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30 May 2007

John Abbott, Deputy Minister of Health
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Dear John:

Further to your request, I am attaching reports that were prepared in relation to the ER/PR issue.

Please note that the reports prepared by Trish Wegrynowski and Dr. Bangrejee were prepared as a peer review request and to that extent we had performed it under our quality umbrella, to ensure its protection from future release.

The report prepared by Dr. Allen Gown was requested by HIROC and therefore not ours to release.

If need be, we can arrange to have the laboratory leaders present on these items.

Sincerely,

George Tilley
President and Chief Executive Officer

Encls (5) reports

Cc Dr. O. Howell, VP – letter only
Heather Predham, Quality – letter only

Quality Review of the Immunohistochemistry Laboratory
Health Care Corporation of St. John's

Prepared For:

Leadership Team of the Laboratory Medicine Program
Health Care Corporation of St. John's

By:

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G1

November 9, 2005

Copy 6 of 8
May 23/07 [illegible]

Copy 1 of 4

Confidential

John Abbott

Dear

Further to your request I am attaching reports that were prepared in relation to the ERI/PR visit

Please note that the report prepared by Trish Wegrzynowski and Dr. B Banerjee were prepared as a peer review report and to that extent we had performed it under our quality umbrella, to ensure its protection from disclosure/further release.

The report prepared by Dr. Allan Gowan was requested by HIRSC staff and therefore not ours to release.

If need be we can arrange to have the laboratory leaders present on these items

G Tilley

Cc. Brian Howard
Health Protection

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1. Introduction

1.1 Executive Summary

The Immunohistochemistry testing performed at the Health Science Center, Health Care Corporation of St. John's was questioned in May 2005, when a change in a patients ER/PR Receptor status occurred.

The inconsistencies associated with formalin fixation, tissue processing and pretreatment methodology compounded by a rotating staff directly affected the repeatability of the Immunohistochemistry results. Also, the lack of Standard Operating Procedures across the Pathology Laboratory contributed to the problem. The high degree of proficiency required to perform, evaluate and interpret Immunohistochemistry testing must be assessed, as both the Technical and Professional staff are accountable for the final outcome. The aforementioned is critical because the reproducibility of Immunohistochemistry results has a direct impact on the Clinicians' therapeutic decisions especially with respect to ER, PR and HER 2-neu.

1.2 Background

The Surgical specimens under review for ER/PR testing were procured, grossed and processed at either the Health Science Center (HSC) or the St. Clare's Mercy Hospital site of the Health Care Corporation of St. John's. All Immunohistochemistry (IHC) testing is performed at the Health Science Center.

From 1997 until 2004 the semi-automated DakoCytomation Autostainer was used for IHC Staining. A Heat Induced Epitope Retrieval pretreatment using Steam was performed manually outside the Autostainer and concentrated Primary antibodies were diluted at the discretion of the Laboratory.

In 2004 the DakoCytomation Autostainer was replaced with the automated Ventana BenchMark IHC/ISH Staining Module which incorporates onboard Antigen retrieval. Predilute antibodies from Ventana were purchased to replace some of the concentrated DakoCytomation Antibodies. IHC is provided by a rotating Registered Technologist staff.

Prior to January 2003, the Formalin fixative was prepared in-house at the HSC and distributed, however, no documentation concerning the pH of this fixative was found. It has since been replaced with commercially prepared 10% Neutral Buffered Formalin fixative.

1.3 Objective

The objectives of this review were as follows:

1. Review the current practices and procedures within the IHC service.
2. Identify issues of concern which may have contributed to the present situation.
3. Provide recommendations pertaining to issues identified.

1.4 Scope

This review will be focused on the Immunohistochemistry service and the procurement and processing from both sites, as tissue fixation and processing provide the basis for accountable Immunohistochemical staining.

1.5 Methodology

Individuals were interviewed to obtain pertinent retrospective and/or current information – Registered Technologists, Pathology Manager, Laboratory Director, Chief Pathologist and Pathologists. The interviews took place from September 20 – 23, 2005. An initial review of the work processes was done.

The intent of this review is strictly professional, and to share relevant knowledge and expertise. All recommendations from my observations are based on College of American Pathologists and Ontario Laboratory Accreditation standards.

2. Histology Laboratory

2.1 Fixation/Grossing

Presently for large Surgical specimens, fixation, grossing and processing are site dependant. Problems with fixation have been identified with breast tissue samples in particular, and those blocks were subsequently reprocessed. The majority of the Breast cases originate from the St. Clare's site. The lack of consistency with fixation and the issue of reprocessing both have had a direct effect on the staining outcome with IHC.

A courier system is in place which transports biopsy specimens to the HSC for grossing and processing from St. Clare's. All embedding, cutting and staining is performed at the HSC on the biopsy specimens, the slides and blocks are couriered back to St. Clare's upon completion.

Frozen sections are performed at both sites. I did not have a chance to review the Quick Section room at HSC site but did at St. Clare's, where the OR Nurse Manager explained how the specimens are handled. Noted however, refrigeration storage is not available for large or unfixed specimens after hours.

Very informal protocols and documentation exist in either laboratory. Procedure Manuals detailing the Standard Operating Procedures do not exist at either site.

Recommendations:

1. Standard Operating Procedures relating specifically to the Grossing/Fixation Procedures must exist for each tissue type to ensure the reproducibility and reliability of results.

2. Three Pathology Assistant positions to be created to facilitate this, rotating between the 2 sites.
   The PA's would be responsible for Quick Sections.
   Autopsy coverage would be arranged on an on need basis with HSC – Pathology Manager.

3. Refrigerator to be available in the Quick Section rooms.

2.2 Processing

Currently each site maintains a Tissue Processor. All specimens grossed each day are placed in the tissue processor at that particular site with the exception of biopsy specimens. The biopsy specimens are handled at the HSC site.

Procedure Manuals outlining the Standard Operating Procedures for the Tissue Processors were not found. Neither signed documentation for the daily maintenance of the processors nor temperature monitoring of the Paraffin wax was found.

Recommendations:

4. To ensure that the Tissue Processing is reproducible, it should be amalgamated to one site. The St. Clare's Tissue Processor should be relocated to the HSC site.
   A Laboratory Assistant to document and maintain the cleaning schedules at one site for the equipment, eliminating duplication.

5. Signed daily cleaning and maintenance schedules for the Tissue Processors must be maintained and retained. Temperature of the paraffin wax must be recorded daily – this is especially important as some antibodies are heat labile.

6. Standard Operating Procedures to be written for the Tissue Processing including identifying different processing, cleaning and maintenance schedules, directions to load and unload the processors, editing and copying the programs and a STAT case policy. Please note this is not a mutually exclusive list.

7. All blocks to remain at HSC site.

8. Couriering of stained slides to remain status quo.

3. Immunohistochemistry Laboratory

3.1 IHC Staffing

Presently three Registered Technologists rotate through the IHC area with an additional Registered Technologist performing the microtomy. Approximately 80 Immunohistochemical tests are performed daily with the majority done on the automated Ventana Benchmark IHC/ISH Staining Module. The HER 2–Neu and Immunofluorescent staining are performed manually on the workbench.

There is no Medical Section Head for the IHC Laboratory. Each Pathologist requests their Immunoperoxidase stains on a request form. Request forms originating from St. Clare's are faxed to HSC. However, any follow up is communicated with the Technologist in the IHC Laboratory for that particular day, or the Pathology Manager.

Both the Technologists and the Pathologist's I spoke with are frustrated with the present situation as there are no clear lines of communication. In addition, the Technologists are overwhelmed as they do not completely understand the theory of IHC and this testing requires high technical proficiency to troubleshoot the methodology.

Recommendations:

9. Three Technologists to be dedicated to perform IHC staining, optimization and validation. The microtomy function to be evaluated at the Pathology Managers' discretion.

10. One of the three Registered Technologists' is to be given the additional responsibility and title to oversee the IHC Labaoratory. The classification to be determined by the Pathology and Laboratory Manager.

11. A Medical Section Head to be designated and responsible for the IHC Laboratory.

    A backup Designate should be selected for the unavoidable times when the Director is not present. This would assist with Succession planning.

12. Lines of authority, communication and organization to be determined prior to establishing these positions.

The Technologist responsible for the IHC Laboratory will report to both the Pathology Manager and the Medical Section Head depending upon the issue at hand.

The Pathologists need to establish a mechanism as to how their IHC concerns/issues will be addressed. Documentation of all concerns/issues must be maintained with the corrective action.

