COMMISSION OF INQUIRY

ON HORMONE RECEPTOR TESTING

BEFORE THE HONOURABLE JUSTICE CAMERON - COMMISSIONER

June 23, 2008

Appearances:

Bernard Coffey, Q.C. . . . . Commission Co-counsel
Sandra Chaytor, Q.C./Mandy Woodland . . . . Commission Co-counsel

Rolf Pritchard/Jackie Brazil . . . . Her Majesty in Right of NL

Peter Browne/Jane Hennebury . . . . . Doctors Kara Laing et al

Daniel Simmons . . . . . Eastern Regional Integrated
. . . . . Health Authority

Ches Crosbie, Q.C. . . . . Members of the Breast Cancer
. . . . . Testing Class Action
Mark Pike . . . . . NL Medical Association
Jennifer Newbury . . . . . Canadian Cancer Society (NL Division)
Blair Pritchett. . . . . Central, Western and Labrador-Grenfell
Regional Integrated Health Authorities

LIST OF EXHIBITS

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COMMISSIONER:

Q. Than you. Please be seated. Good morning. Mr. Coffey.

COFFEY, Q.C.:

Q. Thank you, Commissioner. The next witness is Frances O'Malley, Dr. O'Malley, Registrar, please.

COMMISSIONER:

Q. I think we have additional counsel.

COFFEY, Q.C.:

Q. Yes, I apologize.

MR. CLEMENTS:

Q. Yes, Simon Clements from Toronto, counsel for the four witnesses you're going to hear from this week from Mount Sinai Hospital.

COMMISSIONER:

Q. Welcome.

COFFEY, Q.C.:

Q. Thank you, Commissioner.

DR. FRANCES O'MALLEY (SWORN) EXAMINATION BY BERNARD COFFEY, Q.C.

REGISTRAR:

Q. And would you please state and spell your complete name for the Commission?

DR. O'MALLEY:

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A. France O'Malley, F-r-a-n-c-e-s, O-'-M-a-l-l-e-y.
REGISTRAR:
Q. Thank you.
COFFEY, Q.C.:
Q. Commissioner, I have some additional exhibits, please? They are Exhibit P-1696, 1697, 1698, 1699, 1700, 1701, 1702, 1703, 1704, 1705, 1720, 1721, 1722, 1728 and 1729.
COMMISSIONER:
Q. Entered.
EXHIBITS P-1696 THROUGH P-1705, INCLUSIVE, ENTERED INTO EVIDENCE.
EXHIBITS P-1720 THROUGH P-1722, INCLUSIVE, ENTERED INTO EVIDENCE.
EXHIBITS P-1728 AND P-1729 ENTERED INTO EVIDENCE.
COFFEY, Q.C.:
Q. Thank you, Commissioner. Exhibit, Registrar, please, 1729? Dr. O'Malley, this is a document entitled "Curriculum Vitae for Frances O'Malley" I take it that's your CV?
DR. O'MALLEY:
A. It is, yes.
COFFEY, Q.C.:
Q. Okay. Doctor, it goes on for, I'll just say quite a

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number of pages. I'm not going to take you through them all, but could you please given the Commissioner a brief outline of your educational background and your professional background?
DR. O'MALLEY:
A. Certainly. I graduated from medical school at Trinity College, Dublin in 1985 and started a residency in pathology in Dublin, Ireland, in 1986 after an internship. I then immigrated to Canada in 1988 where I entered the pathology residency program in, at the University of Western Ontario. I completed that residency in 1991 and then spent almost a year and a half doing a fellowship in breast pathology with Dr. David Page at Vanderbilt University in Nashville. I then came back on staff to Victoria Hospital in London and worked there as a staff pathologist with expertise in breast pathology until 1998, when I moved to Mount Sinai to my current position as a breast pathologist at Mount Sinai and professor of pathology at the University of Toronto.
COFFEY, Q.C.:
Q. Doctor, I understand that you've prepared a presentation related to estrogen and progesterone

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receptor testing of primary breast cancer, its clinical importance and technical validation. If we--it's Exhibit 1728, Commissioner, for the record. And I understand that it is a PowerPoint type presentation. So, Doctor, I'm going to ask that with that as an aid, that you go ahead and with an outline of that topic?
DR. O'MALLEY:
A. Certainly. So this presentation is really an overview of the clinical importance of estrogen and progesterone receptor testing in primary breast cancer. And I also want to focus on the technical validation of these tests. So by way of background, this slide just points out the difference, the essentially difference between an estrogen receptor positive breast cancer cell and an estrogen receptor negative breast cancer cell.

So in an estrogen receptor positive breast cancer cell, the circulating estrogen in a woman's breast can enter the cell and it can bind to the estrogen receptor, as indicated by this green object. Through binding to the receptor, a series of cellular events are put into place, leading to proliferation or multiplication of the breast cancer

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cell. Now, importantly, Tamoxifen or other anti-estrogen agents can bind to this receptor, blocking binding of estrogen and in so doing it inhibits the proliferation of the cancer cell.

Now, in contrast, in an estrogen receptor negative breast cancer cell, the receptor is negative, so estrogen, circulating estrogen does not have the same effect on these breast cancer cells, cell--specifically cell proliferation or multiplication of the breast cancer cells is not controlled by estrogen and it's not inhibited by anti-estrogen drugs such as Tamoxifen.

Now, just to go into a little bit more detail what exactly happens at the cellular level when estrogen binds to the estrogen receptor. On binding to the receptor there's actually a confirmational change of this complex, so it's like a key, specific key, and this specific key fits into a very specific lock known as co-activators. These are a bunch of proteins then that help when they bind to the estrogen and estrogen receptor complex which sits in DNA, puts into event a series of events that leads to activation of genes that lead to multiplication of the tumor cells or cell proliferation.

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COFFEY, Q.C.:
Q. And just on that point, Doctor, I take it that cell proliferation when you're talking about tumors is not a good thing?
DR. O'MALLEY:
A. It is not a good thing.
COFFEY, Q.C.:
Q. That's a given?
DR. O'MALLEY:
A. That is absolutely correct.
COFFEY, Q.C.:
Q. Go ahead, I'm sorry.
DR. O'MALLEY:
A. Now, what Tamoxifen does is it binds to that same receptor, the estrogen receptor, but when it binds, it does not cause the same change in shape of the complex, so it's like a different key, and that different key cannot fit into this lock, so it prevents--so while Tamoxifen binds the receptor, it doesn't set into place the activation of genes that lead to cell proliferation, okay.
Now, in terms of treating breast cancer, obviously the most important thing is to excise, surgically excise the breast tumor. However, we do

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know that sometimes breast cancer cells can escape and get into the blood stream and can lodge in different organs throughout the body, such as the lung, the liver, the bone and the breast. What we believe Tamoxifen and other anti-estrogen agents do in the setting of estrogen receptor positive breast cancer is that it links to the estrogen receptor in these tumor cells and therefore prevents circulating estrogen from stimulating these escaped cancer cells which could lead to their growth down the road.
COFFEY, Q.C.:
Q. I take it that's wherever those cells might be in the body?
DR. O'MALLEY:
A. Exactly, exactly. And we do indeed know that from many clinical trials that the use of Tamoxifen in this setting does indeed decrease the risk of cancer recurrence.
Now, for any test that enters the clinical arena, it must undergo very rigorous tests, very rigorous guidelines as outlined by the American Society of Clinical Oncology. And these stipulate that a test, to be clinically useful, must be--must undergo rigorous clinical validation, it must

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undergo rigorous technical validation and obviously it must influence therapeutic decision making. We know ER and PR certainly does influence therapeutic decision making. I want to focus for the remainder of this presentation on both the clinical and technical validation of this test.
So I just want to start off by, start off with a few definitions. So clinical validation means that a test is able to identify subsets of patients with significantly different risks of recurrence or survival. So for ER that means that a patient who has an ER positive breast cancer, it has, those patients have a better disease free and overall survival than patients whose tumors are ER negative.
Now, clinical validation can be divided into two parts, really. When we look at a test, we look at whether it can act as a prognostic factor and/or a predictive factor. So a prognostic factor is a factor that provides information on the clinical outcome in the absence of therapy, okay. So what it basically does, it gives information on the intrinsic biologic potential of that tumor, and that's very different from a predictive factor,

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which is a factor that provides information on the likelihood of response to therapy. So in a setting of ER, ER positivity indicates that that patient is very likely to respond to an anti-estrogen agent, okay.
So I want to talk about the clinical validation of ER in terms of both its prognostic and predictive utility. But before doing that I just want to very briefly review, from a historic perspective, the what we previously used as the gold standard for ER testing, and that was a biochemical test known as the Ligand Binding Assay. And what it entailed was it entailed taking a portion of tumor, once it had been excised by the surgeon, taking about a half or up to one gram of tissue from the specimen and immediately freezing that portion of tumor in liquid nitrogen and then that tumor was sent to a steroid receptor lab.
I can speak to what happened in Ontario. In Ontario in the '80s there were five steroid receptor labs, so even though we have more than 80 hospitals, all of the breast cancers, all of the specimens were sent to one of these five steroid receptor labs. These labs were funded by the provincial government

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and they were highly regulated in terms of their quality control and quality assurance procedures.

The ER content in the tumors that were sent to these labs was assessed by what's known as a DCC method, dextron-coated charcoal. I'm not going to go into details on this because, as I say, this is the historic test. We do not use this test any more.

The advantage, however, of this test beyond what I just mentioned, the strick QC and QA procedures that were in place was that it was a quantitative test, a specific number was generated when the test was performed, and a tumor with a quantitative value of 10fmol/mg was determined as a positive tumor, positive for estrogen receptor. The same cutoff was used for progesterone receptor.

COFFEY, Q.C.:

Q. Doctor, you just then--and I appreciate that some things are second nature to yourself, particularly abbreviations. You referred to QC and QA. Could you expand on that a little bit?

DR. O'MALLEY:

A. I certainly will. And, indeed, I'll be talking quite a bit about that later in the presentation.

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QA is quality assurance and QC, quality control.

COFFEY, Q.C.:

Q. Okay.

DR. O'MALLEY:

A. And as I mentioned, we'll get into that later in the presentation.

Okay, so now back to clinical validation. Just to remind you, I broke this into two components prognostic and predictive factors within clinical validation. And as I mentioned, the biochemical method of assessing ER and PR was a historic method. We now uniformly use immunohistochemistry, and we have a lot of data on its clinical utility in breast cancer, in fact, we've over 25 years of data now on the use of immunohistochemistry for assessing ER and PR in breast cancer.

I'm not going to go into details, technical details on the actual immunohistochemical procedure because I believe Trish Wegrynowski from Mount Sinai will be talking about this later in the week.

But now, back to the clinical validation. We knew from many studies, in fact, we've about 25 studies now in the literature with a cumulative patient database of over 5000 looking at the

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clinical validation of ER. And even though most of these patients have been treated, we do have a number of patients or number of studies that have looked at untreated patients. And just to remind you, we need to look a untreated patients to determine the prognostic utility of a test because that's looking at the intrinsic biology of that test. And from these studies we know that a patient with ER positive disease has about a 10 to 15 recurrence or overall survival benefit over those patients who have ER negative tumors, and this is considered a WEAK Prognostic factor.

COFFEY, Q.C.:

Q. In terms of that, Doctor, I take it that's patients who are untreated?

DR. O'MALLEY:

A. Exactly, exactly.

COFFEY, Q.C.:

Q. Even for somebody who's untreated at all? No Tamoxifen?

DR. O'MALLEY:

A. That's exact it. Untreated patients, a patient with ER positive tumors will do slightly better. 10 to 15 percent, as I say, recurrence or survival benefit

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of ER negative patients untreated, as well. But that's considered a WEAK Prognostic indicator. The main benefit of ER testing is it's is in predictive utility, it is a strong predictive factor, ie, it very precisely, when it's performed accurately, identifies those patients who are going to benefit substantially from hormone therapy. We have data both in the advanced stage disease that is disease that has spread beyond the breast to other organs, as well as the adjuvant setting, that's early breast cancer. I'll show you the early breast cancer data in a moment. This slide summarized the advanced stage disease data where indeed there's a lot of data, approximately 25 studies with about 1500 cumulative patient data. We know from these studies that about 70 percent of patients with ER positive disease will show a statistically significant clinical response to hormone therapy. On the other hand, 85 percent of ER negative patients will show absolutely no response to anti-hormone therapy.

COFFEY, Q.C.:

Q. Doctor, while that slide is up, clinical response in this context means what?

DR. O'MALLEY:

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A. It means a decreased or actually increased disease free survival or decreased recurrences.

COFFEY, Q.C.:

Q. Okay, thank you.

DR. O'MALLEY:

A. Okay. Now this is the data in the adjuvant setting. We have less studies but very, very strong data. Again, ER is a very, very strong predictive factor in early breast cancer, showing a 25 to 30 percent recurrence or survival benefit over patients with ER negative disease. So these are patients who are treated. Okay.

Now I just want to return to the ASCO guidelines. I've talked about clinical validation. I don't think there's any--there's really any controversy over the importance of ER and PR testing in the clinical setting. Why don't I focus on the technical validation of these tests?

