From: "Thompson, Robert" <rthompson@gov.nl.ca>
To: "Pritchard, Rolf" <rolfpritchard@gov.nl.ca>
Date: 27/03/2008 3:28:10 pm
Subject: FW: Request for an Opinion

Here is the copy you requested.

From: Dr. Greg Flynn [mailto:Flynn@qmpls.org]
Sent: Tuesday, March 25, 2008 3:50 PM
To: Thompson, Robert
Cc: Bryan Hewlett
Subject: RE: Request for an Opinion

Dear Robert.

The most important difference between hormone receptor staining and staining for these other 6 markers is that therapy is decided on the basis of ER/PR results. All of the other markers with the possible exception of CD20 are used as an adjunct to diagnosis.

Let me try to put this in more simple terms. When a pathologist makes a diagnosis it is based on the physical characteristics of the diseased tissue. The physical characteristics include its overall architecture and microscopic structure, the component cells and the size and variability of the cell structure, especially the nuclei which contain the cellular DNA. Special stains including IHC are often used to help with the diagnosis, and in some cases to further refine a diagnosis. For many pathologists the diagnosis of cancer is made often without any further special stains. So the diagnosis of a cancer is commonly made before the markers are applied, just as you have described.

So for example, CD3, CD5, CD79a and CD20 are all markers of white blood cells and are used to characterize lymphoma and leukemia. With the exception of CD20 which may be used in planning treatment, there is sufficient redundancy in the antibody profiles of reactivity that it is unlikely that patients would have gone astray as a result of erratic testing. CEA is non-specific marker of malignancy and I do not believe it could have a similar impact on patient care.

The CKHMK-34BE12 is a useful stain in differentiating small irregular shaped glands from well differentiated cases of carcinoma of the prostate. Normal prostatic glands have a layer of cells that encircle

the glands and stain positively for High Molecular Weight Cytokeratin. Accordingly false negative stains could misslead a pathologist into believing that small irregular glands were evidence of a low grade malignancy. It would not be an issue in higher grade prostate cancer, because it is an adjunct to diagnosis, and treatment plans are not dependent on reactivity.

It is not our experience that any of the markers you have specifically asked about are as sensitive to variations in testing conditions as ER and PR. A retrospective review of prostate cancer biopsies would not likely lead to significant numbers of test results that would be changed. The clinically significant "error" would be false negative results resulting in a tendency to overcall small atypical glands as cancer, and if one were to contemplate a review, it would be those cases that would be of most concern. Those individuals may have been subjected to unnecessary radiation or surgical treatment. In the latter situation, examination of the prostate after surgery would have triggered a review of 34BE12 staining.

All of that said, if you do a retrospective review, you will find "errors". You may find clinically significant situations, but the extent is going to be much much smaller, and I believe much less significant for the reasons stated.

In our view, all of the IHC tests currently performed will benefit from improved training, revamped procedures, validation of methodology, quality control/quality assurance, and continuous monitoring of results in the IHC lab. As in all diagnostic services there should be communication and feedback between the lab and the end user as part of the quality system. Results that do not "fit" with the clinical behaviour of a patient's disease should be reviewed, just as they were in the breast cancer situation where cases that an oncologist would have "expected" to be positive were not and when patient's who were reported as "negative" for receptors but who were treated anyway responded to anti-estrogen therapy.

I hope this helps. It would not be our recommendation that there be a retrospective review of additional markers, the explanation for any discordant findings (however few) would be difficult to comprehend by the public.

Sincerely

Greg and Bryan

-----Original Message-----
From: Thompson, Robert [mailto:rthompson@gov.nl.ca]
Sent: March 25, 2008 8:42 AM
To: Dr. Greg Flynn
Subject: Request for an Opinion

Greg:

Thanks again for the recent discussion on lab accreditation. The matter is under assessment and we look forward to responding soon.

Today I want to impose myself upon you again related to ER/PR. Your previous advice has been very helpful.

I am seeking an opinion about a lab testing issue related to ER/PR which I did not ask in December, but is emerging as more significant right now. I am unsure whether this is a simple or complex question. I hope you will be able to help.

In May 2007 we became aware that immuno testing had been suspended at the HSC lab for about 4 weeks in 2003 in order to troubleshoot the staining process. When it was suspended, the senior pathologist identified 8 antibodies which have "remained unreliable, erratic and, therefore, unhelpful for diagnostic purposes." ER and PR were two of the eight antibodies. However, when the lab resumed testing four weeks later, the report only made reference to improvements to ER/PR. The other 6 antibodies were not mentioned.

As you know, the problems with ER and PR became a sensation in 2005, and a retrospective assessment of about 1000 tests was conducted in 2005 and 2006. The other six antibodies were never raised as an issue in 2005 or 2006.

In June 2007 I asked Eastern Health whether there was a need for retrospective examination of the tests related to the other six antibodies. The root of the question was if ER and PR needed retrospective assessment, maybe the others did as well. The answer was that no retrospective assessment was done on the other tests because there was no index case which converted and because none of the other tests are as significant in a treatment context as ER and PR. They said the other tests, individually, are but one of a suite of tests and

factors which help to diagnose a tumour. Therefore, the likelihood of anyone being misdiagnosed because of erratic staining in these tests is very low. The primary basis for diagnosis, in any event, is not immunohistochemistry, which diminishes the significance of these other IHC tests. ER and PR are not used for diagnosis; they are used for planning treatment, and are singularly important in the treatment decision.

Since that time it has been suggested to me that at least one of these other tests is crucial in the staging or typing of prostate cancer. I was told that prostate cancer patients might be very concerned if they knew that the test which is significant in their diagnosis may have been erratic.

Therefore, I am seeking the opinion of an objective third party.

The antibodies in question are: CKHMW-34BE12, CD3, CD5, CD20, CD79a, and CEA.

The specific question is whether retrospective assessment of tests in the 1997-2005 period should be done given the quality control problems with ER/PR testing (which were revealed in the 2005 peer assessments) during this same period? A related question is whether the measures taken to fix quality in ER/PR (e.g., training, monitoring, quality control) will have collateral benefits for other types of IHC testing?

I realize it may be difficult to provide a definitive opinion without additional data. Therefore, a qualified opinion or sense of direction would be a good alternative.

If you would like to discuss this, please feel free to call me at 709-729-4092.

Thanks

Robert