13. Succession planning to be evaluated at both the Technical and Professional level.

3.2 IHC Documentation

Documentation in general was deficient.
Key areas identified in IHC:

- No Test Procedure manual including Standard Operating Procedures.
- Lacking organized current Manufacturer Specification Data Sheets.
- Minimal record keeping of daily/weekly/monthly equipment maintenance.
- No Pipette and thermometer calibration of accuracy.
- No reagent, antibody or detection system evaluation & no validation documentation.
- No equipment documentation and no calibration records
- Retirement of procedures or antibodies not documented
- Retention of records not done.
- Lacking completed Error log and Corrective action
- No Distilled Water monitoring and documentation.

Recommendations:

14. A Procedural Manual outlining the Standard Operating Procedures is to be created outlining all methods and antibodies currently in use.
The manual should be written in compliance with the Clinical and Laboratory Standard Institute (CLSI) using GP2-A4 guidelines for Clinical Laboratory Technical Procedure Manuals.
The Procedure Manual must be available for reference at the workbench. It is to be approved by the Medical Director and reviewed annually by the Medical Section Head.

It would be prudent to send the Technologist responsible for compiling and maintaining the Procedural Manual to a computer course for Word and Excel programs.

Note:
The Ventana BenchMark Operator's Manual was available at the work bench. It is an acceptable component of the overall IHC departmental procedures but does not replace a Procedure Manual.

15. Antibody Data Specification Sheets to be available for all antibodies currently in use.

The Data sheets should be kept in alphabetical order and be available at the workbench for both Technical and Professional reference.
It would be prudent to maintain the specifics of the Lot Number in use, such as the Clone, Expiry Date, Storage conditions and Specific Staining Instructions with the Data sheet for easy reference.

16. Routine Equipment Maintenance must be performed and documented.

Internal Check:
The Ventana BenchMark Staining Module has a daily/monthly/quarterly Maintenance program.
The Registered Technologists currently perform the daily maintenance but do not always document it, this must change.

The quarterly maintenance program includes a computer portion which the Registered Technologist is unable to access. This documentation should then be provided from the Information Technology department and included with the Equipment Maintenance records.

The microscope must be set up for Kohler Illumination daily to ensure optimal resolution and contrast.

Laboratory personnel are responsible for the reliability and proper function of the instruments they work on. Hence, service and repair records or copies must be available to the technical staff operating the equipment. As well, an alternate protocol must exist in case of failure of the automated equipment.

External Check:
Annual Preventative Maintenance records must be maintained.
The Microtome, weigh balance, Microscope and any other piece of equipment not mentioned are to be annually inspected.

17. Guarantee Pipette and temperature accuracy and calibration.

The accuracy of the volume the pipette delivers must be guarded to ensure the reproducibility of the antibody dilutions.

A standard thermometric device or reference thermometer (NIST-certified or guaranteed by manufacturer to meet NIST Standards) is to be available to check thermometers used on all temperature controlled instruments.

Digital Temperature readings do not suffice and thermometers readings are to be recorded.

18. Documented evaluation must be performed to ensure the sensitivity and specificity of the test results. Each component used in IHC staining must be optimized and validated individually to ensure the outcome and to assist in troubleshooting. Presently this is not being done.

For all Detection System components (matched lot reagents must be tested in unison), Parallel testing of old vs. new lot suffices.

Reagents with a pre-defined pH should be monitored. The pH must be taken and recorded when a new lot is received.

Ensure all storage and handling conditions are met.

Records of reagent check records must be kept.

An inventory log would assist in record keeping.

Primary Antibodies
Pre-diluted and Concentrated
Any change in lot number or concentration, the specificity of the antibody must be verified prior to use.
The staining results should be compared to the previous lot using the appropriate controls.

The validation documentation must be approved and signed off by the Medical Section Head prior to use in Routine Service.
Stained Slides used for validation to be kept for reference.

19. Equipment selection criteria and calibration to be documented.

No documentation for the selection criteria used for the Ventana Benchmark IHC/ISH Staining Module.

For any new equipment or instruments purchased, Protocol and Records must be maintained of the Calibration, Performance and Functional checks and verification performed.

Evidence of training and competency of Technical staff on Equipment must be available.

20. Retired Procedures and antibodies information must be retained for 2 years and readily available.
It is recommended that these records are retained for longer for Reference.

21. All issues, concerns and corrective actions must be documented. This should be done by both the Technical and Professional Staff.

22. Distilled water is available on tap in the laboratory. Documentation of the suitable quality of this water for the testing being performed was not found nor was it known.

Type II water is used for microbiology media preparations, histology stains and dyes. reagents to be sterilized and reagents with preservatives. Testing and documentation is to include the tolerance levels of silicates, pH and organic contaminants.

3.3 Immunofluorescent Staining

Currently specimens sent for immunofluorescent staining are not retained after sectioning. The patient samples are left in the cryostat which renders them unusable the following day and they are discarded.

No controls are used and the immunofluorescent staining is performed in a lit environment.

The Fluorescent antibodies are stored correctly.

Recommendations:

23. All tissue samples must be retained for 2 weeks after the final report is issued, the specimen integrity must be maintained. The frozen patient tissue samples are to be labeled and stored correctly to avoid dessication in a frost-free freezer. Specimens will maintain their antigenicity longer when stored at -80°C.

24. Interpretation of every staining procedure must be substantiated with the use of controls, both positive and negative. Controls must be handled exactly as the patient test samples. It is also ideal that the control sections used have a composition similar to the patient samples being tested. Positive controls assure that the specimen staining was correctly performed while negative controls assess non-specific staining.

    The use of frozen sections from previously confirmed positive and negative cases offers the easiest and most practical way to obtain controls for Immunofluorescence studies.

25. To obtain the brightest staining with the lowest background, Immunofluorescent staining should be performed protected from light.

3.4 Her 2- Neu Testing

Currently the HER 2-neu testing which provides predictive/prognostic information is performed manually using a kit. The manual pretreatment method for these markers is the same as was used in the past for the ER/PR testing. The issue of reproducibility and consistency is of concern.

Recommendations:

26. This methodology must be performed in the strictest of conditions. Automation of the procedure is suggested.

    The variation in pretreatment between testing batches must be guarded to ensure that all test results are reproducible. Strict adherence to time and temperature must be maintained.

3.5 Controls

Currently positive tissue controls are placed on every patient tested slide. No negative controls are used.

No daily assessment and documentation of the controls is performed in the IHC Laboratory. Without assessing the controls, no troubleshooting of the procedure is occurring.

Presently, the onus is on the individual Pathologist to assess the control tissue with the patient sample. No documentation from the Pathologists was found.

Recommendations:

27. Negative reagent controls to be run on every block of patient tissue being tested.

28. Negative tissue control slides to be run for each antibody. A multi-tissue or "Sausage" block will serve this purpose.

29. IHC Registered Technologists to be trained to interpret and make an assessment of the quality and specificity of staining for every positive and negative control daily tested.

    Signed documentation of this assesment must be maintained.

    Also, a review of tissue recognition would be an asset.

4. Surgical Reports

Presently each site has their unique report Headings on the Surgical Pathology reports. Also, a standard reporting format was not identified.

Recommendations:

30. Standard Report Headings for both sites of the Health Care Corporation of St. John's.

31. Standard Reporting for all predictive/prognostic information. Investigate Synoptic Reporting capability with Meditech, Medical Information Technology, Inc.

32. All IHC tests providing predictive/prognostic information must include information in the patient report on specimen processing, antibody clone and the scoring method used.

5. Quality Assurance

Currently neither External Quality Assurance nor Inter-Laboratory comparison (excluding Mount Sinai Hospital Retrospective analysis) is performed.
No documentation was seen concerning Internal Quality Assurance for both the Technical and Professional components.

You need to ensure the quality of your Laboratory's results to determine the accuracy and reliability of the procedure. There must also be a mechanism to evaluate the interobserver variability amongst all the Pathologists interpretation of IHC staining.

Recommendations:

33. Membership in the College of American Pathologists.
    Peer assessment/educational program.
    Peer performance programs.

34. Inter/Intra Laboratory Comparison between St. Clare's and HSC Pathologists
    Inter observer interpretation and quantification
    (ER, PR and Her 2-neu)
    Case/Control Review
    Histology/Cytology Correlation

35. Proficiency Testing – Inter-Laboratory testing, develop a mechanism to compare results with other sites.

36. IHC user group
    The ability for the IHC Registered Technologist to discuss issues and advances with their peers.

    It would also be advantageous for the Technologists to attend any Medical Rounds relevant to the work they are involved with to understand the larger scope of practice.