Now ASCO defined technical validation as a test that is sensitive, specific, reproducible and interpreted in a uniform manner from lab to lab, and I'll go over each of these points in detail.

First of all, I want to define sensitivity and specificity. So sensitivity is the percentage of a

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positive test, percentage of positive test results obtained when evaluating only specimens that are truly positive. So ideally, every test--a test should identify every truly positive specimen. On the other hand, specificity is the percentage of the negative test results reported when only truly negative specimens are evaluated. Okay.

So let's go back to the parameters of technical validation and some of the problems with it. In terms of sensitivity, there are several antibodies that are used to assess ER and PR and they differ in their sensitivities. These antibodies also differ in their specificities. When it comes to reproducibility, we have different immunohistochemical methods and as I mentioned, Trish will be going into details on these later in the week. But this certainly affects reproducibility of the test and finally, interpretation in a uniform manner, this is highly influenced by the arbitrary cutoffs that have been used and the methods of scoring these results, and I'm going to touch particularly on this last point.

Another way to look at technical validation is to divide it into three parts, and all of these

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parts are very, very important. First of all, pre-analytical components. Then there's the analytical components and post-analytic components. I'm going to touch on the pre-analytic, but concentrate particularly on the post-analytic, as Trish will deal a lot with the analytic components of technical validation.

So first of all, to pre-analytic components. This is extremely important to assure accuracy of a test, and this relates to tissue handling and fixation. So it's really vital that the time the specimen, the breast specimen spends out of formalin, after it's been removed from the patient, is minimized. This should be a very, very short period of time, and this involves the nursing, the OR nursing staff, the surgeons and the pathologists working very closely together to make sure that that specimen is placed in formalin as soon as possible.

Another very important part of this process is that the specimen should be placed in a sufficient amount of formalin and we recommend at least seven times the volume of formalin to the volume of the specimen to allow adequate fixation. The third very, very important point to assure adequate

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fixation is that the specimen should be sectioned at fairly thin slices before, in fact, it is put into this formalin, because formalin diffuses through tissue very slowly and if the specimen is not sectioned, then the centre of that specimen will not be fixed at all.

COFFEY, Q.C.:

Q. So just on that point, in effect, I take it, a specimen, of course is a piece of human tissue?

DR. O'MALLEY:

A. Yes, that's right.

COFFEY, Q.C.:

Q. In this context.

DR. O'MALLEY:

A. It's the breast cancer with surrounding normal breast tissue.

COFFEY, Q.C.:

Q. And you use the word "diffuse" I believe?

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. In layman's terms, what does that mean?

DR. O'MALLEY:

A. To seep into, penetrate.

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COFFEY, Q.C.:
Q. To seep into or to penetrate.
DR. O'MALLEY:
A. Penetrate.
COFFEY, Q.C.:
Q. Okay, and you've indicated that formalin doesn't--if a specimen, I take it, is put into formalin, it doesn't immediately go all the way through it?
DR. O'MALLEY:
A. That's correct.
COFFEY, Q.C.:
Q. It takes a period of time for it to penetrate through the cells and get deeper and deeper into it?
DR. O'MALLEY:
A. Absolutely.
COFFEY, Q.C.:
Q. Okay.
DR. O'MALLEY:
A. It does.
COFFEY, Q.C.:
Q. And the advantage then of this slicing then of the tissue into, I take it, relatively thin pieces is what?
DR. O'MALLEY:

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A. Yeah, five to ten millimetres.
COFFEY, Q.C.:
Q. Five to ten millimetres. Why is that advantageous, Doctor? What happens?
DR. O'MALLEY:
A. Well, that allows immediate contact of the formalin with every part of the specimen at these very thin slices, so it means that the formalin can penetrate into the specimen at many different parts along the specimen. Some of these specimens can be quite large. They can be several centimetres in maximum dimension, so this is a very, very important step in the process of fixation.
COFFEY, Q.C.:
Q. And I take it then that if a slice of tissue is only five to ten millimetres, well, for example, if it was ten millimetres thick, the formalin then is on both sides of it, so it only--to get to the centre of it, it only has to go five millimetres in each direction?
DR. O'MALLEY:
A. That's right.
COFFEY, Q.C.:
Q. Or if it's five millimetres thick, it only has to go

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two and a half millimetres, and it just gets inside all the way through faster?
DR. O'MALLEY:
A. That's right.
COFFEY, Q.C.:
Q. That's the -
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. It's just a physical process, the thinner, all things considered, the better?
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. Okay.
DR. O'MALLEY:
A. Now this touches on one of the points you raised about the time that formalin does take to fully penetrate the tissue. So it's not only important to have the specimen exposed to formalin, but it does need to sit in formalin for several hours to allow adequate penetration, and optimally, the specimens should sit in formalin for somewhere between six to 48 hours. Now the six-hour, that very short time

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line really only applies to very, very small specimens, such as core biopsies.
COFFEY, Q.C.:
Q. Could you explain what a core biopsy is?
DR. O'MALLEY:
A. So a core biopsy is a very, very thin piece of tissue. It usually measures one centimetre by one millimetre and these are specimens that are usually obtained in radiology and they're usually for diagnostic purposes to make a diagnosis of breast cancer when an abnormality is seen, usually on mammography.
COFFEY, Q.C.:
Q. So for such specimens, if it's one millimetre thick or wide, I take it then you're already down to a very thin specimen and therefore it just doesn't require six hours to ensure that the formalin penetrates through that one millimetre?
DR. O'MALLEY:
A. Exactly.
COFFEY, Q.C.:
Q. To its centre or core.
DR. O'MALLEY:
A. Exactly.

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THE COMMISSIONER:
Q. So if one had a biopsy, would that--as opposed to a surgical removal of -
DR. O'MALLEY:
A. A surgical removal is the next point that I make. Those are larger specimens and they require at least 24 to 48 hours of formalin fixation.
COFFEY, Q.C.:
Q. They'll require 24 to 48 hours, Doctor, having been sliced up into five to ten millimetre thick slices?
DR. O'MALLEY:
A. Yes, yes.
COFFEY, Q.C.:
Q. After you've done the appropriate sectioning, is the word, I gather?
DR. O'MALLEY:
A. Um-hm.
COFFEY, Q.C.:
Q. After it's appropriately sectioned and it still requires at least 24 hours and up to 48, somewhere between 24 and 48 would be optimum?
DR. O'MALLEY:
A. Yes, that's true. Now we do know from several studies that longer fixation is less of a problem,

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in terms of retaining antigenicity when immunohistochemistry is used on these specimens. The big problem is under fixation. If a specimen is fixed for less than six hours, that has a big impact on the accuracy of an immunohistochemical test.
COFFEY, Q.C.:
Q. Any kind of specimen under six or a core under six?
DR. O'MALLEY:
A. Well, even a core under six, but certainly a larger surgical specimen, if it is fixed for less than six hours, then the immunohistochemical test would be--the accuracy of such a test would be severely compromised, and in fact, this gets back to the issue of thinly slicing the specimen. It would be the same as under fixation, because if the formalin has not penetrated fully into that specimen, it would be basically under fixed.
COFFEY, Q.C.:
Q. And I take it under fixed, Doctor, again in--that's a term technologists and physicians use. The practical effect of under fixation is what, in layman's terms? What's the actual practical effect?
DR. O'MALLEY:
A. The tissue dies. The tissue dies.

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COFFEY, Q.C.:
Q. And the effect of that is to do what? In terms of ER and PR testing, what's the practical effect of it?
DR. O'MALLEY:
A. The practical effect is that the test, no matter how sensitive or specific the antibodies are that are used in such a test, they won't work.
COFFEY, Q.C.:
Q. Okay, so that the cells--as you say, the tissue dies. The cells, I take it, their cellular structure comes apart, disintegrates?
DR. O'MALLEY:
A. Disintegrates. Disintegrates, so there's nothing to bind--the antibodies have nothing to bind to because the tissue basically has integrated, disintegrated, I should say.
COFFEY, Q.C.:
Q. So if I understand you correctly, Doctor, at this stage, in terms of tissue handling and fixation, important points are from the time of excision, which is, in effect, the cutting out of the tissue from the patient, to it being immersed in formalin is minimize the time?

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DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. All things considered, do it as quickly as possible, number one?
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. Number two, make sure that if it is any kind of--anything other really than a core biopsy, any kind of sizeable tissue at all, it'd to be sectioned, sliced?
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. Appropriately, thinly, and it's to remain then within formalin for, if it's a core biopsy, a minimum of six hours, and if it's any other type or larger biopsy or any larger specimen, 24 to 48 hours, having been appropriately sliced and put in quickly into the formalin?
DR. O'MALLEY:
A. Yes.
THE COMMISSIONER:

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Q. Can I take it from this that the timing of what I think is called the grossing in the slicing process is important?
DR. O'MALLEY:
A. Yes, it is very important.
COFFEY, Q.C.:
Q. In terms of that, Doctor, as an example, an OR and a tumor is excised and the flesh surrounding the tumor or a woman's breast is removed and it's put in the container of formalin, the timing then, I take it, from that point, because the sectioning does not go in the OR?
DR. O'MALLEY:
A. No.
COFFEY, Q.C.:
Q. The actual slicing by a pathologist or pathologist's assistant doesn't go on there.
DR. O'MALLEY:
A. No.
COFFEY, Q.C.:
Q. That's done in the -
DR. O'MALLEY:
A. It happens in the pathology department.
COFFEY, Q.C.:

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Q. So the timing then, in terms of the Commissioner's question, in terms of that between the actual surgery, as quickly as possible into a formalin container appropriately filled, and the time then at which the sectioning occurs, I take it that you'd want to get it sectioned as quickly as possible. What kind of time frames are we talking about there, Doctor? When would they become problematic, do you think?
DR. O'MALLEY:
A. Well, they become really problematic if, say, a breast, a patient has a mastectomy and that mastectomy is left in formalin over the weekend prior to sectioning, then that would certainly be problematic in terms of under fixation and the possibility of disintegration of the tissue.
COFFEY, Q.C.:
Q. And I take it that's because even though the breast is completely, as a whole, surrounded by formalin, that the interior of the breast, the flesh inside, the interior of the specimen, the formalin on the outside just can't penetrate fast enough in order to preserve the inner tissue?
DR. O'MALLEY:

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A. That's right.
COFFEY, Q.C.:
Q. It just doesn't get there fast enough?
DR. O'MALLEY:
A. That's right.
COFFEY, Q.C.:
Q. Okay, and certainly, over a weekend is problematic?
A Friday afternoon surgery and only doing the sectioning Monday morning could be problematic?
DR. O'MALLEY:
A. It could be problematic. It could be problematic, for sure.
COFFEY, Q.C.:
Q. Is that the point? Thank you. I'm sorry, Doctor, go ahead.
DR. O'MALLEY:
A. So back to the various parameters of technical validation. As I mentioned, I want to focus specifically now on the post-analytic component, as Trish will be dealing with the analytic component. So the post-analytic component has three main important steps and the first obviously is the interpretation of the stain by the pathologist. The second is the reporting of the staining that we see

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and the College of American Pathologists has published guidelines on what should actually be included in a pathology report in relation to ER and PR testing. And then the third huge issue is quality assurance and quality control.
So just to touch on the issue of interpretation. Before we, pathologists, assess a test, ER and PR test, we have to make sure that the test is appropriate for evaluating, and this is particularly--this is a particular issue when there is no staining at all in the tumor. What I have, what I'm showing on the screen here is a histologic section of breast cancer where there is no staining whatsoever. All of the nuclei, as shown here, appear blue. If this was positive, we'd see some brine staining.
COFFEY, Q.C.:
Q. Doctor, while we're here, so this is, in effect, a photograph, photographic reproduction of a slide -
DR. O'MALLEY:
A. That's right.
COFFEY, Q.C.:
Q. - with tumor tissue?
DR. O'MALLEY:

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A. That's right.
COFFEY, Q.C.:
Q. And could you just use the cursor then to show the Commissioner, for example, where the nucleus is in these various cells?
DR. O'MALLEY:
A. So right here, this is a nucleus. Is that clear? There's another nucleus. So these are all separate tumor nuclei. Okay. So in a case like this where the tumor is completely negative, to make sure that the test has worked, of course, the technologist will have assured that the controls, positive controls have worked. But what we look for on the slide is an internal positive control, and this is shown here in the bottom right-hand corner. These are normal ducts in the same specimen that are showing positive staining with the estrogen receptor and these should be positive in all cases. So these are normal breast ducts and each of these nuclei, as you can see, are staining positively.
COFFEY, Q.C.:
Q. And they're actually coloured here, well, I'm not good with colours, but it looks brown, sort of brown or dark brown.

