Host: This is the podcast from *Clinical Chemistry.* I am Bob Barrett.

The June issue of *Clinical Chemistry* included an online report of the updated National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for the use of tumor markers for cancers originating from four different sites, namely, liver, bladder, cervical, and gastric cancers.

These guidelines are intended to encourage more appropriate use of tumor markers by primary care physicians, hospital physicians, surgeons, specialist oncologists, and other health professionals.

Dr. Catharine M. Sturgeon is the lead author of the report and a Consultant Clinical Scientist in the Department of Clinical Biochemistry at the Royal Infirmary of Edinburgh, where she is also Director of the UK National External Quality Assessment Service Proficiency Testing Center, and an honorary senior lecturer at the University of Edinburgh in the United Kingdom. She is our guest in this podcast.

Dr. Sturgeon, let's start with liver cancer. Tell us, how much of a problem is liver cancer worldwide?

Dr. Catharine M. Sturgeon: Well, it really is a really big problem. In fact, liver cancer is the fifth most common cancer in men and the eighth in women. So it ends up as the third most common cause of cancer-related death.

And putting it in context, that means 500,000 new cases are diagnosed yearly. Now, it's interesting also that the incident varies worldwide, and the causative factors are different depending on where one is. So that in Asia and Africa, Hepatitis B virus infection is really relevant, whereas in the West, in Japan, it's Hepatitis C virus that's the main risk factor.

But patients with alcoholic cirrhosis are also at increased risk of liver cancer, and that's really worrying for us, I think, particularly in the West.

So what it boils down to is there are about 350 million people infected with Hepatitis B worldwide and another 170 million with Hepatitis C. So we really are talking about a major health problem.

And I guess in the West also we have the problem of increasing alcohol consumption, increasing obesity. And I gathered from my hepatologist colleagues that this is becoming a really major concern to doctors treating liver disease. Because they are now seeing patients with really serious liver problem in their 20s and 30s. That's what cirrhosis, and we do know that the risk of going on from cirrhosis to liver cancer is really quite high. So that about 2.3% of patients with cirrhosis may develop a liver tumor each year.

Host: Now, tumor markers are not usually considered diagnostic tests. Can any tumor markers contribute to the diagnosis of liver cancer?

Dr. Catharine M. Sturgeon: Well, you are quite right in saying that tumor markers aren't diagnostic tests, and AFP, which in fact is the only tumor marker the NACB recommends for use in routine clinical practice and liver disease, is not a diagnostic marker and can't really be considered as a diagnostic test. But its measurement certainly can contribute very helpfully to the diagnostic process.

And in fact, in one arena, very high levels of serum AFP, as in fact is the case for many of the other markers, are almost diagnostic for liver cancer in patients who have symptoms that are consistent with it.

It's interesting in that vein that various cutoffs have been proposed, but most expert groups, including the NACB, would suggest that the level of aggression of about 200 micrograms per liter, in a patient with a suspected liver cancer would be sufficient to confirm a diagnosis. That's of course provided other possible explanations, so that high level has been excluded.

The trouble really is, that for patient with advanced disease, liver transplant is really the treatment of choice, and we all appreciate the limitations with that, not least the number of organs that are available, and that's where AFP has another role, apart from diagnosing established liver cancer, it can act or it can be used in conjunction with ultrasound and used with serial AFP measurements here we are talking about, to detect small changes in the liver and potentially aid the detection of small tumors at a time when medical intervention is possible.

So this really is semi-diagnostic—well, this is a diagnostic use of the AFP, but really as a complement to ultrasound, so both of them are complementing each other. And very importantly to mention, this

has to be in selected high-risk groups, this isn't for population diagnosis of screening.

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Host: Does it make any difference if the progression to liver cirrhosis is recognized early?

Dr. Catharine M. Sturgeon: Yes, it definitely does. The earlier that progression from fibrosis to cirrhosis is recognized the better, because it's possible now, there are medical interventions that can be put in place to stop the otherwise inevitable or almost inevitable progression on to liver cancer. So the earlier that kind of intervention can be put in place, the better for the outcome. Really is key to improved outcome.

Host: How can tumor markers best be used for people who are diagnosed with liver cancer?