6. Miscellaneous

6.1 Competency Testing

Presently no documentation exits relating to the training of staff to perform their assigned duties.
Competency Assessment for all staff is not performed in the Pathology Division, Laboratory Program. The Pathology Manager has begun to investigate this process.

Recommendation:

37. Staff must be provided with training and given a documented performance appraisal prior to working without supervision.

38. Staff to be assessed for competence to perform tasks following training. Identify requirements of a task, perform gap analysis and develop action plans.

6.2 Reference Tools

Presently the IHC Laboratory does not have the Internet available at the workbench.
No textbooks were found in the IHC Laboratory

Recommendation:

39. Internet availability as a reference tool at the workbench. Purchase Immunohistochemistry textbooks for the Laboratory.

6.3 Continuing Education/Conferences

The National Society of Histotechnology annual convention is an excellent opportunity for Histotechnologists to attend lectures and workshops devoted to Immunohistochemistry.

Recommendation:

40. Funding available for a IHC Technologist to attend the NSH convention.

6.4 Equipment Placement

The Automated Special Stainer is in close proximity to the Ventana BenchMark. Want to ensure that the equipment is not disturbed, it should be unobstructed.

Recommendation:

41. Relocate the Automated Special Staining equipment.

6.5 Safety

The Fume hood located in the IHC Laboratory had Acid bottles (Acetic, Formic and HCl) out on the enclosed work area.

Recommendation:

42. Acid Storage to be in a rigid leak tight safety cabinet which is able to contain an accidental spill.

6.6 Histocollimator

This product assists the Microtomist with aligning and orientating the paraffin blocks for recutting sections.

This device is available through ESBE Scientific, although I do not know if it will fit onto the Leica Microtome.

7. Resources

- Clinical and Laboratory Standards Institute
  GP2-A4
  Clinical Laboratory Technical Procedure Manual; Approved Guideline
  HS1-A2
  A Quality Management System Model for Health Care;
  Approved Guideline—Second Edition
  www.clsi.org

- College of American Pathologists
  www.cap.org

- The National Society for Histotechnology
  The Journal of Histotechnology
  www.nsh.org

- Applied Immunohistochemistry and Molecular Morphology
  Journal AIMM
  www.appliedimmunohist.com

- ImmunoQuery
  www.ImmunoQuery.com

Text Books/Handbooks

- Diagnostic Immunohistochemistry:
  David J., M.D. Dabbs

- Immunohistopathology: A Practical Approach to Diagnosis, 2nd Edition:
  Jules M. Elias

- Introduction to Immunocytochemistry
  J.M. Polak and S. Van Noorden

- Immunochemical Staining Methods Handbook, 3rd Edition:
  DakoCytomation

8. Conclusion

Rotating Pathology Assistants providing the grossing of large specimens would standardize the procedures between the two sites. Standardizing the fixation time of every specimen will have a direct correlation on the quality of IHC staining

The consolidation of Tissue Processing at the HSC site should be implemented. The consolidation would ensure that all specimens are processed in the same manner and that the Tissue Processors are maintained in the same way. Standardizing the processing will positively impact the IHC staining.

Procedure Manuals must be written; in particular for the Manual in the IHC Laboratory, the Standard Operating Procedures must address all methods and antibodies in use. Documentation must be done throughout the Laboratory.

Three non-rotating Registered Technologists to be employed in IHC, with one appointed a level of responsibility. These Technologists will be responsible for all aspects of IHC from validating all elements of every staining procedure to assessing controls.

A Director of the IHC should be appointed. A designate should be selected for when the Director is not available. The Director will assist in the validation process and will act as the conduit between the Technical and Professional staff.

It is essential that the Laboratory becomes involved in a peer assessment program.

Standardization of all processes will result in increased reliability and reproducibility of the IHC results.

The Pathology Laboratory of the Health Care Corporation is more than capable of attaining this degree of competency.

Quality Reassessment Review of the Immunohistochemistry Laboratory Health Care Corporation of St. John's

Prepared For:

Leadership Team of the Laboratory Medicine Program
Health Care Corporation of St. John's

G2

Prepared By:

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May 2, 2006

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1. Introduction

1.1 Executive Summary

The testing performed in the Immunohistochemistry Laboratory operated by the Health Science Centre Site, Health Care Corporation of St. John's was queried in May 2005 as a direct result of a change in a patient's ER/PR receptor status with the reassessment of the tumour.

In September 2005, the Pathology Laboratory's practices and procedures were evaluated. The inconsistencies identified in Immunohistochemistry and the total lack of Standard Operating Procedures throughout the entire Pathology Laboratory for both the Technical and Professional Staff, directly contributed to the lack of reproducibility associated with the ER/PR Receptor status.

1.2 Background

A peer review performed from September 20-23 2005 included both Technical and Professional staff at the Health Science Centre and St. Clare's site's Pathology Laboratory. The emphasis of the review was the Immunohistochemistry service.

Recommendations were prepared for the Leadership Team of the Laboratory Medicine Program in a report dated November 9, 2005.

Two of the Registered Technologists assigned to the Immunohistochemistry service have been sent to other institutions to view their processes since the Quality Review of the service. (Mount Sinai Hospital, Toronto, Ontario and Jewish General, Montreal, Quebec.)

A reassessment of the Immunohistochemistry Laboratory occurred from March 30-31 2006 at the request of Dr. R.J. Williams, Vice President, Quality, Diagnostic and Medical Services.

A Recommendation – Immunohistochemistry Service spreadsheet, compiled on December 16, 2005 and updated March 10, 2006 was reviewed prior to the reassessment.

1.3 Objective

The objectives of this review were as follows:

1. Evaluate the current practices and procedures within the Immunohistochemistry Laboratory.
2. Comment on the progress of the Immunohistochemistry Laboratory.
3. Provide recommendations detailing issues identified.

1.4 Scope

This review will be focused on the Immunohistochemistry Laboratory in particular and Pathology in general.

1.5 Methodology

The Immunohistochemistry Laboratory Technologists processes were assessed from March 30- 31, 2005. The process assessment was evaluated by interviews, the review of written material and observation. A brief discussion also took place with Mr. Barry Dyer and Ms. Catherine Parnell.

The intent of this review is strictly professional, and to share relevant knowledge and expertise. All recommendations are based on the College of American Pathologists and Ontario Laboratory Accreditation Standards.

2. Histology Laboratory

2.1 Fixation/Grossing

The fixation and grossing of the Surgical Pathology specimens has remained site dependant. The majority of the Breast cases still originate from the St. Clare's site. This review did not include a visit to the St. Clare's site and did not review any processes or documentation associated with the fixation of specimens at either site.

The Courier system has been enhanced. A "Stat" courier travels between the two sites four times per day. There is documentation available relating to the receipt of the Surgical specimens.

Frozen sections continue to be performed at both sites. I had an opportunity to inspect the Quick Section room at Health Science Centre on this occasion. Refrigeration storage is still not available for large or unfixed specimens.

Four Pathology Assistant positions have been recently created. This shall provide an opportunity to ensure that all fixation and grossing procedures at both sites are consistent and standardized.

Very informal protocols and documentation exist. Standard Operating Procedure Manuals do not exist.

Recommendations:

1. Standard Operating Procedures relating specifically to the Accessioning, Grossing and Fixation Procedures must exist for each tissue type to ensure the reproducibility and reliability of all test results.

2. Documentation must exist in regards to the Pathologist Assistants relating to the types of specimens and the extent of the examination they may perform and whether there is direct or indirect Pathologist supervision for each type of specimen the PA will gross.

   Documentation must also exist as to the performance of the Pathologist Assistants. They are to be evaluated by the Pathologists.

May 30/06 ordered

3. A Refrigerator in Operating Room Quick Section room at all sites.

   This has not been addressed since the assessment.

done

4. Suggest a time stamp for the receipt of specimens from the courier to avoid any unforeseen circumstances where the time of receipt could come into question by any of the parties.

2.2 Processing

The Tissue Processors are now all located at the Health Science Centre. The specimens which are fixed and grossed at the St. Clare's site are couriered to Health Science Centre. This should improve the reproducibility of the processing and eliminate duplication in the maintenance of the processors.

With the relocation of the tissue Processor from the St. Clare's site, the Technical Staff has been reassigned to the Health Science Centre. This has had a direct effect on the workflow as all processing, microtomy and staining takes place at the one site. This reduces the duplication of maintaining embedding centers at both sites and streamlines the Histology workflow. Also four additional Registered Technologist positions have been created. This should provide an opportunity to review staffing, competency, workflow and hours of operation of the Laboratory. This should benefit the Laboratory especially with the forecasted implementation of the Tissue X-Press Processor.