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DR. O'MALLEY:
A. Yeah, they are brown, under the microscope they're brown.
COFFEY, Q.C.:
Q. And the importance of this part of the process, Doctor, is what? What, as a physician, what does this tell you?
DR. O'MALLEY:
A. Well this tells me that the test has worked. On this particular slide the normal epithelium has stained so I can be confident that the tumor is indeed estrogen receptor negative.
COFFEY, Q.C.:
Q. Because they normal tissue here in the, in this insert on the bottom right, you would have expected that if the process, physical process worked properly, that these would stain, these sorts of normal cells will stain in this context.
DR. O'MALLEY:
A. Yes. Okay. So once we are satisfied that the tests can be interpreted, we then assess the percentage, if there is positivity there, some of the tumor cells are staining, we assess then how many of those tumor cells are staining. And these gets into the

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cut off for what a positive test is, and this cut off actually has varied in the literature. Most labs, certainly in the past have used a cut off of ten percent, so there must be at least ten percent of tumor nuclei staining for that test to be called ER or PR positive. Some labs have used a higher cut off of 20 percent, but we now have fairly solid clinical data from the Baylor Group by Harvey et al, that in the adjunctive setting that as few as one percent, as few as one to ten percent of ER positive tumor cells predicts for a clinical response to anti-estrogen therapy. And I want to spend some time talking about this very important clinical data because it really has impacted on certainly the cut off that we use at Mount Sinai and certainly at other hospitals. So what this study did was it looked at ER in over 1900 patients with primary breast cancer and they used an antibody known as 6F11. To score these results, they used the Allred score and I'm going to go through that in detail and the results were compared, these immunohistochemical results were compared to the previous standard biochemical method, the Ligand Binding Assay results, but most importantly the results were

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compared to clinical outcome of these patients. So just to go through in detail what the Allred score entails, this is a semi-quantitative scoring system that was developed by Craig Allred, the senior pathologist in the Baylor group and it comprises of two components. There's a proportion score and an intensity score. The proportion score is divided into five components, so a score of one is assigned to a tumor where there is absolutely no tumor cells staining or less than one percent of tumor cells--well actually if there are no tumor cells staining, then it gets a score of zero, but there there's less than one percent of the cells staining, it gets a score of one. If there is between one and ten percent--actually, let me just rephrase that, so it gets a score of zero if there is zero percent; less than one percent, one; one to ten percent, two; eleven to thirty-three percent, three; thirty-four to sixty-seven percent, four; and greater than sixty-seven percent, up to a hundred percent, five. Okay? The intensity score is from zero to three, so zero if there's absolutely no positive cells; one if there is staining but it's of a weak intensity; two if the intensity is moderate; and three if the

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intensity is strong. And those cases that I showed you before, those cells that were staining in the normal epithelium, that was staining at a strong intensity.

COFFEY, Q.C.:

Q. And intensity in this context means what, Doctor? Not the implication of it, how do you interpret something as intense?

DR. O'MALLEY:

A. It really--it has to do with the, really with the colour, I mean, if it's weak, it will be a very light brown, if it's strong, it will be a very dark brown, so it's really a difference in shades of brown and actually that can be certain, subjective at times, but this is a case that would be, I would expect would be uniformly interpreted, uniformly interpreted as a tumor that shows almost a hundred percent positivity with a strong intensity. So these are all tumor cells and even at this power you can see that there's a lot of brown staining throughout, okay. This blue stuff here, this is normal tissue, this is fat and this is normal stromal, these are normal stromal cells, so they are negative. Now, I'll just draw your attention to

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this small benign duct, you can see that here we have those normal epithelium cells staining as wells. Now, of course in this case we already know that the test has worked because the tumor is so strongly positive, but this is also nice reassurance that our internal positive control is behaving as it should, okay? So this is easy to interpret as a strongly positive tumor cell, it's this tumor that would be less, it would cause more variability in interpretation where a far fewer of the tumor cells are staining positively. So here you can see the positive cells as evidenced by these little brown dots, but you can see that there's much more blue in this slide indicating negative tumor cells. I believe I have a higher power, yes, here. Here you can see these positive tumor cells and many more negative tumor cells. Here this actually shows the varying intensity of straining that one can see, so where's a weakly positive cell and here's a strongly positive cell, okay. So I want to now return to the data by Harvey et al, and this slide summarizes all of the patients in the study that received endocrine therapy. There were over 770 patients in that cohort of 1900 patients that actually received

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endocrine therapy. So here we're looking at the predictive utility of the test and these--all of these curves summarize all of the possible total immunohistochemical scores for all of the patients tumors. On the X axis we have the time up to 72 months, and the Y we have the disease free survival probability. And what you can see here is that there is a sharp difference between the survival, the disease free survival in the patients whose tumors had a score of zero to two, compared to those patients whose tumors had a score of three and up to eight. And so that was why the cut point of greater than two was used to assess what a positive result or what a positive ER result was. Okay, so is that clear? So a tumor with a composite score of zero or two, is a tumor that's deemed ER negative; whereas a tumor with a composite score of three to eight is a tumor that's ER positive.

COFFEY, Q.C.:

Q. And, Doctor, as well I take it the patients being studied here, are those, all of these patients have received some sort of endocrine therapy?

DR. O'MALLEY:

A. That's absolutely--and see here at the top of the

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slide, all of these 777 patients received endocrine therapy, the vast majority of these patients in fact received Tamoxifen. So again this is looking at the predictive utility of the test and we can see that the patients whose tumors were, did ER positive, did much better, responded to a greater degree to that endocrine therapy than those patients who had tumors that were ER negative. So it's because of this data that we use the greater than two, i.e. three or up as determining what a positive result is. Now let me bring you back to this semi-quantitative scoring system to put that into context. So that means that a tumor with as few as between one to ten percent of the tumor cells being positive, i.e. it gets a proportion score of two, with even a weak intensity, getting an intensity score of one, i.e. two plus one will be deemed ER positive.

COFFEY, Q.C.:

Q. And, Doctor, just looking at that slide, I take it that if you are at the--you've fallen into the category of proportion score, for example two, which falls somewhere between one and ten percent, that if there is between one and ten percent of cells staining that they must have some sort of intensity

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and even the lowest intensity is one -
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. A score of one, so two plus one is three and there you are.
DR. O'MALLEY:
A. Exactly.
COFFEY, Q.C.:
Q. Three and above.
DR. O'MALLEY:
A. Exactly.
COFFEY, Q.C.:
Q. You'd get a benefit.
DR. O'MALLEY:
A. So as I mentioned before, there certainly can be some subjectivity in determining the degree of intensity, but this data shows that it really isn't that important, it's determining the proportion of tumor cells that are positive at any degree of intensity that's the critical step in determining whether indeed a tumor is positive or negative. So back now to this data by Harvey et al and this is the clinical data showing very importantly that ER

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status determined by immunohistochemistry was in fact better at predicting disease free survival of these patients and equivalent at predicting overall survival compared to that standard biochemical test, the Ligand Binding Assay test, so this really does show that immunohistochemistry is a very, very good test when it's performed accurately in giving this important clinical information. And this is a summary of that information showing here that the patients whose tumors were ER negative had a much worse disease free survival than those patients who were ER positive; in fact, there was a 30 percent benefit at five years for the patients who had ER positive tumors. Again, remember this is the predict--these are all--all of these patients have been treated. This is not looking at the intrinsic biologic potential of ER status, this is looking at its predictive utility. Here we can see the data for the Ligand Binding Assay with a 25 percent disease free survival benefit of five years. Okay, so that data was data in early breast cancer, in the adjunctive setting. This data is in the metastatic breast cancer setting.
COFFEY, Q.C.:

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Q. Now I take it early setting, I take it that's before the disease is spread.
DR. O'MALLEY:
A. That's right.
COFFEY, Q.C.:
Q. Beyond its original site.
DR. O'MALLEY:
A. That's right.
COFFEY, Q.C.:
Q. Doctor and this Harvey study was published when?
DR. O'MALLEY:
A. It was published in 1999.
COFFEY, Q.C.:
Q. I'm sorry, Doctor, go ahead, you were about to tell us about the more advanced -
DR. O'MALLEY:
A. Disease.
COFFEY, Q.C.:
Q. Disease, yes, go ahead.
DR. O'MALLEY:
A. Metastatic breast cancer, so this paper came out the year after the Harvey study and this was data from a clinical trial from South Western Oncology group and they looked at both ER and PR by both the

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biochemical Ligand Binding Assay and by immunohistochemistry. Again we're looking at predictive utility of the test because all of these patients were treated with Tamoxifen and there was a significant long-term follow up with a nine year median follow up. Now this summarizes the year of registration and the disease free survival and what we can see here is that not only was there a difference between ER positivity and ER negativity, for actually both ER, positivity and negativity, but also PR negativity and positivity, but the degree of positivity was associated with a greater response to Tamoxifen, so we can see here the red line represents the patients who had negative disease with a score of zero to one. Now what we're looking at here is just the proportion score. So I showed you the Allred score was a combination of both proportion and intensity with a composite score of being somewhere between zero and eight, here, because the intensity score didn't really add anything above and beyond any cell or cells being weakly positive, this study actually dropped the intensity score and just looked at the percentage score which was from zero to five. So here we can

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see those tumors that are negative, i.e. zero or less than one percent of the tumor cells positive had a much worse survival than those patients who had weak or--well not really weak positivity, but positivity somewhere between two and three. That translates to between one to ten percent and up to thirty percent positivity, compared to those who had greater than a third positivity, so all the way up to a hundred percent positivity. And again, there was that same linear relationship for progesterone receptor. So this data would indicate that we not only need to report whether a tumor is ER positive or negative, but that we really do need to include the actual percentage positivity that the tumor displays. Okay, now I want to turn to the very, very important issue of quality control and quality assurance for both ER and PR testing. Now quality assurance is really an indication of how accurate a test is from lab to lab and it really assesses the interlab variability and every lab that performs these tests should be participating in a quality assurance program. One of the best quality assurance programs to my mind is that run out of the UK. It's known as NEQAS and there's also a very,

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very good quality assurance program from the U.S. run by the College of American Pathologists. So, this a study published by the NEQAS Group where they assessed ER and PR staining. This is the ER staining from 200 labs in 26 countries, the vast majorities of these countries were in Europe, but there were a few labs from North America that were included in this study. What the NEQAS Group did was they circulated tumors to all of these participating 200 labs that had high, medium and low levels of estrogen receptor. And what they find was that greater than 80 percent of those labs were able to detect the tumors that had high and medium ER levels. They called--when they repeated the staining in their labs, they find the tumors were indeed positive. However, almost 40 percent of those labs failed to detect--only 40 percent of those labs detected the ER in the tumors that had low levels of ER. Okay. So, over 60 percent of those labs actually did not detect the ER in the circulated tumor that had low levels.

So, what this group did was then it looked at the those labs, it looked at the cutoff that those labs used to determine what an ER positive result

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was. And what they find was that for the labs that used the ten percent cutoff, the false negativity rate was 66 percent. However, for the labs that used the 1 percent cutoff as validated by the Harvey Study, the false negativity was lower. It certainly wasn't zero, but it was much lower than those labs that used the higher cutoff.

COFFEY, Q.C.:

Q. It was down, I take it, about 30 percent?

DR. O'MALLEY:

A. Yes. Now, recently the Canadian Quality Control and Immunohistochemistry combined with the Canadian Association of Pathologists Group has struck this national standards committee. And a recent study was undertaken where 37 different tumors in the form of tissue micro-ray were circulated to 18 labs across Canada, looking at this issue of inter-observer reproducibility. And this is quite reassuring data that of those 18 labs, the concordance for ER was 98.5 percent with a sensitivity of 98.5 percent and the specificity of 98.3 percent. And the concordance for PR was a little less, but still very, very good at 94.4 percent. So, I think this does indicate that we

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can, when there is good quality control, quality assurance in place, that the reproducibility across labs can be very high.

So, I just want to conclude by showing what we do at Mount Sinai. We fix all our specimens in 20 percent neutral buffered formalin for at least 8 and up to 24 hours. Certainly it can be up to 48 hours, but this is the optimal fixation is somewhere between 8 and 24 hours. Obviously, following slicing to allow adequate fixation, as I've discussed earlier, we use the antibodies that were validated in that Harvey Study, that is we use the 6 FL antibody for ER and the 1294 antibody for the PR and we used the Allred scoring system. This is the cutoffs that we used. So, obviously the tumor shows no staining, it's classified as negative. If they're somewhere between 1 and 9 percent, it's categorized as low positive and if there's between 10 and 100 percent staining, then that tumor is categorized as ER and PR positive. And these cutoffs have been--they are certainly supported by the College of American Pathologists consensus document and other international documents.

We use synoptic reporting to report these

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results and this is what our report would look like. So, if a tumor--so, we state whether a tumor is positive or negative. So, here you can see that this tumor is positive, then we report the percentage positive cells, here the tumor showed greater than 90 percent positivity. We include the antibody that was used and then you list the chemical procedure that was used for both ER and PR. We also include a statement about our positive and negative laboratory controls. And we include the data that our cutoff is based on, ie., the Harvey Study.

Now, when I'm giving this talk to medical oncologists, I leave them with three points. I tell them that they shouldn't accept just a positive or negative result from their laboratories. That they really should insist on knowing what that percentage positivity is. And again, all labs who are following the CAP requirements should be including the antibodies used and the methodology used. And the third point is that the medical oncologists should be aware of the labs cutoff point and the data that that is based on. So, that concludes my presentation.