Dr. Catharine M. Sturgeon: In patients who are already diagnosed for liver cancer, it's really post-treatment monitoring, the Routine and A*STAR application, we believe, of most tumor markers. It's probably most worthwhile where there are alternate treatments that can be offered. So really for AFP in liver cancer, as with other tumor markers and other cancers, what we really need is good alternative treatment.

However, even where alternative treatments aren't available, as may be the case for some patients, information of systemic therapy isn't working, can really be very helpful in stopping treatment that is just not doing any good.

So post-treatment monitoring in the usual fashion is desirable. And it's also important to note that that is likely to be particularly helpful where their isn't measurable disease that can be assessed, for example, by ultrasound, and that actually is the case in a number of patients with liver cancer.

Host: What caveats need to be remembered when using AFP? Are there any aspects of analysis that the laboratory should take particular care with?

Dr. Catharine M. Sturgeon: Well, I suppose there are the usual ones that we have to always pay attention to. First of all, is remembering the other causes of raised AFP.

For example, AFP is clearly a normal protein that appears in pregnancy. AFP may be raised in patients with testicular cancer and other malignancies.

Also important to remember that there may be flares in AFP, for example, after a major bout of drinking, etcetera. So one has to remember those caveats, and also the really important one, that a normal value never excludes malignancy if it's suspected.

I think the thing about AFP in terms of the clinical caveats that have to be remembered is that, really ones looking, particularly in the early detection arena, which we talked about, that we are looking for a steadily rising, sustained increase in AFP. We are looking at increases in AFP, for example, at six monthly intervals, at which time one is also looking at the ultrasound scan too. So really AFP isn't flagged for further investigation, but one has to remember those other caveats on the clinical side.

In terms of the aspects of analysis that the lab should take particular care with was really the same things that applied for most of our other analytes, and particularly for tumor markers, as has been indicated in the NACB Quality Requirement section for tumor marker. So that really means well standardized assays, and we are quite lucky that for AFP our assays are pretty well standardized, but there is always room for improvement.

We need to have very good stability at low concentrations, because in the arena of early detection, where one is looking at very small rises of AFP at intervals, we really need to know the assays measured. This week we will get the same result, next week, and the following week. So we need that good stability, which depends very much on the manufacturers providing us with reagents with minimal lot-to-lot variation.

And although it hasn't been much reported for AFP, I think we need to have a good awareness of the possibility of interference. One always has to have at the back of one's mind that if the result really looks clinically unexpected or surprising, it always should be checked out very carefully by the laboratory, for example, just to exclude the possibility of an unusual heterophilic antibody interference or something like that.

And I also think—and this really applies for using AFP to monitor patients post-treatment, as well as in the aid to diagnosis application—the laboratory has a duty to look after the results very carefully and to

report them properly in a fashion that's really as helpful as possible for the receiving clinician.

I think that means that putting the name of the method on the report and ideally, really, especially where we are looking at those sustained increases in relatively low value of AFP, considering whether it's possible to report graphically, so to produce the graphical report that shows the sustained raises. I know in the hospital that I work in, the hepetologist really appreciate the graphical reports that we are able to produce for AFP.

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And I think we also need, really in that same area, to do more work for AFP and also for the other tumor markers on what increase actually constitutes a significant change. Taking into account biological variability, analytical variability, and everything else. And although some work has been done on that, particularly for breast cancer and prostate cancer, we haven't really started to look at that for AFP.

Host: Well, now regarding bladder cancer, how common is bladder cancer, and how is it diagnosed?

Dr. Catharine M. Sturgeon: Well, it's actually really rather a common cancer as well. Each year in the U.S. there are 71,000 new cases diagnosed, and I am afraid 14,000 people die from the disease. The prevalence in the U.S. is about 500,000.

One of the difficulties with it is that, it tends to present with rather nonspecific urinary track symptoms, which could be associated with a whole lot of other benign diseases or disorders. So that's really hematuria and other urinary track symptoms.

The actual mode of diagnosis is really quite invasive. Cystoscopy is necessary with the biopsy, and then of course the immunohistochemistry. Interestingly, in relation to bladder cancer, these are really rather heterogeneous tumors, so there are a number of different types. It's a complex and interesting disease.