Procedure Manuals detailing the Standard Operating Procedures for the Tissue Processors do not exist. I did not have an opportunity to review the Processing area but was informed that Temperature monitoring and Maintenance documentation has begun.

The St. Clare site has 5 Pathologists who assess and evaluate the Surgical Breast samples. All paraffin embedded blocks are kept on site at Health Science Centre for 3 months and are subsequently stored at St. Clare's. This change in workflow expedites the service for all subsequent requested work.

Recommendations:

5. Standard Operating Procedures are to be written for the Tissue Processors. Done

6. Standard Operating Procedures are to be written for the Embedding Centers and embedding protocols for all tissue types.

7. Procedures for the handling of sub-optimal specimens must be developed and documented.

3. Immunohistochemistry Laboratory

3.1 IHC Staffing

The Immunohistochemistry Section is now staffed with three Registered Technologists dedicated to perform the staining, optimization and validation. The staff have also absorbed the microtomy function. One of the Technologists has been given the lead position.

The Registered Technologists have retooled the workflow and have established a rotation in the area allowing for maximum coverage.

A Medical Section Head has been established for the Immunohistochemistry Laboratory. It is my understanding the Section Head may be retiring this year and a Successor has recently been named.

Each Pathologist requests their Immunoperoxidase stains on a request form. The Pathologists from the St. Clare site fax their requests to Health Science Centre. As all blocks are on site, there is no longer a waiting period for the blocks to be retrieved and sent from the St. Clare's site. This has streamlined the process.

Lack of communication between technical and professional staff remains an issue. For example, recently the marker Low Molecular Weight Keratin was added to all Sentinel Lymph node biopsy protocols. The Immunohistochemistry Laboratory was not apprised of this prior to implementation. This had a direct impact on the Laboratory not only regarding the amount of Primary antibody and Detection System required for staining but on the workload in general.

Recommendations:

8. Lines of communication need to be enhanced to ensure uninterrupted workflow to accommodate changes in protocols.

9. Evaluate Succession planning at the Technical level as 2/3 Registered Technologists are and/or will be eligible for retirement in the short term.

3.2 IHC Documentation

The process of Documentation has recently begun in Immunohistochemistry. Key areas identified*:

- Assemblage of a Procedure Manual has been initiated. However, the Manual is not written in compliance with the Clinical and Laboratory Standard Institute (CLSI) guidelines.

- All antibody data sheets have been compiled however, formal documented validation is not present. Templates of examples of validation worksheets were provided during the initial assessment.

- Recorded Maintenance records of the Ventana Benchmark were present.

- NO Pipette and thermometer calibration of accuracy documented.

- Reagent and detection system validation initiated.

- Retirement of procedures and antibodies documentation commenced.

  Ensure documentation is evident in the Procedure Manual as to location of Retired documents and/or Procedures.

  Ensure that obsolete reagents are removed and only currently authorized reagents are available for use.

- Incomplete Corrective action and Error log present.

- Retired Procedures and antibodies information has been gathered. Maintain records for a minimum of two years.

Recommendations:

10. A Procedure Manual outlining all Standard Operating Procedures to be written in compliance with the Clinical and Laboratory Standard Institute (CLSI) using GP2-A4 guidelines for Clinical Laboratory Technical Procedure Manuals.

The Manual shall contain all procedures, methods, antibodies and documentation utilized in the service.*

11. Antibody Specification Sheets have been compiled in alphabetical order.

Formal Documented validation sheets needed for each working antibody detailing its specific requirements for use including the appropriate control tissue and staining pattern

Any change in lot number requires verification of the specificity of the antibody and documentation PRIOR to use. Stained slides used for validation to be kept for reference.

12. Microscope Maintenance and Documentation
The microscope must be set up for Kohler Illumination daily and recorded to ensure optimal resolution and contrast.

This has not been addressed since the assessment.

13. Documentation guaranteeing the Pipette accuracy and calibration.

The accuracy of the pipette delivery volume must be guarded to ensure the reproducibility of the antibody dilutions when using concentrated antibodies.

This has not been addressed since the assessment.

14. Digital Temperature readings do not suffice and thermometer readings are to be recorded.

A Standard thermometric device or reference thermometer (NIST certified or guaranteed by manufacturer to meet NIST standards) is to be available to check all thermometers used on temperature controlled instruments.

This has not been addressed since the assessment.

The refrigerator which contains all the antibodies and detection systems does not have a thermometer in it for daily readings.

This has not been addressed since the assessment.

The refrigerator containing the antibodies and detection systems is not on an alarm. An alarm system should be considered.

Documentation of temperature readings was found. However, there is no evidence of established acceptable limits and corrective actions required when the temperatures fall outside those limits.

15. Documented evaluation performed to ensure the sensitivity and specificity of all test results has commenced. The validation documentation must be stringent.

The Procedure Manual should contain the processes that are in place to assure that all reagents used are appropriately controlled.
Parallel testing of old versus new reagents is acceptable.

Include alternate Protocols in the Procedure Manual in case of a failure with the Automated Instruments, if this is applicable.

The pH is now verified for all pH-dependant reagents.

There must also be a process in place in the Procedure Manual for those instances where the pH is outside of acceptable limits.

16. New Equipment/Instrument selection criteria to be documented.

A generic Equipment selection criteria document could be established by the Pathology Manager regarding any new Pathology equipment purchase.

No evidence of a New Equipment Selection Criteria document was provided despite previous recommendation.

Evidence of training and competency of Technical Staff must be recorded. Evidence of competency/training on the Ventana Benchmark has been completed.

The new Ventana Stainer, Benchmark XT, is still in the evaluation process. Protocols and Records must be maintained as to the Calibration/Function Checks. Ensure both Function Verification and Performance Verification.

17. Corrective Action log to be maintained to record all issues and concerns. This tool will benefit both the Technical and Professional Staff.

18. A policy must be established relating to the non-specific false positive staining associated with staining from endogenous biotin. This is critical as the Laboratory utilizes an avidin-biotin complex detection system.

    Testing which requires pretreatments and heat induced epitope retrieval should be routinely blocked with avidin and biotin to avoid this issue.

*Not a mutually exclusive list.

3.3 Immunofluorescent Staining

Currently the Patient labelled specimen bottles sent to the Laboratory containing the Immunofluorescent sample are not retained after the specimen is sectioned.

No controls are used when performing this testing. This has not been addressed since the assessment.

Cover slipping of the slides is performed in a lit environment.

Recommendations:

19. All tissue samples and their respective labelled containers are to be retained for 2 weeks after the final report is issued. The container is kept in case of any issues concerning the specimen/patient information.

20. Interpretation of every staining procedure must be substantiated with the use of controls, both positive and negative. Controls must be handled exactly as the patient test samples. Positive controls assure that the specimen staining was correctly performed while negative controls assess non-specific staining.

    Using sections from previously confirmed positive cases offers the easiest and most practical way to obtain controls for Immunofluorescence studies.

21. To obtain the brightest staining with the lowest background, both the staining and the cover slipping should be performed protected from light.

3.4 Controls

External positive controls continue to be placed on every patient tested slide.
Negative controls are still not used as suggested in the initial recommendations.

Daily assessment of the external positive controls and documentation are not performed in the Immunohistochemistry Laboratory. Without assessing the controls, internal daily troubleshooting of the procedure is not occurring in the Immunohistochemistry Laboratory.

The Section Head of the Immunohistochemistry Laboratory has initiated training of the Registered Technologists in respect to assessing the control slide. No formal documentation was found.
A multi header microscope has been purchased for the Laboratory and was not yet assembled at the time of this visit. This will be an excellent teaching tool.

The Immunohistochemistry Laboratory is also beginning to establish a documented control tissue bank.

Recommendations:

22. Negative controls are to be stained and evaluated on each block of patient tissue being tested. The negative control assesses non-specific or aberrant staining in the patient tissue related to antigen retrieval and/or the detection system. Ideally, the section of patient tissue is treated in the same manner as the patient test. However, the patient section can be treated with the most aggressive pre-treatment and most sensitive detection system compared to the other antibodies requested on the case. The primary antibody is omitted from the test procedure and can be replaced with a negative reagent control either monoclonal or polyclonal. (Ventana has these products.)

    Negative patient controls should be assessed by the Registered Technologist prior to the slides leaving the laboratory.