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COFFEY, Q.C.:

Q. Doctor, the study that you referred to, the one involving Terry et al in the slide presentation, the most recent study involving the 18 labs, when was that conducted?

DR. O'MALLEY:

A. It was only conducted this year and it hasn't--if we can go back to that data--it has not been published yet. It is in the process of being submitted for publication. But I did check with the authors to make sure I could present this data.

COFFEY, Q.C.:

Q. And this is going on as it were in real time.

DR. O'MALLEY:

A. This is going on in real time. This is what's currently happening across Canada.

COFFEY, Q.C.:

Q. The cutoffs that you refer to that Mount Sinai uses, how long has Mount Sinai been using those?

DR. O'MALLEY:

A. We used those cutoffs--prior to the 1999 study, we actually did use a 10 percent cutoff, but I believe it was in 2000 that we then switched to the Baylor antibodies and used the lower cutoff.

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COFFEY, Q.C.:

Q. Which is the -

DR. O'MALLEY:

A. Which is the percent -

COFFEY, Q.C.:

Q. One -

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. Could you tell the Commissioner, please, because you did make reference in passing to the technologists checking controls.

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. Okay. Could you tell the Commissioner what controls it is the technologists at Mount Sinai check?

DR. O'MALLEY:

A. So we use external controls, and this, we actually use a composite of controls that include a strong positive tumor, a tumor that's positive at a lower level and then a completely negative tumor. And these tumors actually were assessed by the Ligand Binding Assay. We have an archive of tumors that we

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know the results from the previous standard, Ligand Binding Assay, and so we include these in our runs.

COFFEY, Q.C.:

Q. And so the technologists are checking the external control slots?

DR. O'MALLEY:

A. External controls, yes.

COFFEY, Q.C.:

Q. Controls. And in terms of the division of responsibility at Mount Sinai, the pathologists check which controls?

DR. O'MALLEY:

A. Well, we check, obviously, the internal controls, as I mentioned, and we do check periodically the external controls, as well. Certainly if we were concerned, if we had any concerns with the assay, we would check the external controls.

COFFEY, Q.C.:

Q. And in terms of that, can you tell the Commissioner, please, describe for the Commissioner, what actually happens in terms of what has to happen before you, as a pathologist, actually see a tumor slide, I mean, who has checked it and for what before you ever get your hands on it?

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DR. O'MALLEY:

A. A huge, a huge amount of work has gone into the performance of this test, making sure that it is stringently being performed and it is accurate before it ever reaches my desk, and that is really the analytical stage of the technical validation that I alluded to. So the sensitivity and specificities of the antibodies are checked, they have been validated, a large number of tumors have been validated to make sure that the antibodies are working appropriately before they're ever used in a clinical, in a clinical setting.

COFFEY, Q.C.:

Q. And we'll be hearing from Ms. Wegrynowski about that. But in terms of for any one patient, by the time the slide gets to you for an ER interpretation or PR interpretation, you understand what about what controls have been checked before the arrive, the slide arrives in your office?

DR. O'MALLEY:

A. Well, my understanding is that the positive, strongly positive, weakly positive and negative controls have been checked and they have stained and they are staining in the appropriate manner before -

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COFFEY, Q.C.:

Q. Checked by whom?

DR. O'MALLEY:

A. Checked by the technologists, yes, the senior technologists.

COFFEY, Q.C.:

Q. So, that is the arrangement that exists at Mount Sinai?

DR. O'MALLEY:

A. Yes, and if there is any concern at all, then they are checked also by the pathologists.

COFFEY, Q.C.:

Q. And how long have the technologist been checking external controls at Mount Sinai?

DR. O'MALLEY:

A. Well, I've been there since 1998 and it certainly has been happening since then.

COFFEY, Q.C.:

Q. And we'll be hearing, Commissioner, more from Ms. Wegrynowski about that, but from your perspective then, Doctor, I take it as a practising pathologist there that you understand that it wouldn't come to you, the tumor tissue slide would not even arrive for you to interpret without external controls having been certified as it were by the technologists?

DR. O'MALLEY:

A. That's correct.

COFFEY, Q.C.:

Q. How about usage of internal controls as a pathologist. Can you tell the Commissioner, please, about that, how long that has been the practice? How long have you been looking for internal controls in ER and PR slides?

DR. O'MALLEY:

A. Since I've started practising, that's just standard procedure.

COFFEY, Q.C.:

Q. Okay. So, when you, for example--remind me, please, you were at -

DR. O'MALLEY:

A. Victoria -

COFFEY, Q.C.:

Q. Vanderbilt, when? When was that?

DR. O'MALLEY:

A. I was at Vanderbilt in 1991 and 1992.

COFFEY, Q.C.:

Q. Okay. And then when you returned to Canada, just

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after that, I'm sorry, the hospital was?

DR. O'MALLEY:

A. Victoria hospital in London.

COFFEY, Q.C.:

Q. Victoria. And at that time, were they using IHC for ER and PR there?

DR. O'MALLEY:

A. They were.

COFFEY, Q.C.:

Q. And at that time when you were processing patient slides, were you looking for internal controls then?

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. Doctor, the usage of internal controls, in that context, are they peculiar to ER and PR or peculiar to IHC testing or where do they fit? Where do the idea of using internal controls fit in comparison to the uses of external controls? Perhaps you could put that -

DR. O'MALLEY:

A. Well, they certainly apply to ER and PR because we have that in-built normal epithelium that we know should be positive with both ER and PR, but it

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doesn't apply to every immunohistochemical test or isn't that in-built internal control.

COFFEY, Q.C.:

Q. So, internal controls, in that context, are peculiar to certain IHC tests?

DR. O'MALLEY:

A. Yes, that is correct, yes.

COFFEY, Q.C.:

Q. And the ER test and the PR test happen to be two that it applies to.

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. Again, just to put this in some kind of context for the Commissioner, like, IHC stains, immunohistochemistry stains, approximately how many, for example, would there be being utilized right now at Mount Sinai, how many different ones? And I won't hold you to the actual number, but just -

DR. O'MALLEY:

A. Actually Trish will be the -

COFFEY, Q.C.:

Q. Trish would know.

DR. O'MALLEY:

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A. Trish will have that data for you.

COFFEY, Q.C.:

Q. The actual amount, but I take it there's many, many stains.

DR. O'MALLEY:

A. Many, many stains.

COFFEY, Q.C.:

Q. I mean, it's not just three or four or five stains, it's -

DR. O'MALLEY:

A. No.

COFFEY, Q.C.:

Q. - probably well over a--and I anticipate she'll probably tell us well over a hundred. Doctor, in terms of--and I appreciate you practice breast pathology. If you could help the Commissioner please, in terms of these stains and there are many of them, I take it that they're not peculiar to breast pathology. They're used, these stains, IHC stains are used for a whole bunch of other types of sub specialities -

DR. O'MALLEY:

A. That's very, very true, but what's peculiar or different about ER and PR and indeed HER2 is that

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those immunohistochemical stains are used--a semi-quantitative result is given and they are used to drive therapy, rather than a lot of immunohistochemistry is used to just help sort out diagnosis, differential diagnosis. But for ER/PR and HER2, they re used very much to drive clinical decision making.

COFFEY, Q.C.:

Q. Now, is there, to your knowledge, any known correlation between ER positivity of a tumor and PR positivity?

DR. O'MALLEY:

A. Yes, the vast majority of tumors that are ER positive will also be PR positive. Occasionally, however, ER positive tumors will be PR negative. And this is probably due to the estrogen receptor being present, but actually not functional in those tumors. Now, conversely, ER positivity can occur in the face of ER negativity, but that's extremely rare. And -

COFFEY, Q.C.:

Q. Excuse me, what is extremely rare?

DR. O'MALLEY:

A. PR positivity in the face of ER negativity.

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COFFEY, Q.C.:

Q. Is extremely rare.

DR. O'MALLEY:

A. It is and indeed it would be an indication that the ER has failed because we know that the PR, induction of PR is really driven by ER. So, the ER must be functional for the progesterone receptor to be turned on.

COFFEY, Q.C.:

Q. And that rarity, existence of that rarity, how long has that been known? How long have you -

DR. O'MALLEY:

A. I can't put a date--many years.

COFFEY, Q.C.:

Q. Many years, okay. It goes back to the time your training and certainly into the -

DR. O'MALLEY:

A. Certainly since I've been at Mount Sinai.

COFFEY, Q.C.:

Q. If you were to encounter such a result, you know, for a patient you saw what you interpreted or thought, looking through the microscope, at a slide and what you were seeing, thought, well, that's PR positive and the same tumor slide made from the same

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block and the ER result was negative, at least, to the best you could see. Would that cause you to do anything?

DR. O'MALLEY:

A. I would probably repeat the ER, but in terms of just at a pragmatic level, the clinician is going to treat that patient because the tumor is PR positive.

COFFEY, Q.C.:

Q. So, it's your understanding that the oncologist--if, for example, you report that PR is, I don't know, 20 percent positive and even if it's, the ER is reported as 0, your understanding is that the oncologist will treat the patient in any case -

DR. O'MALLEY:

A. Yes, that is my understanding, -

COFFEY, Q.C.:

Q. - as if they're receptor positive and -

DR. O'MALLEY:

A. Yes, because as I mentioned, the PR can only be positive if the ER is functional.

COFFEY, Q.C.:

Q. What sorts of things, Doctor, would, from your perspective, cause you to perhaps question the accuracy of a test result, as you were saying? What

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sorts of things as clinician?

DR. O'MALLEY:

A. When I look down the microscope?

COFFEY, Q.C.:

Q. Yes.

DR. O'MALLEY:

A. Well, there are a number of things. Tumor type is one of them. So, while the vast majority of breast cancers are invasive ductal carcinomas, there are a certain number of special type cancers, invasive lobular cancers, invasive tubular cancers and invasive mucinous cancers are the three most common special type cancers. If one of those special type cancers was ER or PR negative, I would question the test result because the vast majority of those special type cancers are indeed ER and PR positive.

COFFEY, Q.C.:

Q. And questioning in that world means what? What would you do?

DR. O'MALLEY:

A. Well, I would--obviously I would have checked the internal controls and then I would go back and check the external controls, talk to the technologists about that particular run and ask for a repeat if

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necessary.

COFFEY, Q.C.:

Q. Repeat in the sense of have just have the slide or the tissue--another section -

DR. O'MALLEY:

A. Another section taken from the tumor and the testing -

COFFEY, Q.C.:

Q. The whole process gone through again.

DR. O'MALLEY:

A. Repeated, yes.

COFFEY, Q.C.:

Q. Now, Doctor, on that point, I take it though occasionally, example, lobular invasive carcinomas, have you ever encountered a lobular invasive that upon retest even, you were satisfied that it was a negative ER negative?

DR. O'MALLEY:

A. It's so rare that I can remember the one case that I did, that did come across my desk. It does happen, but it is very rare that a classic invasive lobular cancer would be negative for both ER and PR.

COFFEY, Q.C.:

Q. And, in fact, when did that occur? Do you recall

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when?

DR. O'MALLEY:

A. It actually occurred last year and it had been sent to three other labs before it arrived at Mount Sinai.

COFFEY, Q.C.:

Q. Doctor, do you know if Mount Sinai has tissue samples sent to it that are still in formalin from other hospitals? Like, sent across town, as it were in Toronto?

DR. O'MALLEY:

A. That would be quite unusual. The vast majority of the specimens that we receive have already been fixed and are in wax box, yes.

COFFEY, Q.C.:

Q. Okay. And in terms of if that was to occur, I take it, Trish would be at the technologists level even, that she would be perhaps aware of the pros and cons of doing that or the potential pitfalls of doing that?

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. I should take it up with her, right?

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DR. O'MALLEY:
A. Yes, indeed, indeed.
COFFEY, Q.C.:
Q. I'm not suggesting it does happen at all, not at all, I just wanted to ask you about it for a reason that will become apparent to the Commissioner at some later stage. One example, that case that you did refer to that you understood had gone to a number of other labs and to hospitals before it ended up at Mount Sinai, that lobular invasive, at the time I take it, it was your understanding that was being kind of shipped around for second and third opinions because it was perceived to be just so unusual.
DR. O'MALLEY:
A. That's correct.
COFFEY, Q.C.:
Q. And in performing those, carrying out or giving a second or third opinion, you would do what? Go through the whole processing procedure in the lab for external controls, internals controls and -
DR. O'MALLEY:
A. Yes, external controls and yes, I mean, they're used in every run.

