Eastern Health

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July 19, 2006

Mr. George Tilley
President and Chief Executive Officer
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Corporate Office

Dear Mr. Tilley:

I am writing concerning the national issue we have been advocating for concerning setting up a reference lab for laboratories that do ER & PR testing in the Country.

I've attached a proposal from a group called the Canadian Coalition for Quality in Laboratory Medicine with a proposal with respect to immunohistochemistry. Their proposal deals with Class I tests, which does not include the important ER & PR component. Dr. Don Cook advises that at the weekend meeting of the Canadian Association of Pathologists held in St. John's this matter was discussed on their agenda. The Canadian Association of Pathologists, through their president, Dr. Diponkar Banerjee, will be writing the Canadian Coalition for Quality in Laboratory Medicine supporting the trust of their initiative, but recommending that Class II tests also be included in their proposal. He will also be writing the Canadian Association of Medical Oncologists, the Canadian Association of Radiation Oncologists, the Canadian Association of Provincial Cancer Agencies, and the Canadian Cancer Society to ask for their support in setting up some kind of a national quality testing program for Immunohistochemistry, perhaps similar to that in place in other jurisdictions.

This is good news and, hopefully, this will lead to national standardization and assurance that labs testing in this area would be part of a national quality assurance program.

Yours sincerely,

R.J. WILLIAMS, M.D., M.P.H.
Vice President, Quality, Diagnostic and Medical Services

/dd
Enclosure
c Dr. Nash Denic
Mr. Terry Gulliver
Ms. Pam Elliott
Ms. Heather Predham

Denise Dunn

From: Donald Cook
Sent: Wednesday, July 12, 2006 1:50 PM
To: Dr. Robert Williams
Subject: FW: QC for Immunoperoxidase

From: Laurette Geldenhuys MD [mailto:Laurette.Geldenhuys@cdha.nshealth.ca]
Sent: Wednesday, July 12, 2006 10:35 AM
To: <Diponkar Banerjee; Donald Cook
Subject: QC for Immunoperoxidase

Diponkar and Don,

I received these documents from Ermina Torlakovic. Since we discussed this issue at an executive meeting recently, I thought you might find these interesting. I attach.

Laurette

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"Proposal for Establishment of a National External Quality Assurance Program for Clinical/Diagnostic Immunohistochemistry"

Quality assurance in laboratory medicine includes: a) constant checking of test reliability by internal quality control (IQC), b) external quality assessment (EQA) by an independent agency to check performance of a number of laboratories at intervals in order to obtain a retrospective indication of their performance, and c) proficiency control by supervision of pre-test and post-test phases of laboratory work, from specimen collection to delivery of report to the clinician. Currently, diagnostic immunohistochemistry has in excess of 100 tests on the menu, and none are currently uniformly assessed since there is no national Canadian external laboratory independent agency to check their performance.

1) **Proposed name:** **cIQc** (for **c**anadian **I**mmunohistochemical **Q**uality **c**ontrol)

2) **Proposed program:**
   a) To organize in Canada an external laboratory quality control group, which would promote the quality of clinically applied immunohistochemistry by providing national standards.
   b) To expand education in clinical immunohistochemistry/immunophenotyping at all levels, with emphasis on continuing medical education

3) **Mechanisms**

a) Arrange three to four external challenges per year for assessing the performance of participating clinical laboratories in support of their internal quality control programs.

b) Provide education in immunohistochemistry on several levels, including: creation of web page with examples of good protocols and other information (descriptions of epitopes; technical solutions etc. similar to one that is created by **NordiQC**, a Scandinavian organization for external laboratory quality control in immunohistochemistry: www.nordiqc.org); arrange yearly seminars in Clinical Immunohistochemistry on national and international level in cooperation with Canadian Pathology Association and/or other national and international medical associations for continuing medical education in diagnostic

immunohistochemisty with national and international experts in clinical immunohistochemistry.