    This has not been addressed since the assessment.

23. Negative tissue control blocks to be run for every antibody. A multi-tissue or a "sausage" block will serve this purpose. The control will assess the specificity of the antibody.

24. Immunohistochemistry Registered Technologists to be trained to assess the Quality of the external Positive and negative patient controls tested daily.

    Signed documentation of this assessment must be retained. Retention of all QC records for at least 2 years.

25. The Pathology Laboratory is intending to change their processing equipment. The X-press Tissue processor uses very different technology and reagents than the historical Tissue processors.

    Controls must be guarded to ensure that the patient testing is compared to control tissue that is handled in the exact same manner. They must both have had the same fixation and processing applied to them.

    The effects of tissue processing and preparation on performance characteristics of each antibody should then be established and monitored through the use of the appropriate control tissue.

4 Surgical Reports

Each site continues to utilize their unique report headings on the Surgical Pathology reports. A standardized template or reporting format has not been established as of yet.

Recommendations:

26. Standard Report headings and templates for the Eastern Health Integrated Health Authority.

27. Standard reporting for all predictive/prognostic information. Investigate Synoptic reporting capabilities with Meditech, Medical Information Technology, Inc.

28. Results regarding Immunohistochemistry testing providing predictive/prognostic information must include information in the surgical report regarding the specimen processing, antibody clone and the scoring method used.

5. Quality Assurance

Great improvements have been made in this area. The laboratory has become involved in the External Quality Assurance Programs with the College of American Pathologists and the United Kingdom National Quality Assessment Scheme. Both of these programs can be used as benchmarks of peer-based performance.

The Immunohistochemistry Laboratory has participated in a Peer evaluation/education performance comparison program with the UK NEQAS and the tabulated results of the Immunohistochemistry Laboratories stained slides have been received by the Laboratory.

The Laboratory has also received the Journal of UK National Quality Assessment Scheme. This Journal is an excellent reference tool for the Technologists and Pathologists alike as it covers topics such as:

Guidelines used in validation.
Score staining pattern.
Technical parameters used by the participants.
Features of optimal immunostaining.
Features of suboptimal immunostaining.
Importance of good fixation.
Conclusions from the data and References.

Senior Administration has given approval and support for a Total Quality Management Program. The Quality Management system will encompass all processes relating to quality assurance with a major focus of continual improvement. There must be standards of performance A goal of the program is to provide a system which is as failure resistant as possible.

The Quality Management Program for the Laboratory will have representation from both the Technical and Professional staff. A Full time equivalent Registered Technologist has been designated to this position as has a .2 Full time equivalent of a Pathologist. The job description and Title of the Registered Technologist had yet to be determined. Also to be determined are the lines of authority, committee representation and delegated areas of responsibility.

6. Conclusion

Pathologist Assistants are in the process of being hired. Training has yet to be established. The training period will provide an opportunity for the Pathology Department to develop Orientation and Training records which can be used at a later date for Performance evaluations in respect to both General Performance and Competency.

A Procedure Manual for the Surgical Specimen Handling must be created. It should include documented instructions for the proper dissection, description and histological sampling of the various tissues. There must also be a clearly defined documented policy as to the type of specimens and the extent of the examination which can be performed by a non-pathologist. Bear in mind that all gross examination must be done by a Pathologist, Resident or under the supervision of a Qualified Pathologist.

The Pathologist Assistants will rotate between the Health Science Centre and the St. Clare's sites. This shall provide an opportunity to ensure that all fixation and grossing procedures at both sites are consistent and standardized.

The consolidation of the Tissue Processors to the Health Science Centre has streamlined the workflow, eliminated duplication and enabled the department to insure that the processing of all specimens is controlled. This should provide Management an opportunity to review staffing, competency, workflow and hours of operation of the Pathology Laboratory.

The Immunohistochemistry Laboratory has enhanced their practices since the initial Quality review. The area is now staffed by 3 non-rotating Registered Technologists. This has enabled them to begin working on the Standard Operating Procedures and Policies for the area. It has also provided them with the opportunity to begin formal validation of the antibodies, detection systems and reagents used.

The Director of the Immunohistochemistry Laboratory has begun teaching the Registered Technologists how to assess the external positive controls. This will be facilitated by the addition of a multi-header microscope in the Laboratory. After the training is completed and competency documentation is signed, evaluating the external positive and negative patient controls will become part of their scope of practice. This is essential, because the Laboratory director or their designee should be reviewing all controls slides each day of patient testing.

Recommendations:

29. The Quality Management initiative by the Eastern Regional Integrated Health Authority be shared with the other regions of Newfoundland to ensure the Best Medicine practices.

This initiative will assist in providing reproducible Immunohistochemistry results as the Health Science Center is the reference site for the province.

30. The Quality Management team should be involved in the quality improvement activities within the organization and with the user Physicians.

30. The Laboratory is to establish quality indicators to monitor the Laboratories contribution to patient care.

31. For a successful Quality Management team, the Laboratory management shall ensure that opportunities identified for improvement are dealt with.

32. Corrective action logs should be assessed from each area and include an investigation to determine the underlying root causes. The results of the corrective actions should be monitored to ensure they were effective in solving the original problem. Trends may also be identified which will aid in the development of policies and/or procedures.

Also, keep in mind with the change of processing techniques, new control tissue must be collected to ensure that the patient samples and known positive controls are treated in the exact same manner. Testing of patient samples should not be done until after validation is completed.

The stringency required to ensure the reproducibility of all Immunohistochemistry testing is paramount. No antibodies should be used on patients until after documented validation is completed.

The Immunohistochemistry Laboratory has become involved in peer assessment programs. This has had a positive impact on the service.

All Procedure Manuals should be written in compliance with the Clinical Laboratory Standards Institute and in particular, the Clinical Laboratory Procedure Manual; Approved Guideline.

The Surgical reports should have Standard Report headings and templates for the Eastern Health Integrated Health Authority. This would ensure that all Clinicians received patient information in the same format.

Senior Administration has given approval and support to a Total Quality Management Program for the Pathology Laboratory. The impact of this decision will be far reaching. A major focus of this initiative will be Continuous Improvement as you strive to build a system which is as failure resistant as possible.

The Quality Management initiative by the Eastern Regional Integrated Health Authority could be shared with the other regions of Newfoundland to ensure the Best Medicine Practices for the province.

BC Cancer Agency
CARE & RESEARCH

VANCOUVER

October 17, 2005

Dr. Donald Cook
Clinical Chief
Department of Laboratory Medicine
St. Clare's Mercy Hospital
154 LeMarchant Road
St. John's, NL
A1C 5B8

63

Dear Dr. Cook:

Re: External Quality Review of the Immunohistochemistry Service

Please find enclosed my report as requested. I would be happy to clarify any issues that may arise once you have had a chance to discuss my report with the Leadership Team of the Laboratory Medicine Program.

In addition, please convey to Dr. Robert Williams, Vice President, Medical Services, that beyond the specifics of my report, there should be recognition of the following issues that have bearing on the sustainability of a quality laboratory program:

- Pathologists' compensation should be competitive with those of other provinces, otherwise your department will face ongoing staff turnover as pathologists move to more rewarding positions elsewhere. Unless this "revolving-door" syndrome is dealt with, it will only lead to deterioration of the quality of staff as you will continue to lose your best people.
- For a high quality cancer program in the province, your department must invest in subspecialization, continuing education, and central pathology review for the entire province, in order to provide the highest quality of service and cancer diagnosis, so that your oncologists can manage their patients optimally. All cancer patients deserve the same standard of care regardless of where they live. Accurate pathology diagnoses, grading and staging are essential for clinical decision making and these activities cannot be compromised.

With the 2 recommendations implemented, you will be able to attract and retain the best pathologists.

I also enclose my expense receipts. I waive my consultation fees as a courtesy to a colleague.

Sincerely,

D Banerjee

D. Banerjee, MB, ChB, FRCPC, PhD
Provincial Program Leader – Cancer Pathology
Director, Department of Pathology & Laboratory Medicine

Encl.

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Confidential

External Quality Review of the Health Care Corporation of St-John's Laboratory Medicine Program's Immunohistochemistry Service

October 17, 2005

Dr. D. Banerjee

Provincial Program Director, Cancer Pathology

& Director of Laboratories

BC CANCER AGENCY

Clinical Professor of Pathology and Laboratory Medicine

University of British Columbia

DBanerjee

Copy 7 of 8
May 23/07 to W.D.