Host: Is surveillance necessary of bladder cancer patients who are diagnosed with tumors that have not invaded into the muscle?

Dr. Catharine M. Sturgeon: Well, the root problem with it is that, although that looks like a really good initial diagnosis, the tumor

hasn't spread, which in most malignancies is really glad tidings for eventual good outcome. For bladder cancer, there is really a rather high risk of progression within five years.

And the problem with identifying that, is again, it requires repeated cystoscopic evaluation; again, very invasive and relatively expensive, and it's for that reason that surveillance for the urine markers would in principle be very attractive, obviously much less traumatic and much easier for the patient.

Host: What tumor markers for bladder cancer have been cleared by the FDA for use in the United States and what are their recommended applications?

Dr. Catharine M. Sturgeon: Well, they are quite interesting different types of markers and these are quite different from the big ones associated with breast cancer or colorectal cancer, etcetera.

One of them, the BTA-Stat and TRAK tests, now these are interesting tests which detect complement Factor H and related proteins in urine. Now, the FDA has cleared them, but has cleared them only for use in combination with cystoscopy and for monitoring bladder cancer. In fact, the NACB recognizes that the—the Guideline Committee—recognizes that the actual effect of this on outcome is still very unclear. So we do not recommend the use of these markers in routine practice.

The next test is nuclear matrix protein or NMP22 test, and this again is cleared for use by the FDA, as an aid in the diagnosis of patients at risk or with symptoms of bladder cancer.

Again, the utility and the effect on outcome are not clearly defined as yet, and they are not recommended again for routine use by the NACB.

And the final test is quite a different test. It's a multi-target FISH test called the UroVysion test. It detects cancer cells based on aneuploidy of selected chromosomes. And it seems to be particularly promising for detecting high grade bladder cancer and potentially could predict recurrence and progression earlier. And there are hopes that it might even have the potential to replace cytology.

But the problem with it is, it's costly, it's complex, really highly trained staff and expensive equipment

are required for this. So it's likely to be quite difficult to bring this test into routine practice.

The other thing about it is actually, we still also need to understand better how to interpret the results. So there is really quite a lot of work to do with this.

Host: Finally, do you think there is role for tumor markers in bladder cancer?

Dr. Catharine M. Sturgeon: Well, I do think that the invasiveness of cystoscopy, the complexity of that procedure is rather problematic, so that urine markers really would be highly desirable, and I am sure would be very much appreciated by the patient who otherwise would need to go cystoscopy.

However, we really will have to do a lot of work to refine the markers. We have hopefully to develop and identify new ones, and most importantly, we also need outcome studies. We really have at the moment no evidence that monitoring bladder cancer patients with these markers actually leads to improved outcomes. So again, a great deal of work to be done.

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Host: What about cervical cancer? What are the major current issues for this type of cancer?

Dr. Catharine M. Sturgeon: Well, the major current issues for cervical cancer really is that we need to redouble our efforts to prevent cervical cancer, that's the major issue.

We have been very lucky and having screening with the Papanicola test since I think sometimes in the 50s. Because we know that cervical cancer is so closely related to incidents of the human papillomavirus, we now have really, really exciting possibility of prevention with vaccines against that virus. So hopefully this will become a disease of the past in the future.

Host: Are there any markers that are helpful?

Dr. Catharine M. Sturgeon: Well, the major marker that's helpful is in fact squamous cell carcinoma Antigen or SCC. Now, it is relevant only in the cervical cancer, such as the squamous cell type. But in fact, that constitutes about 85% of them, so it's really the most potentially useful at the moment.

The NACB group, which considers cervical cancer, looked at this very carefully, and really the utility of SCC, which isn't in fact very widely used in routine clinical practice at the moment, is majorly in detecting or aiding the detection of lymph node involvement, which is really important for treatment planning. In other words, in diagnosed cervical cancer patients, whether lymph nodes are involved or not, makes a major difference to the treatment and also unfortunately to the outcome.

Host: So what are the recommended applications for squamous cell carcinoma antigen?