In the United States, College of American Pathologists has organized **CAP Laboratory Accreditation** program, which provides external laboratory testing by self-assessment and it is based on the comparison with other laboratories rather than how laboratory performance relates to optimal results of the test. Also, it does not provide sufficient information for improvement of the tests. In the United Kingdom, the National External Quality Assessment Scheme for Immunocytochemistry (**UK-NEQAS**-ICC; *www.uknegasicc.ucl.ac.uk*) has for several years carried out IHC quality assurance for about 450 laboratories in the United Kingdom, where it is compulsory, as well as in other countries. This is a very large organization, which provides useful results, which are published together with suggestions for improvement in their Journal (*Journal of Cellular Pathology*) sent to participants at the end of the assessment schemes. However, the organization is too large for individual contacts and guidelines are generalized rather than personalized. Therefore, so far, only **NordiQC** from Scandinavia provides directly applicable information for each participating laboratory as well as direct communication and personal approach in problem solving. However, with the number of experts in pathology and clinical immunohistochemistry, there is no reason for Canada not to have its own external laboratory testing in clinical immunohistochemistry.

3) **Background:**

Immunohistochemistry (IHC) is currently very widely used in routine Anatomic Pathology diagnostic work (over 200 tests available). It is a very common part of scientific reports in pathology and cytology, and its outcome is one of the essential elements in such things as: our understanding of biology of diseases; the basis for tumor classification; selection of treatment options/choices and also predicting prognosis.

Despite all of the above, standardization of IHC is significantly lagging. It has become apparent that the results of immunohistochemistry can vary greatly among different laboratories depending on the technical expertise and protocols employed. The results of the immunohistochemical staining rely on technical aspects of the methods applied, but also on the interpretation of the results. This is well illustrated by the studies of

Rhodes and Balaton (both from UK-NEQUAS organization for external quality control in clinical immunohistochemistry from UK), whose results indicated that the main problem in detection of hormone receptors in breast carcinoma is due to suboptimal protocols, while in Her2/neu detection, inappropriate interpretation appears equally important.

Even though the problems in testing breast carcinoma for these markers is a very popular topic, it is of note that diagnostic immunohistochemical laboratories may perform more than 100 and in some cases more than 200 diagnostic or prognostic tests, about which very little is known by medical community outside of pathology and even less or practically nothing by the general public. The significance of these tests, however, is of outmost importance for correct diagnosis, tumor classification, and application of appropriate therapy to patients. This may include choice between radiation therapy vs. surgery vs. chemotherapy, anti-inflammatory therapy or no therapy at all, all depending on the results of immunohistochemical tests and their interpretation by the pathologist.

Based on the clinical risks, the FDA has classified immunohistochemical tests into three classes.

Class I tests provide the pathologist with adjunctive diagnostic information that may be incorporated into the pathologist's report, but that is not ordinarily reported to the clinician as an independent finding. These tests are used after the primary diagnosis of tumor (neoplasm) is made by conventional histopathology using nonimmunologic histochemical stains such as hematoxylin and eosin. Examples of class I tests are differentiation markers, such as keratin. Class I tests are subject to general controls including "current good practice regulations", which are not further classified.

Class II tests are intended for the detection and/or measurement of certain target analytes by immunological techniques in order to provide prognostic and predictive data that are not directly confirmed by routine histopathologic internal and external control specimens. These tests provide the pathologist with diagnostic information that is ordinarily reported as independent diagnostic information to the ordering clinician, and the claims associated with these data are widely accepted and supported by valid scientific

evidence. Examples of class II tests are those intended for semi-quantitative measurement of an analyte, such as hormone receptors in breast cancer.

Class III tests are those that do not meet the criteria for class I or II, or are tests that meet those criteria but raise new issues of safety and effectiveness. Examples are markers used to identify new target analytes in tissues that are claimed to be clinically significant genetic mutations and that cannot be confirmed by conventional histopathologic internal and external controls specimens.

Recent rapid technical advancement in clinical immunohistochemistry has created significant and specific problems in diagnostic pathology. The tests are more sensitive and more specific. The results that we achieve today are not only better, but different than those of 5 years ago and also may be more complex for interpretation. Currently, many of the results and guidelines published in the literature before 2005 are not applicable any longer and many of the original observations need to be re-evaluated.

At this time, we do not know and are not able to predict what the degree of the problem (if any) on the national level we may have in clinical immunohistochemistry. We do not know if most or all laboratories are using currently available technically advanced methods, which provide excellent sensitivity and specificity of the tests and if these methods are implemented, what is the level of internal and external quality control the laboratories use in daily practice? Are appropriate positive and negative controls used? Who is creating optimized positive controls, are quantitative tests supplied by quantitative positive controls, etc.