Background

In 1997, a Dako Immunostainer was installed for the immunohistochemistry service, replacing the testing of estrogen (ER) and progesterone receptors (PR) by the biochemical method.
This was replaced in 2004 with the Ventana Benchmark system with on-board deparaffinization and antigen retrieval.

The incident problem case:

The case is that of a patient with invasive lobular carcinoma whose tumour was tested in 2002 on the Dako Immunostainer and reported as negative for ER and PR and when retested in 2005 on the Ventana Benchmark, was strongly positive for both receptor proteins.

It should be noted that invasive lobular carcinomas are frequently ER+ (92%),[1] thus the initial negative result should have been questioned.

Four other patients previously tested as negative in 2002 were also retested, and all tested positive with the Ventana System. This led to a review of other (57) cases reported in 2002 as negative which on retesting on the Ventana Benchmark, resulted in a high conversion rate from negative to positive (38/57=67%).

Review of cases

I reviewed a number of cases from the retrospective testing set with Dr. Donald Cook. All of the cases that had converted from negative to positive by switching platforms had one or more of the following characteristics:

1. Poor fixation
2. Negative internal controls (normal ductal epithelium, when present, was completely negative).
3. Absent internal controls (no normal ductal epithelium present to evaluate).

It is apparent that too much reliance is being placed on external positive controls with no attention paid to internal controls.

Literature Review of Dako vs. Ventana Immunostainer Performance

A Medline search revealed no recent published studies comparing the Ventana Benchmark and the DAKO immunostainer. One study was published in 1998, but this was based on earlier versions of the two systems, and may not be relevant for the current discussion.[2]

Literature review about the effects of formalin fixation on ER immunostaining:

Fixation time in formalin does not affect ER results as long as 2 mm thick slices of tissue are placed in fixative within 15 minutes of surgical excision and adequate heat-induced antigen retrieval is performed.[3] However, the effects of under-fixation due to >2 mm thick slices remains a possibility. It should be noted that earlier literature on ER immunohistochemistry using frozen sections or cytology preparations indicates that inadequate fixation leads to loss of ER protein

through diffusion out of the cell nucleus.[4] It is possible that inadequate exposure to formalin would result in diffusion of ER protein out of the cell nuclei during tissue processing. No amount of antigen retrieval would have any effect if the protein has been completely lost during processing. Since the Ventana System did detect ER protein in previously negative cases, one must conclude that even if there was partial loss of ER protein due to poor fixation, the failure of the Dako system was largely due to inadequate antigen retrieval or inadequate antibody and/or detection system optimization, or a combination of these factors. It should be noted that many laboratories, including ours, use the Dako system successfully, having optimized all the steps. It remains possible that even with complete optimization of antigen retrieval and immunostaining protocols, if fixation is not optimized, there will be an irreducible number of false-negative cases. Thus the importance of proper fixation cannot be overemphasized.

Choice of antibody:

Although most laboratories are using mouse monoclonal antibodies against ER protein for ER IHC, the recent availability of rabbit monoclonal antibodies with superior staining performance suggests that the sensitivity of ER IHC could be improved even further, in some cases obviating the need for antigen retrieval. Rabbit anti-estrogen receptor monoclonal antibody (clone SP1) has reactivity even without heat-based antigen retrieval of fixed, paraffin-embedded tissue resulting in intense nuclear immunostaining with very low cytoplasmic staining. SP1 yields the same results as the mouse monoclonal antibody to estrogen receptor (clone 1D5), but the antibody affinity of SP1 is 8 times higher than that of 1D5.[5,6] The SP1 antibody results correlate better with patient response to tamoxifen than the mouse monoclonal antibody results (David Huntsman; personal communication).

Interlaboratory variability

A number of publications indicate poor concordance between laboratories for ER assays, especially for the weakly positive cases, and this is attributed to variation in antigen retrieval protocols.[7,8]

Conclusions about the reasons for test failure

1. Is the Dako system faulty? This is unlikely as there are many laboratories using the Dako system successfully. The reason for test failure was most likely due to a lack of test optimisation, including antigen retrieval method and antibody/detection system titration, as positive controls showed weak staining in general, and internal controls failed in all of the false negative cases.
2. Is the Ventana System too sensitive? There is no evidence that the Ventana system creates false positive results. However, the system still requires optimisation to avoid non-specific cytoplasmic staining.
3. Is there a problem with tissue fixation? There appears to be inadequate attention paid by the grossing pathologists to the thickness of tissue slices, quality and adequacy of fixation and there is no standardised fixation protocol that everyone adheres to.
4. Inadequate or no attention is being paid by the reporting pathologists to the status of internal controls, with inappropriately exclusive reliance on external positive controls. Negative test results in the absence of positive internal controls should have triggered

corrective procedures (optimisation of method, choice of a better fixed block, choice of a block with benign ductal epithelium included, etc.) and should not have been released without troubleshooting, and in the event that poor fixation resulted in internal control failure in all available blocks, this should have been noted in the reports as an uninterpretable cases due to failure or absence of internal controls.

6. Inappropriate choice of blocks with no representative normal ductal epithelium
7. Better education required for technologists, pathologists and clinicians about the pitfalls of IHC, the importance of quality control, and interpretation of IHC results.

Other System Flaws Observed:

1. Lack of dedicated immunohistochemistry technologists. A rotation system is used. This prevents the technologists from gaining in-depth expertise in troubleshooting.
2. Lack of an officially designated pathologist as director of immunohistochemistry service - technologists thus get conflicting feedback from a large number of pathologists. There is no accountability for the quality of the service.
3. Lack of standard operating procedures for grossing, fixation, tissue processing, block selection, positive control block selection, method optimisation through systematic titration, incubation time and antigen retrieval time for each analyte.
4. Lack of subspecialization amongst pathologists, leading to the lack of in-depth knowledge about IHC technical and interpretation details and pitfalls.
5. Disconnect between Laboratory Program Director, Division Manager, Clinical Site Chief, and Laboratory Director in decision making. The organizational charts indicate a complete separation of reporting structures into technical and clinical streams with no matrixed cross-reporting between technical and medical leadership. This leads to frustration and resentment on both sides, lack of communication, lack of accountability, and lack of buy-in. The Division Manager and Program Director appear enthusiastic and keen on modernizing the laboratory, but their efforts have not been appreciated by the pathologists and workflow changes have not been mapped out and implemented (e.g. Sakura Express implementation has failed due to lack of planning of workflow changes). Superior outcomes could be achieved by ensuring better linkages between technical, managerial and medical leadership.
6. Attendance by both medical and technical staff at various conferences with a focus on new technology should be encouraged. Consensus-driven innovation should be the goal.
7. The department needs dedicated Pathologist Assistants to ensure gross room consistency in tissue handling, trimming, and fixation.

Recommendations:

1. Pathologists should subspecialize if possible, covering 2 or more sites each, with one designated leader for each major tumour site.
2. One pathologist should be appointed Section Medical Director for the Immunohistochemistry Service, with a 3 Year term and defined performance expectations. All feedback from individual pathologists should be channeled through the tumour site pathologist leaders to the Section Medical Director, who would instruct technologists about method optimization, choice of antibodies, introduction of new antibodies, etc.

3. Consideration should be given to switching to the rabbit monoclonal antibody SP1 for ER IHC.

4. An appropriate number of technologists must be dedicated to the IHC service and be accountable to the Section Medical Director for all technical quality issues, test menu, choice of reagents and equipment purchase decisions must be based on appropriate discussion and consensus. Technologists should be capable of quality assurance of each staining run and not release slides if internal and external controls have failed. QA/QC failures noted by the reporting pathologists should be documented and reviewed periodically by the Section Medical Director, with corrective measures implemented as soon as possible.

5. Tumour site pathologist leaders must regularly attend appropriate educational and scientific conferences in order to stay current with standards of practice.

6. Pathologist assistants should be hired and trained in order to standardize and optimize gross room procedures and free up pathologists to complete microscopy and sign-out in a timely manner.

7. In order to allow implementation of the Sakura continuous flow tissue processing system, pathologists and technical staff should jointly redesign workflow practices.

8. The Ventana platform is performing adequately, and with improvement in and standardization of fixation protocols, there is no reason that the service could not be resumed without further delay.

9. The laboratory should subscribe to external quality assurance programs such as CAP (http://www.cap.org/apps/docs/proficiency_testing/histoqip_details.htm) or NEQAS (http://www.ukneqasicc.ucl.ac.uk/index.shtml) and should continue to monitor performance by interlaboratory comparisons with appropriate large volume teaching hospital laboratories in Canada of the US.