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COFFEY, Q.C.:
Q. Yes. And if I could, Doctor, what I would like to do now, is I'm going to move on to the actual involvement such as it was that you had in the matter involving St. John's, in the hospitals here.
THE COMMISSIONER:
Q. Mr. Coffey, if i can interrupt just briefly before you do that, because there are a couple of things that I'm curious about -
COFFEY, Q.C.:
Q. I was going to say, in fact, in terms of -
THE COMMISSIONER:
Q. - on this, so it's just--while it's in my mind, things have a tendency to slip through. One is the business of the cutoff. I notice for example that, which as I understand it has been 10 percent or 1 percent or in some cases, 20 percent or even 30 percent, who in the specialities determines what is positive and what is negative? Is that something for pathologists?
DR. O'MALLEY:
A. That is decided by the pathologists, yes.
THE COMMISSIONER:
Q. And how does--is that something that is decided by

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each pathology department in each hospital?
DR. O'MALLEY:
A. It is, through their own validation and also review of the literature. So, why we chose the 1 percent is because we feel that that paper is the best evidence, both from a clinical and technical validation and we use those specific antibodies.
THE COMMISSIONER:
Q. So, is there a procedure at Mount Sinai where you regularly look at this or is it that some new study comes out and the leadership of pathology at Mount Sinai says, maybe we ought to think about it. How does that get done?
DR. O'MALLEY:
A. Well, it gets done through regularly reviewing the literature and for breast disease then, it would, I would make some of those decisions in conjunction with the leadership and the technical staff. So, the steps would be that we would, for example, with the 6F11, I had head that they didn't even present it. I was particularly impressed by that data and then I discussed the, bringing those antibodies into the lab with the head of surgical pathology and then I discussed it with the senior technologists in

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immunohistochemistry.
THE COMMISSIONER:
Q. Okay. Now, that point about the particular antibodies and I noticed that in the last slide that you presented, in terms of the information that you provide to oncologists, you said that they should insist on the reporting of the percentage of positivity, the antibodies used and the methodology. Now, why is it that you tell the oncologists which antibodies you used? I can relate to why you tell them percentages. I'm just wondering why is it you tell them which antibodies you use?
DR. O'MALLEY:
A. Well, because different antibodies have been associated with different cutoffs. So, again it's just another step to make sure that--it's really following the College of American Pathologists guidelines. And it's just another validation step in the process.
THE COMMISSIONER:
Q. All right. So, the decision made by Mount Sinai respecting percentage of positivity, in turn is something that relates, in any event to the antibodies used, correct?

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DR. O'MALLEY:
A. Well, it's related to the scoring of the antibodies.
THE COMMISSIONER:
Q. All right. So, really what you're trying to do in respect of communicating with the oncologists is to allow the oncologist to understand the basis for your cutoff, in terms of the science so that -
DR. O'MALLEY:
A. Exactly.
THE COMMISSIONER:
Q. - if they want to do an assessment, then they know your reference point is this particular science?
DR. O'MALLEY:
A. Exactly.
THE COMMISSIONER:
Q. All right, and the only other thing that I had a note of was this business of the lobular invasive and the expectation in respect of lobular--sorry, I'm having trouble getting my tongue around all these medical terms--would be negative?
DR. O'MALLEY:
A. The expectation is that an invasive lobular cancer, particularly a low grade classic invasive lobular, that it would be positive.

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THE COMMISSIONER:
Q. I'm sorry, you're right.
DR. O'MALLEY:
A. Over 90 percent.
THE COMMISSIONER:
Q. I got positive written down, but I said negative.
DR. O'MALLEY:
A. Over 90 percent of ER -
THE COMMISSIONER:
Q. Ah, okay, that was my question. One, what the percentage was that you would--what percentage would one--might one expect would be negative.
DR. O'MALLEY:
A. Less, way less than ten percent. Way less than, in fact, five percent.
THE COMMISSIONER:
Q. Okay.
DR. O'MALLEY:
A. Would be negative. So we would expect, as I say, 90 to 95 percent of classic ILC's to be ER positive.
THE COMMISSIONER:
Q. And how long has that been known?
DR. O'MALLEY:
A. I can't put a date to that, but I've certainly known

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about that for years.
THE COMMISSIONER:
Q. And well, can we relate it to the same thing that you related earlier, you said that since you--you made the reference to since you've been practising at Mount Sinai, which would have been since '98?
DR. O'MALLEY:
A. '98, well, I probably would have known that when I was practising in Victoria, at Victoria Hospital in London, which was '93 to '98.
THE COMMISSIONER:
Q. All right. So that would have been known in that period of time, and the other thing is, is this data tracked in your lab?
DR. O'MALLEY:
A. Yes, we do track the percentage positive and percentage negative ER and PR results that we have.
THE COMMISSIONER:
Q. In general, and also in respect of the different kinds of breast cancer, or that's what I'm--you know, there's -
DR. O'MALLEY:
A. In general. In general. If we wanted to look at specific, we can do that, but it's not as easily

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retrieved as the overall percentage positivity.
THE COMMISSIONER:
Q. So within Mount Sinai, you would know, with the push of a button, what your yearly statistics were in terms of percentages of positive and negative results?
DR. O'MALLEY:
A. Yes.
THE COMMISSIONER:
Q. All right. Thank you. Sorry to interrupt, Mr. Coffey, but while it was on my mind I thought I'd better.
COFFEY, Q.C.:
Q. Doctor, while I'm on it, as clarifying something again, which is, I gather, second nature to yourself. A synoptic report, what does synoptic mean?
DR. O'MALLEY:
A. It just means a very formatted report. So the information is in the same place in the same sort of format throughout the report.
COFFEY, Q.C.:
Q. And you also, in the last slide, made reference to in its title, in fact, information for medical

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oncologists and you indicated that when you do speak to medical oncologists as a group, as it were, or groups of them, that there are certain things you try to ensure that you tell them, to in effect demand of the pathologists that you're dealing with. Could you tell the Commissioner, and ask you just a couple of questions about kind of the relationships with other professionals. Technologists at Mount Sinai, what interaction do you have on a routine basis with technologists and who reports to whom? Could you just lay that out?

DR. O'MALLEY:

A. We work very, very closely with technologists when it comes to immunohistochemical staining, on a daily basis actually.

COFFEY, Q.C.:

Q. And who reports to--like in terms of the immunohistochemistry, who reports to whom?

DR. O'MALLEY:

A. We have a head of immunohistochemistry.

COFFEY, Q.C.:

Q. Is that a doctor?

DR. O'MALLEY:

A. That's a doctor, yes. So actually Dr. Pritzker will

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be able to address those reporting issues.

COFFEY, Q.C.:

Q. Okay, the organizational thing.

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. And so I'll take him through that, but in terms of yourself and your own interaction with technologists, I take it if you weren't here today, you were at work in Toronto, it would not be at all unusual for you to interact with the IHC techs routinely?

DR. O'MALLEY:

A. Absolutely. As I say, on a daily basis.

COFFEY, Q.C.:

Q. And with respect to oncologists, how much interaction at Mount Sinai do you have, as a pathologist, as a breast pathologist, with oncologists?

DR. O'MALLEY:

A. A lot of interaction. Maybe not on a daily basis, but certainly on a weekly basis. We have multi-disciplinary tumor boards where we discuss all of the patients that have been diagnosed with invasive

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breast cancer that week, and those conferences include medical oncologists, surgical oncologists, nurses, sometimes radiation oncologists come along too, and of course, ourselves.

COFFEY, Q.C.:

Q. And that practice has been going on for how long?

DR. O'MALLEY:

A. Since I've been at Mount Sinai.

COFFEY, Q.C.:

Q. Commissioner, I'm going to--as I'm going to pass on to something else and -

THE COMMISSIONER:

Q. Would you like to take the morning break?

DR. O'MALLEY:

A. - perhaps we can take the morning break, and I'll come back and finish my questions.

THE COMMISSIONER:

Q. Yes, of course.

COFFEY, Q.C.:

Q. Thank you.

THE COMMISSIONER:

Q. Take 15 minutes.

(RECESS)

THE COMMISSIONER:

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Q. Please be seated. Mr. Coffey, before you proceed, if you don't mind, I'm going to interrupt again.

COFFEY, Q.C.:

Q. Sure.

THE COMMISSIONER:

Q. Dr. O'Malley, at the end of your presentation, you did speak a little about those occasions when you might meet with oncologists and other professionals regarding the patient. Can you just give me a little more detail about under what circumstances the pathologist and oncologist might meet?

DR. O'MALLEY:

A. Certainly. These are regular meetings. They occur once a week in our breast centre, and the patients that we discuss are all of those patients that have come to Mount Sinai and have had a diagnosis of invasive breast cancer that week. So all of the patients have already had a diagnosis, either a core biopsy diagnosis or they've already undergone a lumpectomy or a mastectomy. So the discussions with the radiologists, the medical oncologists, surgical oncologists, are really around what type of chemotherapy these patients are going to have, and that's where they want to know the ER and the PR and

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the HER2 status of the tumors of those patients.
THE COMMISSIONER:
Q. So it's at treatment stage, rather than diagnosis stage?
DR. O'MALLEY:
A. It's at treatment stage, yes.
THE COMMISSIONER:
Q. And in your world at Mount Sinai, is there a place for a joint effort by pathologists and oncologists at the diagnosis stage?
DR. O'MALLEY:
A. The communication would really more often happen between the pathologist and the radiologist when they're performing the core biopsy for diagnosis and we would often meet and discuss those patients.
THE COMMISSIONER:
Q. All right. But I take it that primarily, on the diagnosis end of things, your communication is the written report that you provide to people?
DR. O'MALLEY:
A. That's right.
THE COMMISSIONER:
Q. Okay. Thank you.
DR. O'MALLEY:

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A. We're ultimately responsible for making that -
THE COMMISSIONER:
Q. Yes.
DR. O'MALLEY:
A. - the definitive call of cancer or not.
THE COMMISSIONER:
Q. Okay, thank you. Mr. Coffey.
COFFEY, Q.C.:
Q. Thank you, Commissioner. Now Doctor, if I could please, Registrar, Exhibit P-1698? Now, Doctor, I bring up this exhibit just simply because, although it's not--it didn't come from you, nor was it sent to you, you are referenced in it, okay, and it relates to another exhibit which is a letter which was sent to you on the same day, so I'm just going to take you to a little bit of this first. It's July 14th 2005. It's a letter to Dr. Donald Cook. It's from Dr. Beverley Carter. Do you know Dr. Carter?
DR. O'MALLEY:
A. I do.
COFFEY, Q.C.:
Q. How do you know Dr. Carter?
DR. O'MALLEY:

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A. I know Dr. Carter for many years. We both trained with Dr. David Page and we went through residency programs in Ontario. So we met as residents, and so we've known each other since our residency days.
COFFEY, Q.C.:
Q. Which would be, I take it, now getting onto a couple of decades.
DR. O'MALLEY:
A. Many years.
COFFEY, Q.C.:
Q. And this is where Dr. Carter is writing to Dr. Cook and she is suggesting here that certain measures be undertaken, okay, to conduct an investigation and she'll be telling us about that in due course, but toward the--in the second paragraph, she says--she begins by saying "as quickly as possible, I would like to know the estrogen receptor status of every patient tested in our laboratory between 1997 and 2004," and then she goes on from there, and toward the bottom of the paragraph says "all slides then have to be reviewed. They need to be reviewed by me, both estrogen receptor negative and estrogen receptor positive patients. Estrogen receptor negative patients should be given priority. Blocks

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will be pulled from those cases and estrogen receptor progesterone receptor status reordered. This test should be carried out as quickly as possible. Ten percent of cases should be randomly selected for outside quality assurance consultation. Dr. Frances O'Malley at Mount Sinai Hospital has agreed to act in this capacity. Problematic cases, as defined by a multiplicity of reasons, should also be sent for outside testing." And then she goes on to speak about a computerized database.

So Doctor, if we could bring up then, please, Exhibit P-1697? And this is a letter dated July 14th, 2005. It's addressed to yourself and the Department of Pathology, Mount Sinai Hospital, and if we look at the second page, it's from Dr. Carter, and she writes "Dear Dr. O'Malley, as per our telephone discussion on July 13th, 2005, could you please have ER/PR staining done on the following and also provide interpretation for same." And then there's a listing of a number of surgical block numbers, patient's name and date of birth, the MCP number and the specimen, what it's described as.

Do you recall speaking with Dr. Carter in July?
DR. O'MALLEY:

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A. I do recall.
COFFEY, Q.C.:
Q. Could you tell us then about what you recall about that?
DR. O'MALLEY:
A. Yes. I recall Dr. Carter calling me and telling me that she was concerned about the ER and PR testing in her lab and just wondered if we would be amenable to retesting a small number of cases, I think 10 or 15 cases, and I said I didn't think that would be a problem. I would talk to our head of surgical pathology, but that I certainly didn't think that that would be a problem.
COFFEY, Q.C.:
Q. And who was the head of surgical pathology?
DR. O'MALLEY:
A. Back then, well, I guess it was Ken Pritzker.
COFFEY, Q.C.:
Q. Ken Pritzker. Then eventually it ended up with Ken Pritzker.
DR. O'MALLEY:
A. It eventually ended up very fast to Dr. Pritzker.
COFFEY, Q.C.:
Q. And what then happened, in terms of that particular

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aspect of the matter?
DR. O'MALLEY:
A. Well, what happened was I believe that Dr. Cook called Dr. Pritzker and I'm not privy to that conversation, but my understanding is that many more cases--Dr. Cook wanted to send many more cases to Mount Sinai for testing and really, I didn't have much involvement in the whole process after that.
COFFEY, Q.C.:
Q. Doctor, with respect to the initial phone call from Dr. Carter, did she initially want you to get involved in this?
DR. O'MALLEY:
A. Just insofar as retesting a small number of cases.
COFFEY, Q.C.:
Q. And we understand that Trish Wegrynowski -
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. - got involved, and she will be testifying in the coming days. Do you know anything about how she ended up getting involved?
DR. O'MALLEY:
A. Yes. Dr. Carter did talk about some of the issues

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surrounding the ER/PR testing and my understanding from what she relayed to me was that the problems were probably at the analytic stage, involving the technical procedure of the immunohistochemical test. So I suggested that it would be better to have a senior, very experienced technologist, such as Trish Wegrynowski, to review the process.
COFFEY, Q.C.:
Q. So Dr. Carter was in effect asking you if it is at the analytic stage, a problem that she, at the time, was conveying to you, she thought perhaps it was, it was your view expressed to her that "look, well if it involves that, talk to Trish," as it were?
DR. O'MALLEY:
A. Exactly.
COFFEY, Q.C.:
Q. And "I'll put you in touch with her or her in touch with you" and it went on from there?
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. And now who is Trish Wegrynowski, just so--you've referred to her a number of times this morning. Who is she?

