

December 7, 2005

Dr. Robert Williams
Vice-President,
Quality, Diagnostic and Medical Services
St. John's Hospitals, Eastern Health
General Hospital Site
St. John's, Newfoundland
A1B 3V6

Dear Dr. Williams:

I was most recently asked by Dr. Don Cook to comment on the suggestion of Mr. Barry Dyer that stated that he felt that the Ventana testing for estrogen receptor, progesterone receptor and Her2/neu could be started at any time. I find this comment quite startling in the face of the two fairly damning reports sent by Dr Banerjee and Trish Wegrynowski on their review of our immunohistochemistry laboratory with special emphasis on the predictive factors for breast cancer patients. I am quite concerned for the health of the people of Newfoundland and Labrador diagnosed with breast cancer if their treatment plans are based on ER/PR and HER2/neu results generated in our laboratory.

Breast pathology (indeed all of anatomic pathology) is often very difficult and is subject to a myriad of influences that can lead to poorer outcomes for our patients. In a small study carried out at the NIH a good pathologist was positively correlated with increased disease free and long term survival in breast cancer patients. Immunohistochemistry is an exact science, which must be meticulously carried out and stringently controlled.

As stated by Dr Banerjee and Ms Wegrynowski and vehemently supported by me there are multiple major issues that must be addressed prior to any breast testing being reported from our immunohistochemistry laboratory.

The most important of these is organization of the immunohistochemistry laboratory. Our technologists need to be dedicated to the immunohistochemistry laboratory (my most recent ER/PR/ Her2/neu validation meeting with them, booked in advance, required taking one technologist from the frozen section room and one from the grossing room) and one of them should be deemed the charge technologists (or other equal terms).

These technologists need then to be educated at an acceptable training institution (not at individual local pathologists' desks) in the theory of immunohistochemistry. They need to learn about the pitfalls of immunohistochemistry, troubleshooting and quality control.

This education must be documented and competency testing carried out. Textbooks and internet references need to be made available in the laboratory. Further, there must be documentation of training and competency of the staff on all equipment used in the laboratory. Continuing medical education of an approved and pertinent manner must be carried out, and monies provided for it.

These technologists need to document the optimization and validation of every antibody (including ER/PR and Her2/neu) currently in use. All validations must be documented (in readily available format, available to any staff in the absence of technologists), signed off by the pathologist who acts as section head (or a designate) and the slides kept permanently and readily available. They need to derive standard operating procedures for the staining protocols for every antibody in the laboratory (and not a copy of the Ventana manual). These SOP's need to be in agreement with well-known regulatory guidelines such as CSLI.

All antibody specification sheets must be available at the workbench again in readily available format. The technologists must set up an appropriate internal and external quality assurance program. An alliance with a large volume teaching hospital should be forged for use as an occasional quality advisor.

An appropriate organizational chart must be designed whereby the immunohistochemistry technologists are professionally responsible to the section head and designate and not to the laboratory manager and the laboratory director. Of course, the technologists must also be professionally responsible to them and should not look to pathologists to solely make decisions about the technical aspects of immunohistochemistry (e.g. antibody selection, control selection, adequacy of tissue sample). Rather the technologists must act as equal partners, presenting their decisions to the section head for approval.

There must be a well documented user friendly system set up whereby individual pathologists complaints and concerns about immunohistochemistry are registered and a mechanism set up by which these problems are investigated and actions taken forwarded to the pathologist and the section head.

Appropriate positive and negative controls must be selected for ER/PR and Her2/neu. The immunohistochemistry technologists need to be trained in the basics of interpretation of ER/PR and Her2/neu so that appropriately stained slides only leave the laboratory. The her2/neu protocol must be moved to the automated machine, the Her2/neu antibodies must fall into compliance with the recent recommendations of the Canadian consensus.

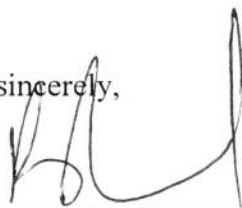
A microscope needs to be placed in the laboratory for the use of the technologists. Routine equipment maintenance schedules must be set up and carried out- under readily available standard operating procedures. Some of the equipment in the immunohistochemistry laboratory must be moved to ensure optimal operation.

I feel that all of the above recommendations must be fully in place before we can begin to release ER/PR/Her2/neu status reports from our laboratory. I am unaware that any of these have taken place.

The pathologists must standardize their approach to the accessioning and gross handling of all breast specimens. All tissue processing must be amalgamated and standardized. Pathologists should be educated around block selection in breast cancer cases. They should be taught basic information about the reporting of predictive factors in breast cancer, including aspects of internal controls, surrogate markers and handling of discordant results. Serious consideration should be given to limited numbers of pathologists reporting these often difficult diagnoses. Standardized reporting of immunohistochemistry results should be used that lists the clone, the percentage positivity and the procedure, to minimize oncologists' chance of misinterpretation. Inter- and intra- pathologist variability in reporting must be assessed.

I would be happy, after a presentation by Mr. Dyer *proving* that all of the above have occurred and a tour of the immunohistochemistry laboratory to review the changes made, to advise my clinical colleagues that our laboratory and the results it generates are reliable, accurate, and not dangerous to those Newfoundlanders and Labradoreans having breast cancer.

Yours sincerely,



Beverley A. Carter, MD, FRCPC

Pathologist

Phone 709-777-5530 / 709-777-5493

Fax 709-777-5178

c.c. Dr. Donald M. Cook
Mr. Terry Gulliver
Dr. Gershon Ejeckam