10. Consideration should be given to organisational chart redesign in order to provide better joint technical and medical accountability, planning, and communication.

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[1] J Clin Oncol. 2005 Jan 1;23(1):41-8.

[2] Clinica Chimica Acta 278 (1998) 185–192

[3] J Clin Pathol 1995;48:429-432

[4] J Clin Pathol. 1982 Apr;35(4):401-6.

[5] Appl Immunohistochem Mol Morphol. 2005 Mar;13(1):91-5.

[6] Am J Clin Pathol. 2005 Aug;124(2):295-302.

[7] Am J Clin Pathol. 2002 Nov;118(5):675-82.

[8] Am J Clin Pathol 2001;115:44–58.

BC Cancer Agency

VICE PRESIDENT

MAY 25 2006

MEDICAL SERVICES

May 23, 2006

Dr. Robert Williams
HealthCare Corporation of St. John's
300 Prince Phillip Drive
St. John's, NL
A1B 3V6

Dear Dr. Williams

Re: Report on Immunohistochemistry Service

Please find enclosed a report based on my last site visit of the Laboratory Medicine Department. I trust this is helpful and will allow the department to proceed with the implementation of the remaining items from my previous recommendations.

With best wishes.

Sincerely,

DBanerjee

Diponkar Banerjee

Encl.

BC Cancer Agency

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copy 284

Confidential

Post-Implementation External Quality Review of the Health Care Corporation of St-John's Laboratory Medicine Program's Immunohistochemistry Service

May 21, 2006

GU

Background

At the request of Dr. R. Williams, I reviewed the performance of the immunohistochemistry laboratory on April 24, 2006, in order to determine whether the quality of immunohistochemistry has improved since my last review, and whether my previous recommendations had been implemented.

Prior Recommendations	Implementation Status
1. Pathologists should subspecialize if possible, covering 2 or more sites each, with one designated leader for each major tumour site.	In progress
2. One pathologist should be appointed Section Medical Director for the Immunohistochemistry Service, with a 3 Year term and defined performance expectations. All feedback from individual pathologists should be channeled through the tumour site pathologist leaders to the Section Medical Director, who would instruct technologists about method optimization, choice of antibodies, introduction of new antibodies, etc.	Implemented- Drs. Fontaine & Elms appointed.
3. Consideration should be given to switching to the rabbit monoclonal antibody SP1 for ER IHC.	Under discussion

4. An appropriate number of technologists must be dedicated to the IHC service and be accountable to the Section Medical Director for all technical quality issues, test menu, choice of reagents and equipment purchase decisions must be based on appropriate discussion and consensus. Technologists should be capable of quality assurance of each staining run and not release slides if internal and external controls have failed. QA/QC failures noted by the reporting pathologists should be documented and reviewed periodically by the Section Medical Director, with corrective measures implemented as soon as possible.	Implemented. 3 dedicated technologists have been assigned to the IHC service. However, a succession plan is required now in order to minimise future problems related to attrition due to retirements. The phenotype of future staff for the IHC section should be based on their knowledge base and minimum educational standards as this area will experience much expansion and highly skilled staff are required for implementing new antibodies, probes of FISH, troubleshooting and maintaining high standards. University graduates at BSc or MSc level should be recruited and trained to perform IHC/FISH at reputable laboratories.
5. Tumour site pathologist leaders must regularly attend appropriate educational and scientific conferences in order to stay current with standards of practice.	In progress
6. Pathologist assistants should be hired and trained in order to standardize and optimize gross room procedures and free up pathologists	Implemented. 3 PAs hired. Issues around qualifications and training to be discussed

to complete microscopy and sign-out in a timely manner.	with senior HR consultants, as these are individuals who will perform delegated medical tasks, requiring a minimum level of education (currently the Canadian Association of Pathologists' guidelines indicate that these should be at a master's level, with formal training as PAs.
7. In order to allow implementation of the Sakura continuous flow tissue processing system, pathologists and technical staff should jointly redesign workflow practices.	Not implemented yet.
8. The Ventana platform is performing adequately, and with improvement in and standardization of fixation protocols, there is no reason that the service could not be resumed without further delay.	Verified that ER and PR IHC quality is acceptable. Her2neu staining still to be validated using FISH as the gold standard.
9. The laboratory should subscribe to external quality assurance programs such as CAP http://www.cap.org/apps/docs/proficiency_testing/histoqip_details.htm or NEQAS http://www.ukneqasicc.ucl.ac.uk/index.shtml and should continue to monitor performance by interlaboratory comparisons with appropriate large volume teaching hospital laboratories in Canada of	Implemented. Only a single survey completed so far. This should be monitored indefinitely.

the US.	
10. Consideration should be given to organisational chart redesign in order to provide better joint technical and medical accountability, planning, and communication.	Not implemented.

Recommendations:

1. ER and PR tests may be resumed effective immediately.

2. Cut-off thresholds for positivity should be based on current published consensus.

3. Her-2neu testing should not be implemented until correlation of results with F.I.S.H has been verified.

4. Other established IHC tests for diagnostic purposes may resume effective immediately.

5. External quality assurance through NEQAS should be continued indefinitely.

6. A succession plan is required now in order to minimise future problems related to attrition due to retirements. The phenotype of future staff for the IHC section should be based on their knowledge base and minimum educational standards as this area will experience much expansion and highly skilled staff are required for implementing new antibodies, probes of FISH, troubleshooting and maintaining high standards. University graduates at BSc or MSc level should be recruited and trained to perform IHC/FISH at reputable laboratories.

7. Organisational structure redesign is required in order to provide better technical and medical accountability, planning, and communication.

8. Pathologists should subspecialize, covering 2 or more sites each, with one designated leader for each major tumour site.

9. Issues around qualifications of pathologists' assistants (PAs) and training

to be discussed with senior HR consultants, as these are individuals who will perform delegated medical tasks, requiring a minimum level of education (currently the Canadian Association of Pathologists' guidelines indicate that these should be at a master's level, with formal training as PAs).

Respectfully submitted

Dr. D. Banerjee
Provincial Program Director, Cancer Pathology
& Director of Laboratories
BC Cancer Agency
Clinical Professor of Pathology and Laboratory Medicine
University of British Columbia
Vancouver, British Columbia
May 21, 2006

Mr Tulles
- Now that you have seen this document, can we discuss implementation
- this is for all Immunohistochemistry not just ERDPR.
BN
Oct 31/2005

Review of Immunohistochemistry Lab The General Hospital Site, St. John's Eastern Health

G6

Prepared for:

Dr. B. Williams, VP
Quality, Diagnostic, & Medical Services

Prepared by:

Terry Gulliver, Program Director
& Dr. D. Cook, Clinical Chief
Laboratory Medicine

October 13, 2005

1. Introduction

1.1 Background

The Pathology Department at The General Hospital performs all Immunohistochemistry testing for the province. Approximately 100 antibodies are utilized in this section of the Lab for various investigations related to most types of cancer, e.g. breast, bowel, lung, brain, prostate, etc. The Lab currently processes approximately 15,000 slides per year for these investigations utilizing an automated system acquired through a 5-year reagent lease with Ventana Medical Systems in April, 2004.

In June, 2005, several breast cancer patients who were tested for ER/PR receptors in 2002 were repeated and a different result was obtained. At this time, Eastern Health has decided to retest all patients who tested negative or weak positive on their original samples from 1997 to present at the Mt. Sinai reference Lab in Toronto.

1.2 Objective

The objective of this proposal is to identify the requirements needed to implement a complete quality assurance program for the Immunohistochemistry Lab ensuring that we provide a standardized and reliable service equivalent to the Mt. Sinai reference lab in Toronto.

1.3 Scope

The scope of the proposal includes a review of all components of the Immunohistochemistry service from grossing the specimen to Pathologist's interpretation.

1.4 Methodology

Work processes were reviewed internally by the Lab Program including the Pathology Manager, Technologists, Site Chief, Clinical Chief, and Program Director. Additionally, suggestions from the Q.I. review by Heather Predham and the on-site visits by Dr. D. Banerjee from B.C. Cancer Agency and Trish Wegrynoloski from Mt. Sinai are also incorporated in this proposal.

2. Process Review

2.1 Grossing/Processing

Currently, the gross dictation and dissection of surgical samples (~ 30,000/year) is performed by Laboratory Technologists and Pathologists/Residents. Several years ago, due to shortages of Pathologists, it was decided to assign grossing

duties for most small biopsy tissue samples to the Technologists. The Pathologists retained the grossing function of all large tissue samples, e.g. breast, bowel, prostate, etc.