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DR. O'MALLEY:
A. She is one of our senior immunohistochemical technologists at Mount Sinai, very, very experienced technologist.
COFFEY, Q.C.:
Q. And was she there when you first arrived at Mount Sinai?
DR. O'MALLEY:
A. I believe she came in 1999, so a year after I arrived.
COFFEY, Q.C.:
Q. Now with respect to others who might or who ended up involved, Dr. Brendan Mullen, who is Dr. Brendan Mullen?
DR. O'MALLEY:
A. Dr. Mullen is a staff pathologist at Mount Sinai with a lot of experience in many areas of pathology and in breast pathology as well.
COFFEY, Q.C.:
Q. And in terms of the retesting process that the Commissioner is going to hear more about in the coming days, Dr. Mullen, as opposed to yourself, who ended up being most heavily involved in it?
DR. O'MALLEY:

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A. Dr. Mullen.
COFFEY, Q.C.:
Q. Okay, and in terms of that, what level within the Mount Sinai's organization decided that? Who ended up making that decision?
DR. O'MALLEY:
A. My understanding is that it was made by Dr. Pritzker, in conjunction with Dr. Mullen, obviously.
COFFEY, Q.C.:
Q. If we could, please, Exhibit P-1703? Now Dr. O'Malley, this is a series of e-mails but the first of them, at the bottom of the first page of the exhibit, is from George Tilley, October 20th, 2005, at 2:38 p.m. to a Dr. Robert Bell. It's copied to Dr. Bob Williams, Robert Williams, and there's a reference at the bottom of that page by Mr. Tilley saying "our laboratory clinical chief will be contacting the two individuals you referenced to also see what insight they can offer in terms of national follow," and he says "it appears that there is a gap in terms of a national entity who can take the lead with this issue, so we will likely have to take a shotgun approach to the follow up and hope that there is someone who can keep it moving. In

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the meantime, we will write the Canadian Association of Pathologists and others that we may subsequently identify. I will also seek Phil's help at the CPSI." Signed George.

Then above, there's an e-mail following that from Dr. Robert Bell, October 23rd, 2005, 8:13 p.m. to George Tilley. He's copied it though to Bruce Youngson and yourself, Dr. Frances O'Malley, and he says "thanks, George. The two individuals with the most expertise around ER testing in Toronto are Drs. Frances O'Malley and Dr. Bruce Youngson," and then Dr. Bell writes "Bruce and Frances, you have probably heard about the issue of retesting breast cancer specimens in Newfoundland. Some ER negative specimens have been reinterpreted as positive. The chief of pathology from Newfoundland may contact you as to any advice regarding reliability of ER testing," and then you, the next day, October 24th forwarded that to Dr. Pritzker for his information.

So in October, late October 2005, from your perspective, Doctor, who at Mount Sinai was addressing the matter with Newfoundland?
DR. O'MALLEY:
A. Dr. Pritzker.

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COFFEY, Q.C.:
Q. Pritzker. And I take it on a day-to-day level, Dr. Mullen, in the sense of actually getting the retesting done?
DR. O'MALLEY:
A. Yes.
COFFEY, Q.C.:
Q. And the technologist arranging to have the tissues, the slides processed?
DR. O'MALLEY:
A. Um-hm.
COFFEY, Q.C.:
Q. Okay. So, Doctor, other than being interviewed by Sandra Chaytor and myself, okay, which happened sometime late last year, actually, late 2007, and coming here to testify, have you had any other involvement in this matter?
DR. O'MALLEY:
A. I've had minimal involvement, which really the only involvement that I can remember is sometimes when Dr. Mullen had a difficult case from a diagnostic point of view or a case that he find difficult to interpret, he would ask for my opinion. And there were a few occasions, very few occasions when he was

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on vacation when he would ask me to sign out some of the prospective ongoing cases that came from Newfoundland.
COFFEY, Q.C.:
Q. They would be the current cases?
DR. O'MALLEY:
A. The current cases, but I -
COFFEY, Q.C.:
Q. Current, ongoing?
DR. O'MALLEY:
A. Yeah.
COFFEY, Q.C.:
Q. Okay. Commissioner, they're the questions I have. Doctor, there may be other lawyers who have some questions.
COMMISSIONER:
Q. Mr. Pritchard, do you have any questions?
COFFEY, Q.C.:
Q. I'm going to move aside.
MR. PRITCHARD:
Q. Thank you, Commissioner, I don't have any questions of this witness. Thank you -
COMMISSIONER:
Q. Mr. Simmons?

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DR. FRANCES O'MALLEY, EXAMINATION BY MR. DANIEL SIMMONS

MR. SIMMONS:

Q. Thank you, Commissioner. Good morning, Dr. O'Malley, my name is Dan Simmons and I'm here representing Eastern Health. Just some background questions first for you on, about Mount Sinai and its lab. The Mount Sinai as an institution, does it operate from a single location in Toronto?

DR. O'MALLEY:

A. Yes, it does.

MR. SIMMONS:

Q. It is. Is it affiliated in any formal way with any other hospitals operating from any other locations from which it provides services to those?

DR. O'MALLEY:

A. It's affiliated with the university health network in terms of many of our clinicians work at both sites.

MR. SIMMONS:

Q. Right, okay. And we've heard some mention along the way in this Inquiry of the concept of a reference laboratory. Does Mount Sinai operate what would be referred to as a reference laboratory?

DR. O'MALLEY:

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A. Yes, it does. It operates a reference, it functions as a reference laboratory for Her2 testing specifically.

MR. SIMMONS:

Q. Okay. And what does it mean then to be a reference laboratory?

DR. O'MALLEY:

A. We receive so we're part of a quality assurance program within the province, and we receive cases from other labs that are performing Her2 testing for retesting in our lab to ensure that there is good interlab concordance.

MR. SIMMONS:

Q. Okay. And in--with this particular matter we know that many ER/PR cases were retested at Mount Sinai from Newfoundland and that there were also current cases from Newfoundland that went there for retesting, and you referred to those, some of those a moment ago. Does Mount Sinai lab provide that sort of service to any other hospitals as well, to do testing for other people?

DR. O'MALLEY:

A. Yes, we do. Yes, we provide that service for many other hospitals.

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MR. SIMMONS:

Q. Right, okay. And do I understand that within Mount Sinai there's actual two separate laboratories where IHC or immunohistochemical testing can be performed, there's a research laboratory and then there's the clinical laboratory?

DR. O'MALLEY:

A. Yes, yes, but they work very, very closely together. The same procedures, the same SOPs are in effect in both parts of the lab.

MR. SIMMONS:

Q. Okay. Why the division, what's done differently in the research laboratory versus the clinical laboratory?

DR. O'MALLEY:

A. It's just a streamlining of work, so research studies are just funnelled through the research laboratory and all of the service cases are dealt with in the clinical lab.

MR. SIMMONS:

Q. Okay. In the research laboratory is there a service there provided to industry to carry out contract testing for drug companies and things such as that?

DR. O'MALLEY:

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A. Yes.

MR. SIMMONS:

Q. Yes.

DR. O'MALLEY:

A. Dr. Pritzker will be able to elaborate on that.

MR. SIMMONS:

Q. Yes, okay. You told us about the method that was used prior to immunohistochemical testing for assessing the presence of estrogen receptors and progesterone receptors and I think you called that the Ligand Binding Assay?

DR. O'MALLEY:

A. Yes.

MR. SIMMONS:

Q. LBA?

DR. O'MALLEY:

A. Um-hm.

MR. SIMMONS:

Q. And that it was a method that had been in use, I gather, for some time before the immunohistochemistry methods were developed?

DR. O'MALLEY:

A. That's true.

MR. SIMMONS:

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Q. Okay. You mentioned that when you--when the Ligand Binding Assay was in use in Ontario, I believe you said there were five laboratories that were somehow sponsored or approved -

DR. O'MALLEY:

A. Licensed, approved, yes.

MR. SIMMONS:

Q. - or licensed by the government for carrying out that testing?

DR. O'MALLEY:

A. Um-hm.

MR. SIMMONS:

Q. So within Ontario at that time were those the only five institutions that were -

DR. O'MALLEY:

A. Performing those tests, yes. That, to my understanding, yes, that was the case.

MR. SIMMONS:

Q. Do you know anything about how much government supervision there was or regulation there was over the activities of those laboratories in performing those tests?

DR. O'MALLEY:

A. I don't know a lot because I wasn't directly

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involved in any of those laboratories, but my understanding is that direct funding came from the provincial government to support the activities in those laboratories and there was strick quality assurance and quality control procedures between all labs.

MR. SIMMONS:

Q. That were mandated, I guess, in that case, were they?

DR. O'MALLEY:

A. That were mandated as part of the funding, yes.

MR. SIMMONS:

Q. Okay. Now, when the move came to switch from the Ligand Binding Assay to the IHC method, if I understand correctly, there were advantages to moving to the IHC, naturally, or it wouldn't have been done, and one of the significant advantages was that the Ligand Binding Assay required a relatively large volume of tissue in order to carry out the test?

DR. O'MALLEY:

A. That's right.

MR. SIMMONS:

Q. And that as detection of breast cancer became

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possible in earlier and earlier stages, in many cases there would not be a tissue sample large enough to provide that?

DR. O'MALLEY:

A. Exactly.

MR. SIMMONS:

Q. Sample size?

DR. O'MALLEY:

A. Um-hm.

MR. SIMMONS:

Q. And that that was one of the reasons for moving towards the IHC test. When that happened in Ontario, was there the same approach taken to confine the IHC testing to certain approved laboratories the way it had been for the Ligand Binding Assay?

DR. O'MALLEY:

A. No, no, that did not happen, that did not happen. Each laboratory--because most of these laboratories were already performing immunohistochemical tests.

MR. SIMMONS:

Q. I see, yes.

DR. O'MALLEY:

A. So it just became incorporated into that process.

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But unfortunately, there wasn't, standardization was not introduced at that time.

MR. SIMMONS:

Q. Right.

DR. O'MALLEY:

A. So each laboratory was responsible for their own validation and standardization of the ER and PR tests.

MR. SIMMONS:

Q. Okay. And so different laboratories, any laboratory, I guess, that wanted to add the ER and the PR antibodies to their arsenal of immunohistochemistry tests could choose to do so and it was up to them to determine exactly how they implemented it?

DR. O'MALLEY:

A. That is my understanding.

MR. SIMMONS:

Q. Right, okay. Now, has that changed in Ontario now, has there been anything happen in Ontario to bring back any kind of mandated QA or QC for this type of testing?

DR. O'MALLEY:

A. Not in Ontario, but there is now this national

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initiative. And I showed some of the early data from that.

MR. SIMMONS:

Q. Yes.

DR. O'MALLEY:

A. Which will hopefully bring in national standards. But all laboratories who--all laboratories that are performing these tests are really are recommended to take part in a quality assurance program such as the UK program that I discussed, and the US or College of American Pathologists program. We at Mount Sinai participate in both of those quality assurance programs.

MR. SIMMONS:

Q. Right, okay. Now, there are, I understand, different antibodies available that can be used in the technical performance of the ER and the PR testing?

DR. O'MALLEY:

A. That's correct.

MR. SIMMONS:

Q. And they come from different manufacturers?

DR. O'MALLEY:

A. Um-hm.

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MR. SIMMONS:

Q. And are there known to be different sensitivities and specificities from those different antibodies?

DR. O'MALLEY:

A. Absolutely.

MR. SIMMONS:

Q. Okay. And in addition to the antibodies, and we'll hear more, I know, from Ms. Wegrynowski about the technical side of the testing, but are there also differences in the types of materials, things like what we may hear of as detection systems and so on that can be used in performing the ER and the PR tests?

DR. O'MALLEY:

A. There are, yes.

MR. SIMMONS:

Q. And do you know from, I guess, from your interactions with other counterparts of yours in Ontario, in the Toronto area, are there differences among the different labs even now in the Toronto area of which antibodies they choose to use and which other procedural components they choose to use in performing these tests?

DR. O'MALLEY:

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A. There are.