Dr. Catharine M. Sturgeon: Well, the recommendations are extremely circumspect. In fact, the NACB states, and this is in agreement and accord with other expert bodies, that SCC might be used to individualize treatment planning, and that is in patients who have lymph node involvement, but that it's not routinely recommended.

So really, again, we need to know a lot more about this test and about the disease before getting too excited about tumor markers and cervical cancer. We need better markers for sure.

Host: Well, lastly, let's discuss gastric cancer. What's known about predisposing factors for this type of cancer, and what action is currently being taken?

Dr. Catharine M. Sturgeon: Well, again, gastric cancer is interesting as well, because there is very good evidence that the major predisposing factor is infection with *Helicobacter pylori*. So eradication of that is definitely the number one goal in terms of reducing the incidence; early recognition of helicobacter infection, and then medical treatment to address it.

Host: And what tumor markers are available for gastric cancer?

Dr. Catharine M. Sturgeon: For gastric cancer, some of the original tumor markers that we have known and loved for ages, Carcinoembryonic Antigen, CA 19-9, CA 72-4. So all of these can be raised in gastric cancer, and of course they would not be at all useful diagnostically because they are raised in so many other cancers as well. But they would have the potential for monitoring patients post-treatment.

Host: Is their application and monitoring likely to be helpful?

Dr. Catharine M. Sturgeon: Well, here we don't know. I mean, with gastric cancer, again, we have problems with quite often late diagnosis, quite often treatment possibilities are relatively sparse. So at the moment these markers are not recommended for routine use. There is basically no evidence that they are beneficial or have an effect on outcome.

Everything of course could change for these markers, as with the others, with the development of effective therapy. As soon as there is effective therapy, even a marker which has some limitations, may suddenly become useful in establishing whether the therapy is working or not, or giving an additional indicator of that.

Host: Well, in summary, Dr. Sturgeon, how do you see the role of tumor markers developing for these cancers during the next five years or even the next ten years?

Dr. Catharine M. Sturgeon: Well, I think it's—I hope, I am always an optimistic—I hope that actually things will change in the next ten years, and we are already seeing this in some other malignancies as well. As better therapies are developed, I think that tumor markers that accompany them are likely to be developed as well. So that we may have expensive drugs, which may be antibody therapies or whatever else, that are developed for these cancers, which will only be effective and will only be appropriately used in subgroups of patients. And I think if this happens for cervical cancer, for bladder cancer, and for gastric cancer, we really will see some exciting possibilities.

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That's really going towards—a move towards personalized medicine—and it does depend on the colleagues in the drug development industry. But it's quite interesting just thinking about, especially gastric cancer, to consider what's happening with lung cancer, where the available treatments in the past such as lung cancer, has always had a slightly pessimistic sort of crest. But in fact, now we have some tumor markers and we have some therapies which are producing major, almost Lazarus like resurrections of patients who with advanced non-small cell lung cancer.

Now, in terms of assessing whether patients would benefit from that, it's absolutely essential that those

lung cancer patients are positive for either the HER2 or the EGFR receptor. I think if similar things happen for gastric and cervical cancer, bladder cancer, then we will really see a revolution in tumor markers.

For AFP, where we have so many people worldwide who are at risk of developing liver cancer, I think we may well see continued and better use of AFP in conjunction with liver ultrasound, in the way I have described.

And the advantage there is, where we are talking worldwide about a really major health issue, that's Hepatitis B, Hepatitis C infection, AFP is relatively straightforward, simple, and inexpensive test, which properly be used at routine intervals, such as six months, as recommended by the NACB, could really make a difference to a lot of people, in terms of identifying the disease at an early stage, when it's possible to do something about it.

So I am very optimistic for the future. I think the bottom line will be also, that in the future we will have to do much more in intelligently targeting our measurement of tumor markers to the clinical situation.

Host: Dr. Catharine M. Sturgeon is the lead author of the NACB Laboratory Medicine Practice Guidelines and a Consultant Clinical Scientist in the Department of Clinical Biochemistry at the Royal Infirmary of Edinburgh, where she is also Director of the UK National External Quality Assessment Service Proficiency Testing Center and an honorary senior lecturer at the University of Edinburgh in the United Kingdom.

She has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.

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