha-fetoprotein and beta-HCG in testicular cancer actually are one of the best set of tumor markers and they actually can be used together. The levels correlate with tumor burden or increase with increasing stage. Following orchiectomy, the levels fall in accordance with the serum half-life, unless there's residual tumor. Following effective chemotherapy, the level falls by a log, typically, per cycle of chemotherapy, if it's effective.

(SLIDE)

Surveillance Following Orchiectomy Alone in Stage I Nonseminomatous Testicular Cancer

Ref.	No. Patients	No. with Relapse (%)	Detection By: Markers alone (%)	Detection By: Markers with other findings (%)
1	62	18 (30)	1/18 (6)	12/18 (67)
2	147	37 (25)	8/37 (22)	25/37 (68)
3	36	12 (33)	4/12 (30)	7/12 (58)
4	54	11 (20)	1/11 (9)	5/11 (45)

[1] *J Clin Oncol* 1986; 4:35-40.
[2] *Radiology* 1987;164:671-674.
[3] *J Clin Oncol* 1988; 6:1597-1603.
[4] *Cancer* 1987; 591:578-580.

People have used tumor markers to try and determine early relapse after orchiectomy alone for stage one, to try to have conservative surgery for testicular cancer. Approximately 80% of patients have their recurrent cancer detected by tumor markers. The only caveats here are that while rising or persistent levels almost always indicate recurrence, there can be discordant results between the two markers, due to differing sensitivities of the two marker-producing populations, and some patients never have marker elevation at the time of recurrence. There can be other reasons to have an increased level, but typically rising and persistent levels of alpha-fetoprotein after surgery or cytotoxic treatment for testicular cancer mean a recurrence.

(SLIDE)

Second-Look Procedures Done on the Basis of an Elevated Carcinoembryonic Antigen (CEA) Level in Patients with Colon Cancer

Study (Reference)*	Patients Who Had a Second-Look Laparotomy	Patients Who Had Recurrent Disease Found at Laparotomy	Patients Who Had a Repeat Curative Resection
	n		n(%)*
Wanebo et al. [1]	14	14	7 (50)
Martin et al. [2]	146	139	81 (55)
Minton et al. [3]	43	38	23 (53)
Attiyeh et al. [4]	37	33	16 (48)
Steele et al. [5]	16	15	4 (25)
Evans et al. [6]	14	11	1 (7)
Wilking et al. [7]	13	7	2 (15)
Fucini et al. [8]	5	1	...
August et al. [9]	15	14	6 (40)
Total	303	272 (90)*	140 (46)

*Percent of total number of patients who had a laparotomy.

[1] *N Engl J Med* 1978; 299:448.
[2] *Ann Surg* 1985; 202:310.
[3] *Cancer* 1985; 55:1284.
[4] *Cancer* 1981; 47:2119.
[5] *Am J Surg* 1980; 138:544.
[6] *Cancer* 1978; 42:1419.
[7] *Surg Gynecol Obstet* 1986; 162:465.
[8] *Dis Colon Rectum* 1987; 30:273.
[9] *Cancer Metastasis Rev* 1984; 3:303.

Now how about CEA in colon cancer? How does it do in monitoring therapy? Can you detect a curable recurrence? Studies have been done looking at second-look laparotomy for a total of around 300 patients. Among those, 272 had recurrent disease found at laparotomy, so that would be a 90% sensitivity. That number is high because patients weren't taken to surgery unless they had a steadily rising CEA and nothing else was found on clinical exam that could account for it. Of those patients, about half were able to have a repeat resection. Of these patients, some of them have gone on to have longer survival than you would have expected. The precise value of doing a second-look procedure in recurrent colorectal cancer is still controversial.

If CEA can be used in colorectal cancer to detect a recurrence, what about in postoperative patients who are being followed for breast cancer? Studies recorded in one review evaluating whether CEA was of value in the early detection of recurrence showed that 47% of patients with CEA elevation had true positives and 53% had false positives. (*Am J Med* 1986; 80:241.) I don't think that's good enough to be used in the postoperative monitoring of patients with breast cancer.

How about CEA in the monitoring of chemotherapy of patients with metastatic breast cancer? One report monitored changes in CEA during therapy in 42 breast cancer patients with an elevated CEA. Of 29 responders 15 had the CEA go down appropriately, but 14 had their CEA go up. (*J Clin Oncol* 1986; 4:46.) In the 13 non-responders, 2 had their CEA go down, 5 had their CEA go up, and the rest didn't change. So, it's a mixture, and you can't use CEA to monitor the cytotoxic treatment of metastatic breast cancer.