MR. SIMMONS:

Q. Okay. Is there any, has there been since this testing was transferred over from Ligand Binding Assay to IHC, has there been any source that labs can go to in Ontario or in Canada to give them a set of approved recommendations for choice of antibody, chose of detection system, method of performing the test, method of interpreting the test and all those different elements?

DR. O'MALLEY:

A. Well, there are many publications reporting results for different antibodies in different detection system, etcetera, but it's really up to the individual lab to, you know, the pathologists and technologists working together to make the final decision regarding the specific antibodies that are used in the specific detection systems that are used. But when that decision is made then, there is a rigorous validation process that must be put in place to make sure that those results are giving an accurate -

MR. SIMMONS:

Q. Right, okay.

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DR. O'MALLEY:

A. - those tests are giving an accurate result.

MR. SIMMONS:

Q. And is that validation process something that is an external requirement imposed upon laboratories and health care institutions or is it just part of good practice to do that?

DR. O'MALLEY:

A. Well, in the setting Her2 it is mandated and for ER.

MR. SIMMONS:

Q. Okay.

DR. O'MALLEY:

A. And PR too.

MR. SIMMONS:

Q. How is it mandated for ER and PR now, who mandates it?

DR. O'MALLEY:

A. Well, it's not currently mandated, but through--I mean, it's highly, highly recommended, but through the national standards committee that has just been struck, my understanding is that it will be mandated.

MR. SIMMONS:

Q. Okay. Can you tell me a little more about that

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national standards committee, who makes it up and what its task is to be or do you know?

DR. O'MALLEY:

A. I don't know a lot about it, but I do know that it is based in Saskatchewan.

MR. SIMMONS:

Q. Yes.

DR. O'MALLEY:

A. And Nina Toilacovik (phonetic) is heading up this initiative.

MR. SIMMONS:

Q. Are there any organizations or groups that are sponsoring that effort or standing behind it?

DR. O'MALLEY:

A. Yes. The Canadian Association of Pathologists.

MR. SIMMONS:

Q. Okay. Are there any governmental agencies or regulators that you are aware of that have set any kind of standards in Canada for the performance of this type of testing and the interpretation of it?

DR. O'MALLEY:

A. I'm not aware of any governmental agency.

MR. SIMMONS:

Q. And aside from the work currently under way

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sponsored by Canadian Association of Pathologists, are you aware as to whether there's been any other kind of national standard available to turn to in Canada for this type of testing?

DR. O'MALLEY:

A. No.

MR. SIMMONS:

Q. So from the point of view of individual laboratories then, is it fair to say that there has been and continues to be a choice of different antibodies, materials and procedures that can used for ER and PR testing?

DR. O'MALLEY:

A. Yes.

MR. SIMMONS:

Q. And that there's no mandated choices to be made, each lab has to use its best processes to determine what to do?

DR. O'MALLEY:

A. That's correct.

MR. SIMMONS:

Q. And is there an understanding that sometimes what works in one lab may not be the best for another lab?

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DR. O'MALLEY:

A. That is absolutely correct.

MR. SIMMONS:

Q. Can you tell me something more about that, about why that would be the case?

DR. O'MALLEY:

A. Well, again, Trish can elaborate on that. But it definitely is the case that one antibody in a particular lab with a different detection system will be more sensitive than the same antibody in another lab with a different detection system, for example.

MR. SIMMONS:

Q. Okay. Now, you've given us some very helpful evidence about the cutoffs and determining the cutoff points for designating a test result as either positive or negative. And the first question I wanted to ask you is kind of a follow up on one that the Commissioner asked you. Because if I understand correctly, it is the oncologists who ultimately determine the treatment for the patient and whether or not an adjuvant therapy such as Tamoxifen will be recommended for that patient or not?

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DR. O'MALLEY:

A. Yes.

MR. SIMMONS:

Q. That's right? And but you as a pathologist would be aware that there are pros and cons to do those decisions because there are adverse effects that can result from Tamoxifen therapy as well as beneficial effects? You would be aware of that in a general sense?

DR. O'MALLEY:

A. Yes, yes.

MR. SIMMONS:

Q. Yeah, okay. And I'm just curious as to why it would be expected for a pathologist in the laboratory setting to have to designate a test as positive or negative at all rather than just give the percentage to the oncologist and leave it entirely to the oncologist to determine what course of treatment to take based on that percentage and the other factors that they have to take into account?

DR. O'MALLEY:

A. Well, no, it's not quite as simple as that.

MR. SIMMONS:

Q. Okay.

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DR. O'MALLEY:
A. Because the cutoff is really dependent on the antibody used and because of the issues of sensitivities and specificities, so you know, while we use a one percent cutoff because we have those very sensitive antibodies, another lab still may be using a ten percent cutoff, so it would not be the best practice for a clinician to be deciding what the cutoff is for a particular lab.
MR. SIMMONS:
Q. Um-hm.
DR. O'MALLEY:
A. Having said that, the NIH in the States has recommended, indeed, that any tumor positivity for both ER and PR should be considered positive.
MR. SIMMONS:
Q. Yes.
DR. O'MALLEY:
A. But again, that's consistent with, really, the Allred score.
MR. SIMMONS:
Q. Right. NIH, I think, is National Institutes of Health in the United States?
DR. O'MALLEY:

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A. Yes.
MR. SIMMONS:
Q. Is there any comparable recommendation from any comparable body in Canada that you're aware of?
DR. O'MALLEY:
A. Not that I'm aware of.
MR. SIMMONS:
Q. Okay. So from what you've said then, because at Mount Sinai you're using a particular antibody, you're satisfied that you know what the sensitivity and specificity of it is in your lab's hands, you've adopted the one to ten percent as being something that would be positive enough to merit a recommendation for treatment?
DR. O'MALLEY:
A. That is correct, yes.
MR. SIMMONS:
Q. Are you aware if that is the case in other comparable institutions in the area where you are in Toronto, if they've adopted that or if there's variation in the cutoffs?
DR. O'MALLEY:
A. There certainly has been variation, but my understanding is that certainly Sunnybrook has

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adopted the one percent cutoff.
MR. SIMMONS:
Q. How recent is that?
DR. O'MALLEY:
A. In the last few years.
MR. SIMMONS:
Q. Okay. And are you aware of whether or not there have been other institutions in--that you would be familiar with in the Toronto area that haven't moved to the one percent and have stayed at the ten percent for their results?
DR. O'MALLEY:
A. I couldn't comment on every lab, but I would not be surprised if some of those labs are still at the ten percent. But remember, they may be using different antibodies and that's ten percent may be relevant for those particular antibodies.
MR. SIMMONS:
Q. Right. Are you familiar with an organization called ASCP?
DR. O'MALLEY:
A. Yes.
MR. SIMMONS:
Q. And that's the American Society of?

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DR. O'MALLEY:
A. Clinical Pathology.
MR. SIMMONS:
Q. Clinical Pathologists. And ASO I think is the American Society of Oncologists?
DR. O'MALLEY:
A. ASCO, yeah.
MR. SIMMONS:
Q. Okay. Do you know whether--and they are organizations in the United States, I guess, one of them might be the comparative group to the Canadian Association of Pathologists, would it?
DR. O'MALLEY:
A. College of American Pathologists would be equivalent to the Canadian Association of Pathologists.
MR. SIMMONS:
Q. Okay. Are you aware of whether ACSP and ASO have done or been doing any work to develop any guidelines for ER and PR testing?
DR. O'MALLEY:
A. Actually, ASCO and CAP, so the oncology group and the pathology group in the States recently published guidelines on Her2 testing. I do know that while there are no published recommendations on ER and PR,

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they are in the works, that is my understanding.
MR. SIMMONS:
Q. Okay. So in the United States, then, the organizations that would typically be taking the responsibility for publishing these sorts of guidelines have done so for the Her2 testing but note yet for ER and PR?
DR. O'MALLEY:
A. That's correct.
MR. SIMMONS:
Q. You mentioned some of the work that had been done in Europe and you mentioned the NEQAS program, which I understand is something that was developed in the UK in response to the interlaboratory variability studies that had been done in Europe.
DR. O'MALLEY:
A. That is my understanding too.
MR. SIMMONS:
Q. Do you know whether in UK and Europe there is anything equivalent to a set standard for the performance of ER and PR testing, something which we don't have yet in Canada and the United States?
DR. O'MALLEY:
A. Well through that program, a certain competency has

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to be reached in terms of concordance with the reference lab.
MR. SIMMONS:
Q. Okay, and the program you refer to is the quality assurance program sponsored by the NEQAS organization, is it?
DR. O'MALLEY:
A. Yes.
MR. SIMMONS:
Q. Now we've heard mention along the way a proficiency testing, is that you're referring to there something similar to that?
DR. O'MALLEY:
A. That's exactly--it's just another term for what we're talking about.
MR. SIMMONS:
Q. And as I understand it, the NEQAS organization, if you enrole with that, it will send a sample to your laboratory for you to process onto a slide and stain and then have your pathologist interpret it. The results in the slide are sent back to the NEQAS organization in the UK and they grade you on how well you've done with it.
DR. O'MALLEY:

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A. That's correct.
MR. SIMMONS:
Q. And how long has that been available, that service, would you know?
DR. O'MALLEY:
A. I don't actually know offhand, many years, I believe, but I can't give a specific date.
MR. SIMMONS:
Q. In one of your slides where you mentioned that, you had footnoted, I think, a study from Rhodes there from 2000? Does that sound familiar?
DR. O'MALLEY:
A. Uh-hm. Yes.
MR. SIMMONS:
Q. Would that be around the time of the study, one of these studies of the interlaboratory variability?
DR. O'MALLEY:
A. Yes, it was, but NEQAS has been in existence, you know, before that.
MR. SIMMONS:
Q. Okay, all right. And do you know how long Mount Sinai has been enroled in the NEQAS program?
DR. O'MALLEY:
A. Just in the last few years, we've been enroled in

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the CAP program, the College of American Pathologist's program for many years, but we just joined NEQAS in the last few years.
MR. SIMMONS:
Q. So aside from the College of American Pathologist's program available from the United States and--oh, by the way, that -
DR. O'MALLEY:
A. Oh there's also a provincial QMPLS -
MR. SIMMONS:
Q. In Ontario.
DR. O'MALLEY:
A. Yes, yes.
MR. SIMMONS:
Q. Do they do proficiency testing or do they--are they the equivalent of an accreditation body for provincial laboratories in Ontario?
DR. O'MALLEY:
A. No, not--to my understanding the equivalent of an accreditation program, but again, Dr. Pritzker should be able to address that more fully.
MR. SIMMONS:
Q. Good, thank you. Now immunohistochemistry in general and the ER/PR testing here in particular,

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which is what we're concerned with, can you tell me if there's been any process of evolution in understanding of how this test works and on understanding the most effective ways to do it and interpret it over time, since you first became familiar with it?

DR. O'MALLEY:

A. I would--yes, there definitely has been an evolution.

MR. SIMMONS:

Q. Uh-hm. I'm putting you on the spot now I know, but can you give me some sort of overview of what sorts of things might have changed over time regarding the usefulness of it and how reliable it is?

DR. O'MALLEY:

A. Well the usefulness has been known for many, many years as I allude to that it has been a clinically validated test for a long time. I guess what we have learned over the years is that, you know, we've learned that the different antibodies have very, very different sensitivities and specificities and we have to pay very particular attention to that, as well as the different detection systems giving, affecting the sensitivity and specificity of the

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test as well.

MR. SIMMONS:

Q. Have some of the potential problems with the test become better known and more clearly understood over time?

DR. O'MALLEY:

A. I would think so, but Trish will be able to elaborate on that.

MR. SIMMONS:

Q. Right, okay. You were asked some questions concerning external controls and just to make sure I understand what you're referring to there, if I understand it correctly, when a batch, a group of ER or PR tests are performed, a series of twenty or forty of fifty slides will be processed together at the same time, they'll go through the process with the antibodies and the different chemical reagents being applied and the different steps being done. That's generally the way they are processed in the laboratories, right?

DR. O'MALLEY:

A. Yes.

MR. SIMMONS:

Q. And that typically one of the slides will have a

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piece of tissue with a known outcome and in your case, you described there being a strong positive, a weak positive and a negative.

DR. O'MALLEY:

A. Uh-hm.

MR. SIMMONS:

Q. And that that slide would be processed as part of the same batch?

DR. O'MALLEY:

A. Yes.

MR. SIMMONS:

Q. And that slide is what's being referred to as the external control, I believe?

DR. O'MALLEY:

A. That's right.

MR. SIMMONS:

Q. So the purpose of that then is to ensure that the external control slides stains the way it's supposed to, because if it doesn't, it's an indicator that maybe the process didn't work.

DR. O'MALLEY:

A. That's absolutely correct.

MR. SIMMONS:

Q. Okay, now in Mount Sinai it's the technologists who

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assess the external control slide to see if the test worked before released the patient slides to the pathologists for them to look at?

DR. O'MALLEY:

A. Yes.

MR. SIMMONS:

Q. Is there any particular advantage to having a technologist review the external control slide instead of having a designated pathologist review the external control slide?

DR. O'MALLEY:

A. Well, I mean, as long as the technologist is highly trained then, you know, it can be completely adequately performed by the technologist. If there's any concern, then the pathologist will review those external controls as well.