Three senior Technologists were trained for this function and these Technologists are the same three who also work in the Immunohistochemistry section of the Lab and they rotate between these two sections. While this change in practice helped with the Pathologists' workload, the Lab still had up to 18 different Pathologists rotating through the gross bench along with the Technologists. It did not provide any opportunity for the standardization of the grossing function and also placed a greater demand on the Technologist's time allocated to the Immunohistochemistry section.

Most major Labs in Canada have trained Technologists for the complete grossing of surgical specimens and several Labs also have these staff assist the Pathologist during autopsy grossing/dissection. As indicated above, this change in practice was necessary to address the shortage of Pathologists in Canada, thereby, allowing the Pathologists more time dedicated to the interpretation and diagnosis of specimens as opposed to the physical grossing and dissection. A byproduct of this change in process has been the ability of those Labs who have trained Pathologists' Assistants to have a dedicated core of Technologists who are skilled in this function and thereby, have been able to standardize the grossing function.

It is recommended that:

a. **Most grossing/dissecting functions be performed by trained Technologists (Pathologists' Assistants).**

b. **Purchase gross workbench for The General site.**

2.2 Technical Processes

Currently there are three Technologists who are trained for the Immunohistochemistry section of the Lab. As indicated above, these Technologists also rotate on the gross bench. The Lab processes approximately 15,000 slides per year in this section and continues to experience increased demands for this service (20% over the past 2 years). As the provincial reference site, this section of the Lab generates approximately $75,000 per year in revenue.

This section of the Lab has more than 100 antibodies that can be tested for depending on the Pathologist's investigation and type of cancer suspected. On any given day the Technologist may produce 80 slides using 15 – 25 different antibodies including ER/PR. These slides when complete are then submitted to the individual Pathologists for interpretation and diagnosis. Known controls are performed daily with each batch of slides.

It is recommended that:

c. **Three FTE's be dedicated solely to the Immunohistochemistry section of the Lab.**

d. **The Technologists be trained to review all patient/control slides before release to the Pathologist.**

e. **Install a third instrument to deal with patient volume increases and new requirements for additional control slides.**

2.3 Pathologist's Interpretation

Currently, each Pathologist requests Immunohistochemistry procedures based upon the type of tissue and possible type of cancer they are investigating. The Technologist completes the procedures and returns the slides to the Pathologist. There is a need for subspecialization of Pathologists, particularly in breast cancer where interpretation of immunoperoxidase stains and monitoring of trends is crucial. There is also a need for a single Pathologist to oversee the service and to provide direction to technical staff and to liaise and consult with Pathologists.

It is recommended that:

f. **One Pathologist be assigned the responsibility for all aspects of the Immunohistochemistry service.**

g. **While all Pathologists will continue to interpret/report Immunohistochemistry cases, it is recommended that they be given the opportunity to subspecialize for certain cases, e.g. 2-3 Pathologists would interpret all breast cancers.**

3. Quality Assurance

Currently, the Lab runs known positive controls with each batch on a daily basis depending on the antibody being tested for. These slides are reviewed by the individual Pathologists. The Lab does not participate in outside proficiency testing for Immunohistochemistry. The Lab has never had the opportunity to participate in either conferences, teleconferences or able to network with other I. P. Labs.

It is recommended that:

h. **The Immunohistochemistry Lab enroll in outside proficiency testing, e.g. CAP.**

i. **All recommendations by Trish Wegrynoloski be implemented (cutting of blocks, documentation, log books, equipment maintenance, etc.).**

j. **Recommend a separate C. E. budget be established for books, journals and conferences.**

4. **Space**

The Immunohistochemistry section of the Lab was physically located in the main Pathology Lab at The General Hospital until mid-2003. Upon recommendation by Dr. Ejeckam, this section moved adjacent to the main Lab in the former Hormone Assay Lab space. Plans have been in place for several years to have the Pathology Lab as a whole renovated incorporating the former Hormone Assay Lab which had been identified as a new separate Immunohistochemistry Lab.

It is recommended that:

k. **The current space identified be dedicated for Immunohistochemistry services only and Facilities Management complete the proposed renovations.**

5. **Overall Impact/Analysis of Recommendations**

a. **Most grossing/dissecting functions be performed by trained Technologists (Pathologists' Assistants).**

Based upon current and future volumes, the Pathology Lab will require 4 FTE's to be trained as Pathologists' Assistants and 1 FTE Lab Assistant to provide assistance for processing/labeling cassettes, etc. The PA's would replace the grossing function currently performed by the 3 Technologists in the Immunohistochemistry Lab and the 18 Pathologists who rotate through the gross bench, thereby allowing the Lab to standardize its fixation and grossing function.

It is anticipated that the Lab Technician at St. Clare's will retire in the next couple of months. This position should be upgraded to a Pathologists' Assistant position, thereby 3 new positions need to be created.

3 FTE PA's including benefits	$183,600
1 FTE MLA including benefits	$ 45,600
Upgrade 1 Lab Technician to PA	$ 9,000
Replacement staff during training of PA's	$ 40,000

b. **Purchase gross workbench for The General site.**

Cost ~$40,000

c. **Three FTE's be dedicated solely to the Immunohistochemistry section of the Lab.**

As outlined above.

d. **The Technologists be trained to review all patient/control slides before release to the Pathologist.**

Send 1 Technologist for approximately 4 weeks to Jewish General in Montreal for training in addition to on-site training by Pathologists.

One time cost to cover expenses ~$5,000

e. **Install a third instrument to deal with patient volume increases and new requirements for additional control slides.**

Request quote from Ventana Medical systems on increased cost to current reagent lease to install a third instrument.

Cost (add to base budget 2006/07) $30,000

f. **One Pathologist be assigned the responsibility for all aspects of the Immunohistochemistry service.**

Completed - Dr. Ejeckam has accepted this responsibility.

g. **While all Pathologists will continue to interpret/report Immunohistochemistry cases, it is recommended that they be given the opportunity to subspecialize for certain cases, e.g. 2-3 Pathologists would interpret all breast cancers.**

Dr. Cook will liaise and consult with Pathologists to determine subspecialties. This is solely dependent on the maintenance of current allocated Pathology manpower levels and competitive remuneration with the rest of Canada to ensure retention and recruitment of Pathologists.

h. **The Immunohistochemistry Lab enroll in outside proficiency testing, e.g. CAP.**

Currently enrolled in CAP. Cost/Year $5,000
Dr. Ejeckam has requested to enroll in UK proficiency testing program $7,000

i. **All recommendations by Trish Wegrynoloski be implemented (cutting of blocks, documentation, log books, equipment maintenance, etc.).**

This will require the addition of 1 FTE Technologist I to be dedicated to the proper orientation and cutting of all Immunohistochemistry cases on a daily basis. This Technologist would also ensure the organization/ documentation of referral cases and daily maintenance.

1 new FTE Technologist I Savings ($8,000)

There is a pending retirement (Technologist III) in our Cytology Laboratory and this position can be transferred to Pathology.

Send 1 senior Technologist to Mt. Sinai for 2 weeks to review their Laboratory setup/protocols and quality assurance.

Cost ~$3,000

j. **Recommend a separate C. E. budget be established for books, journals and conferences.**

Annual Pathology C.E. Fund $10,000

k. **The current space identified be dedicated for Immunohistochemistry services only and Facilities Management complete the proposed renovations.**

Dr. Ejeckam and Barry Dyer are reorganizing the space in the old Hormone Assay Lab to ensure that only Immunohistochemistry services are provided in that area.

Cost of renovations to be determined by Facilities Management.

6. Conclusion

If all of the recommendations outlined above are implemented, The General Hospital site should be able to offer an Immunohistochemistry service equivalent to that available at the Laboratory at Mt. Sinai. Some of these recommendations have already been implemented, others can be implemented fairly quickly, however, it may take 6 to 9 months to complete all recommendations.

Overall adjustments required to be added to base budget:

$238,200	Staffing
$ 30,000	Operational/Reagents
$ 12,000	Annual Proficiency Testing
($ 8,000)	Savings from Cytology Staff Transfer
$ 10,000	CE Fund
$282,200	

One-Time Costs Associated with Staff Training:

$ 48,000

One-Time Costs Capital Purchase:

$ 40,000

We look forward to a favorable response to this proposal. If you require any further information or need further clarification, we would be happy to meet with you.

Terry Gulliver, Program Director
Laboratory Medicine

Dr. D. Cook, Clinical Chief
Laboratory Medicine