Another study, looking at CA15-3 and CEA, recently came out, CA15-3 being the new marker for breast cancer. (*Cancer Res* 1988; 48:4107.) The conclusion by the authors was that CA15-3 is more useful than CEA for monitoring the clinical course. But, in fact, if you looked at patients who were having progression of their cancer during their chemotherapy, 75% of them had an increase in CA15-3 as it should, and 58% in CEA. In regression of disease, 38% of them had a correlation with their clinical course, but the others had either no change or it increased. So, if you add all these numbers together, it means that you're going to incorrectly assess your patient in 60% of the cases using CA15-3, and incorrectly assess it 75% of the time with CEA. I don't think those are very good numbers, and I wouldn't be able to conclude that CA15-3 was clearly more useful in monitoring the clinical course of breast cancer.

(SLIDE)

Evaluation of Serum CA15-3 Determination with CEA and TPA in the Post-Operative Follow-up of Breast Cancer Patients

Brit J Cancer 1991; 64:154.
285 Post-op cancer patients:
In 21 elevated markers preceded relapse

		Lead time
CA15-3	11 pts.	2.7 mo.
TPA	17 pts.	3.4 mo.
CEA	2 pts.	3 mo.

In 169 non-relapsed patients, elevated markers noted:

		Specificity	Reported
CA15-3	24 pts.	86%	98%
TPA	123 pts.	25%	98%
CEA	18 pts.	90%	99%

If you can't use it in monitoring treatment, can you go back to that question about the post-operative patient? After all, we don't currently have a curative therapy for metastatic breast cancer. But if we could detect it at the time it was truly occult, those patients might be able to undergo bone marrow transplantation, and that might be a setting in which you could talk about really prolonging survival. So investigators asked whether CA15-3, CEA, and TPA can perform in the setting of 285 post-operative breast cancer patients. (*Br J Cancer* 1991; 64:154.) In 21 of the patients, elevated markers preceded relapse; 169 patients never relapsed; and in the remaining patients, relapse and elevated markers appeared at the same time. For the ones in whom the markers preceded the relapse, the lead time was 2.7 months for CA15-3 compared to 3 for CEA. Not a big improvement. Interestingly, you can use it then in your post-op breast cancer patients to say, definitely, that they've not relapsed. Well, in 169 patients elevated markers were noted, for CA15-3, in 24 patients. In the other marker they were looking at, TPA, elevations were noted in 123 patients. And, for CEA, in 18 patients. The specificity I calculated for these markers is 86% for CA15-3, and 25% for TPA, and CEA was 90%. The authors reported a very high specificity for all of these markers in these non-relapsed patients, and basically concluded that you could use all three of these markers in following your patients to be sure that they had not relapsed. But how did they get to this excellent specificity?

(SLIDE)

A Case Study in How to Increase the Specificity of a Tumor Marker

169 pts:	Increased Markers:	
Isolated:	# Times	# Pts.
CA15-3	18	16
TPA	109	77
CEA	16	14
Constant:		
CA15-3	13	7
TPA	69	32
CEA	7	4
Progressive:		
CA15-3		1
TPA	20	14
CEA	0	0

They took the 169 patients, and among those who had increased markers said, all right, how many of them have isolated elevations? Well, CA15-3 was elevated 18 times in 16 patients, TPA 109 times in 77 patients. Since

we know that the isolated elevations mean nothing, these were ignored and only the constant and progressively increasing values were considered as possibly indicating a recurrence of cancer. So, these they would call the "true" false positives. And if you add those together then, this ends up being elevations in 8, 46 and 4 patients for the three tumor markers.

Next, patients in whom the elevation could be explained were excluded. The explanations included fatty liver, renal failure, some pancreatic problems, a list of a variety of miscellaneous causes of elevated markers that relate to liver disease or kidney disease. Once they detected one of those explanations, then they didn't count those people either. They were left with only a handful of patients in whom the marker elevation was not explained. By subtracting those numbers, they were able to assign, in this post-operative group, a specificity of 98% for CA15-3 and 99% for CEA. Such an analysis may work for a group but cannot be precise enough for an individual patient who has a previous history of a fatty liver, or has a few liver function abnormalities, and you want to know if that post-operative elevation of CEA or CA15-3 means that the patient's cancer has come back. I would submit that if you had a steadily rising CA15-3 or CEA, it could be indicative of cancer. But correlative clinical evidence would be required for institution of further anti-cancer therapy.