No national surveys are available to answer these and many other basic questions relevant to laboratory performance in clinical immunohistochemistry.

Immunohistochemical tests are basically either qualitative or quantitative. Both could be of diagnostic or prognostic relevance, while quantitative tests are currently used for scoring of results in determination of hormone receptors or Her2/neu in breast carcinoma, which are **class II** tests. Since **class II** tests are very few, but require particular expertise in both technical aspects and interpretation of the results, it appears most appropriate that

additional specialized organization provides means for their standardization and quality control. These tests would not be the subject of **cIQc**, which would try to focus on the remaining > 100 **class I** tests.

4) **Methods:**

a. Assessment schemes would be primarily based on routine immunostaining of slides from standard processed human histological specimens with varying expression of antigens. These multitissue blocks would be prepared by the members of the core group themselves or by designated expert laboratory in the area relevant to epitopes being tested. The results of the staining would be assessed by core group members and rotating invited assessors from different participating laboratories.

b. All slides would be scanned for virtual microscopy and put on-line for all participants to evaluate and compare. At the moment, scanning of the slides would be provided by Dr. Blake Gilks and the web page for this purpose and storage capability has been provided by the University Of Saskatchewan College Of Medicine. The results of the assessments would be distributed electronically only (to cut the cost of operations). All results would be anonymous and the information on laboratory performance would not be shared with other laboratories. If the results of the testing would indicate suboptimal or poor performance with any of the tests, guidelines/suggestions for improvement would be provided to the laboratory. Also, the laboratory would be allowed to request re-evaluation after implementation of the suggestions with no additional fees.

c. Unidentified data of the results would be used for statistical analyses and as such would be used for presentations, publications, or research.

d. Educational materials on the web would be available for free to all and no password/username would be necessary to use educational material posted on the web. Educational material would be internally peer reviewed and regularly updated to provide relevant information for daily practice to both, pathologist who use the results of immunohistochemistry in clinical work and to technologists/technicians who perform the tests.

e. The organization would organize yearly seminars/workshops for practicing pathologists and pathology residents, which would address technical information regarding methods used in clinical immunohistochemistry, which are relevant to pathologists and also current diagnostic use, suggestions/guidelines for use of immunohistochemistry based on published research and also on experience of national and international experts in clinical immunohistochemsitry. Currently, a proposal for an upcoming CAP Workshop is being submitted to cover the topic on immunohistochemical

evaluation of undifferentiated tumours and unknown primary tumours, which we believe are common challenge in diagnostic pathology.

Financially independent organization

cIQc would be a professional and scientific non-for-profit organization independent of economical or political interests. However, the participating laboratories would pay yearly fee to cover expenses related to real cost of testing, web page maintenance, and organization of educational activities. These fees would be dependent on the number of participants (larger the number, smaller the fees) as well as other support and would be very similar to that currently paid for participation in other QC programs (**CAP** from USA, **UK-NEQAS** from UK and **NordiQC** from Scandinavia).

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Proposal for establishment of a Canadian National External Laboratory Quality Control in Diagnostic Immunohistochemistry

Emina Emilia Torlakovic, MD, PhD and Blake Gilks, MD, PhD

11 July 2006

Canada does not have a national external laboratory QC program in diagnostic immuohistochemistry. Other countries including USA, United Kingdom, and Scandinavian countries have established such programs adapted for their own national needs and arena.

Quality assurance in laboratory medicine includes: a) constant checking of test reliability by internal quality control (IQC), b) external quality assessment (EQA) by an independent agency to check performance of a number of laboratories at intervals in order to obtain a retrospective indication of their performance, and c) proficiency control by supervision of pre-test and post-test phases of laboratory work, from specimen collection to delivery of report to the clinician. Currently, diagnostic immunohistochemistry has in excess of 100 tests on the menu, and none are currently uniformly assessed since there is no national Canadian external laboratory independent agency to check their performance.

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pathology and clinical immunohistochemistry, there is no reason for Canada not to have its own external laboratory testing in clinical immunohistochemistry.

We would like to invite Canadian Association of Pathology to support our intention to develop such a program to serve pathology community in Canada and hope that despite the differences in individual practices, the common goal and future benefits of such an organization would unite all interesting parties to contribute in the development of this service.

Enclosed is also a more detailed proposal with additional pertinent information.