(SLIDE)
PSA Serum Levels in Patients Undergoing Radical Prostatectomy

Preoperative levels are higher in patients who recur. (mean 23.5 vs. 10.5 ng/ml)
Half-life PSA 2.2 ±0.3 days
Without prostatic tissue, PSA ≤0.2 ng/ml
Rising PSA values are followed by documented recurrence in 12-43 months
All patients with clinical recurrence have PSA ≥0.4 ng/ml
Some patients with rising PSA values still have not recurred at 65 months

J Urol 1989; 141:873.

Now turning to prostate cancer, is PSA any better in monitoring therapy of patients who are in complete remission after radical prostatectomy? Without remaining prostatic tissue, the PSA should be less than 0.2. Rising PSA values have been typically followed by documented recurrence. All patients with a clinical recurrence, who actually have been documented clinically to have recurrence, have levels over 0.4. It has been presumed, as best can be documented in studies, that these patients probably are going to develop recurrent disease. When patients in this category have been submitted to needle biopsy, they have been found to have residual tumor in a high proportion. So that PSA, I think, stands in better shape so far, in terms of an elevation indicating recurrent disease, than do the other markers that I've shown you.

(SLIDE)
Serum CA125 Levels After 3 Cycles of Chemotherapy: Relationship to Survival

	Normal CA125 Levels	Elevated CA125 Levels
Patient No.	15	13
Median survival (mths)	15+	6+*
No. of deaths	0	7
Patients free of disease	12	0

* $p<0.025$

CA125 is useful in monitoring ovarian cancer therapy. After surgery and then after chemotherapy, CA125 levels in epithelial ovarian cancer decline, and, in fact, correlate with survival after three cycles of chemotherapy. (*Hum Reprod* 1989; 4:1. *Ir J Med Sci* 1989; 158:59. *Obstet Gynecol* 1987; 69:223. *Gynecol Oncol* 1990; 37:44.) If the CA125 has normalized after 3 cycles of chemotherapy, then survival is longer and there is a greater chance of being disease-free than in patients who have elevated CA125 after three months. So CA125 is very useful for monitoring therapy of ovarian cancer. But what if the CA125 is normal? Although there is a greater chance of being disease-free at the time of second-look laparotomy, it's not absolute. In fact, patients who have had normal CA125 at the time of second-look laparotomy, have a 50% incidence of tumor. So those will be 50% false negatives. And this is shown easily by patients who, at the time of the second-look laparotomy, have a normal CA125 and then go on to develop recurrent cancer.

(SLIDE)
The Ideal Marker

Produced by the tumor
Specific for the tumor
Readily detectable in blood or body fluids
Absent in health and benign disease
Detectable when occult malignancy is present
Level reflective of tumor burden
Level falls with response to therapy
Level falls with relapse of disease

My goal here was to show you that while none of these markers really reaches the ideal, they can play a role in clinical oncology. The ideal marker would be produced by the tumor, specific for the tumor, readily detectable in blood or body fluids, would be absent in health or benign disease, and detectable when an occult malignancy is present. The level would be reflective of the tumor burden, would fall with response to therapy, and rise with relapse of disease. I think for the insurance industry, the ideal marker would be somewhat different, and I'm not sure you would want to formulate it exactly like this, but this is the clinical oncologist's goal for a tumor marker.

I've tried to show you pieces of data to support the conclusions that alpha-fetoprotein in a hepatocellular carcinoma can be used for screening and can be used for monitoring therapy. And AFP and HCG in testicular cancer can be used in diagnosis, prognosis, monitoring therapy, and detecting relapse. LDH as well, in testicular cancer. CEA in colon cancer can be used to detect relapse only. It can't be used to detect relapse reliably in breast cancer, gastric cancer or small cell carcinomas. PAP and PSA can be used in monitoring treatment after prostate cancer therapy. Also, PSA is probably going to be useful in screening. CA125 can be used in some settings with diagnosis, monitoring, treatment response or detecting relapse. These, I would say, are of proven value.

Probably of value are CA15-3 and CA19-9. The exact role of these in clinical medicine is not yet clear. And then there are the long lists of markers that have potential value in these same settings, of which I've only touched the surface. (*applause*)

SCHWARTZ: Thank you, Dr. Bates. At this time, Dr. Herbert Fritsche. Dr. Fritsche is Chief of the Clinical Chemistry Division at the M.D. Anderson Cancer Center and Dr. Fritsche has been involved in tumor markers for some time. Indeed, he has been responsible for the evaluations of many of them, and I think no one is more capable of discussing the role of tumor markers and monitoring than Dr. Fritsche.