MR. SIMMONS:

Q. I understand that for the technologist to be the one to review the external control, they require the degree of training, understanding and proficiency to be able to do it reliably, but on the other hand, is there any--would there be anything that would be problematic about having a pathologist perform that part of the process, instead of a technologist?

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DR. O'MALLEY:
A. No, no, just as a time issue.
MR. SIMMONS:
Q. Okay. The fact that I have to take time to review my notes is a good sign, it means I don't have much more to ask you. You've referred a number of times to a particular antibody that Mount Sinai uses which is the 6F11 antibody.
DR. O'MALLEY:
A. Yes.
MR. SIMMONS:
Q. And I've seen reference to that as a mouse monoclonal antibody, I think.
DR. O'MALLEY:
A. Uh-hm.
MR. SIMMONS:
Q. We've also heard this inquiry of another antibody that's available for ER testing designated, I think, SP1.
DR. O'MALLEY:
A. Rabbit.
MR. SIMMONS:
Q. Yeah, rabbit something or another.
DR. O'MALLEY:

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A. Yes.
MR. SIMMONS:
Q. Has Mount Sinai moved to the SP1 antibody?
DR. O'MALLEY:
A. No, we haven't because we're very confident and comfortable with the performance of the 6F11.
MR. SIMMONS:
Q. When the pathologist gets the final slide and is satisfied that it's interpretable and does the interpretation, scores it, uses whichever method is going to be used, the pathologist, of course, has to prepare a report in some written form, to pass that information on to the oncologist and so it forms part of the permanent patient record.
DR. O'MALLEY:
A. Uh-hm.
MR. SIMMONS:
Q. And you've referred to synoptic reporting, which I take it to mean for at least some parts of this process, using standardized language -
DR. O'MALLEY:
A. That's correct.
MR. SIMMONS:
Q. - for reporting it. Can you give me some idea of

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what sort of process is available at your institution for automating or this process of preparing pathology reports, are they just dictated and someone types them up? Are they entered directly into a computer system? How do you--what do you do in a hands-on way when you have to do one of those reports?
DR. O'MALLEY:
A. Well through our lab information system both can be done, but many times we enter the data right on the screen.
MR. SIMMONS:
Q. Uh-hm, okay, is there any narrative portion in those reports or is it all filling in fields where there are set terminology to be used for every field?
DR. O'MALLEY:
A. The gross description of the specimen is still in a narrative form, but the actual microscopic portion of the report, which includes the ER and PR and HER/2neu results is all now in synoptic format.
MR. SIMMONS:
Q. And has that process been in use at your institution since you've been there or introduced along the way somewhere?

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DR. O'MALLEY:
A. No, it was introduced along the way. I believe we moved to synoptic reports in 2005.
MR. SIMMONS:
Q. In 2005.
DR. O'MALLEY:
A. Yeah, I believe that is correct.
MR. SIMMONS:
Q. So prior to 2005 then, was there any fixed standardization in the pathology reports about how the results of the ER and PR tests were recorded?
DR. O'MALLEY:
A. Generally they were reported in very similar manner from one pathologist to the next -
MR. SIMMONS:
Q. Yes.
DR. O'MALLEY:
A. There might have been a slight variation, but it was pretty standard, even before that time.
MR. SIMMONS:
Q. And was that reporting done in the narrative portion of the report or in particular fields of the report?
DR. O'MALLEY:
A. It was in the microscopic portion of the report.

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MR. SIMMONS:
Q. In the microscopic, so the pathologists would have to dictate the ER--or type, the ER/PR results as part of the narrative portion and there was some potential then for different pathologists to use some variation in the way, the language they used to report that, was there?
DR. O'MALLEY:
A. That's correct, yes.
MR. SIMMONS:
Q. Positivity rates on an annual basis, how does your lab handle designating someone to monitor and collect that data for what portion of ER and PR tests are positive on an annual basis?
DR. O'MALLEY:
A. Well that is generated through the immunohistochemistry lab.
MR. SIMMONS:
Q. Uh-hm, okay, so that's done within the lab itself, is it?
DR. O'MALLEY:
A. Yes.
MR. SIMMONS:
Q. And is there anyone designed on the, any physician

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designed to take responsibility for assessing those results, those positivity rates looking for trends, those sorts of things from a management perspective?
DR. O'MALLEY:
A. Well the head of the immunolab would look at those rates.
MR. SIMMONS:
Q. Okay. So you wouldn't have been involved, I guess, over the years in monitoring those rates yourself?
DR. O'MALLEY:
A. Well actually, yes, I'm involved as well.
MR. SIMMONS:
Q. Okay, and what's your involvement in it, how does that work?
DR. O'MALLEY:
A. Well I'm just, you know, very interested in what goes on, so yeah, I would make it my business to know what those rates are.
MR. SIMMONS:
Q. Okay. We've heard some mention here of type of diagnosis that has been abbreviated DCIS, which I think is ductal carcinoma in situ?
DR. O'MALLEY:
A. That's correct.

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MR. SIMMONS:
Q. Are ER and PR tests normally done for those cases?
DR. O'MALLEY:
A. At Mount Sinai we do not routinely perform ER and PR on DCIS.
MR. SIMMONS:
Q. Any particular reason why that would be the case?
DR. O'MALLEY:
A. We don't feel that the data is strong enough to support that. The data actually that has really driven the performance of ER and PR is the setting of ductal carcinoma in situ is one study that's been only published in abstract form, so we certainly wouldn't change procedure based on that limited data.
MR. SIMMONS:
Q. Okay.
DR. O'MALLEY:
A. On the other hand, if a medical oncologist asks us specifically to perform ER and PR on a case of DCIS, we obviously will do that.
MR. SIMMONS:
Q. Right, so from the pathologist's point of view then in getting a new case into the lab for assessment,

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while it would be standard and routine in a breast cancer case to order an ER and PR on any type of an invasive cancer, it would not be the pathologist's routine to order the test if it's a ductal carcinoma in situ?
DR. O'MALLEY:
A. At Mount Sinai that's the practice, yes.
MR. SIMMONS:
Q. Right, which is, I guess, a type of non evasive cancer?
DR. O'MALLEY:
A. It's a non-evasive breast cancer and Tamoxifen is really used in that case as a chemo-preventative agent because the therapy for DCIS is excision and radiation.
MR. SIMMONS:
Q. Okay. We've--I understand that there is some new technology on the horizon or may be available now to assist pathologists with the assessment of the percentage of positivity?
DR. O'MALLEY:
A. Image analysis.
MR. SIMMONS:
Q. Image analysis, yes. Have you had any experience

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with that at Mount Sinai?
DR. O'MALLEY:
A. Yes, we do have an image analysis system, but we use it in the research setting. We have not moved it into the clinical setting.
MR. SIMMONS:
Q. Okay, is there any particular reason why you haven't moved it into the clinical setting?
DR. O'MALLEY:
A. Cost, expertise needed.
MR. SIMMONS:
Q. Uh-hm.
DR. O'MALLEY:
A. And also the vast majority of ER and PR are really quite easy to read manually. So it wouldn't save us time reading the vast majority. I see its role is really assessing those cases where the percentage of positivities are around the one to ten percent range and that's where it could be quite useful.
MR. SIMMONS:
Q. So it's used in the research laboratory, which is a physically separate laboratory from the clinical laboratory at your institution?
DR. O'MALLEY:

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A. That's--yes.
MR. SIMMONS:
Q. And not for the clinical cases. Okay. Thank you very much, Dr. O'Malley, I don't have anything else for you.
THE COMMISSIONER:
Q. Mr. Browne?
DR. FRANCES O'MALLEY, EXAMINATION BY MR. PETER BROWNE
MR. BROWNE:
Q. Good morning, Dr. O'Mally.
DR. O'MALLEY:
A. Good morning.
MR. BROWNE:
Q. My name is Peter Browne. I represent a number of individual physicians who have been asked to testify, including pathologists and oncologists. You'll be glad to know that Mr. Simmons has covered some of the areas that I was planning on questioning you on. I'd like to begin with, however, your curriculum vitae, I have a number of just sort of curious questions and one of which relates to, it looks to be either an abstract or an article and it's at page 26, item No. 93. It's an abstract that you were involved in in 2005 and it's entitled

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"Standardization of Estrogen and Progesterone receptor assay values." Do you recall that publication?
DR. O'MALLEY:
A. Just -
MR. BROWNE:
Q. Number 93 I have, and it's page 26, Chapman, Jasani, Miller and yourself.
DR. O'MALLEY:
A. Yes, that's just an abstract, it has not been published as a peer review article yet.
MR. BROWNE:
Q. Is there any relevance to, I guess some of the issues we talked about this morning in this abstract and if so, could you explain that to the Commissioner?
DR. O'MALLEY:
A. Well really it was just looking at variability from different labs, the variation that occurs between labs.
MR. BROWNE:
Q. Okay, just here in Canada or worldwide?
DR. O'MALLEY:
A. It was looking at the situation worldwide, well

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mostly between Canada and the UK.
MR. BROWNE:
Q. And some of the individuals in fact who you've partnered with on this abstract are members of the UK NEQAS program, is that correct?
DR. O'MALLEY:
A. That's correct.
MR. BROWNE:
Q. Now if I could, please, just to go back on some of the general areas and beginning with, I guess some of the basic biology of estrogen receptor expression, ER is that--ER expression, is that something that increases with the patient's age and following menopause?
DR. O'MALLEY:
A. That's correct, most, many more post menopausal tumors are tumors that occur in women who are post menopausal will be ER positive than the situation of pre-menopausal setting, but it's also related very closely to grade of the tumor, so the vast majority of grade, low grade cancers and as I mentioned before, special type cancers will be ER and PR positive as opposed to high grade cancers.
MR. BROWNE:

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Q. Right, and just talking about the low--and does it also include moderate grade as well or just low grade?
DR. O'MALLEY:
A. Low and moderate grade.
MR. BROWNE:
Q. Low and moderate. And they also, in my note here says these types of tumors also display some degree of tubal formulation. Can you explain what that means to the Commissioner as well?
DR. O'MALLEY:
A. Well that's just one of the parameters that we assess when we're grading a tumor, so the more tubal formation there is in a cancer, the more likely it is to be low grade, so it sort of recapitulating what the normal breast looks like, compared to a high grade cancer that just grows in solid sheets and I showed you the immunohistochemistry in such a case that was ER negative where the tumor was just growing in a solid sheet.
MR. BROWNE:
Q. Okay, and I think we've heard, at least in my recollection is the term heterogenicity and homogenicity in relation to ER/PR. Am I correct in

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understanding that generally ER expresses in a homogeneous fashion, but there are a subset of tumors that express heterogeneously and if you can explain the difference to the Commissioner, what that means?
DR. O'MALLEY:
A. So homogeneity means that the tumor is staining in a very uniformed fashion. So I showed an example of that where almost a hundred percent of the tumor cells were staining positively, but heterogeneity does occur and in fact, I did show an example where only about ten percent of the tumor cells were actually staining positively, so that's heterogeneity, so one can understand that if a portion of that tumor, only a portion of that tumor was assessed, it may be assessed as negative because the portion is actually positive, it would be missed in the assessment or in the testing.
MR. BROWNE:
Q. Now again going back to the low and intermediate range tumors of ER expression, has there been studies in literature which correlate that these types of tumors have a low response to Tamoxifen?
DR. O'MALLEY:

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A. I showed you the data from Elledge's Group showing that indeed there was a linear relationship between the response to Tamoxifen and the percentage of positivity of the tumor cells. So there certainly is that data available in the literature.
MR. BROWNE:
Q. And if we look at, I guess the history of immunohistochemistry and ER/PR and look at, I guess, HER/2neu, has there been a different approach in terms of, again, the worldwide pathology world in sort of rolling out, and I use the term "rolling out", say HER/2neu testing verses IHC testing, and if so, is there a marked difference between how, in terms of standards and recognition of validation of the various tests that have occurred, vis-a-vis each other? It's a convoluted question -
DR. O'MALLEY:
A. Yes.
MR. BROWNE:
Q. But I see a difference at least in the literature that the approach that's being adopted with HER2/neu verses what was done with ER/PR when it first was introduced.
DR. O'MALLEY:

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A. Yeah, there definitely is a difference in approach. Now I just want to clarify the vast majority of HER2 testing is also an immunohistochemical test.
MR. BROWNE:
Q. Yes.
DR. O'MALLEY:
A. We use FISH, florescence in situ hybridization in setting HER2 testing as well, but yes, it's absolutely correct that HER2 immunohistochemical tests were rolled out in a very, very different fashion than ER and PR. Standards were implemented much faster and in fact, we not only have the ASCO CAP guidelines for HER2 testing, but we also have Canadian national standards for HER2 testing as well.
MR. BROWNE:
Q. Whereas we don't with ER/PR?
DR. O'MALLEY:
A. Whereas we don't for ER and PR.
MR. BROWNE:
Q. Yes. ER/PR has been around much longer than HER2/neu.
DR. O'MALLEY:
A. Yes, absolutely true.

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MR. BROWNE:
Q. Okay, and as a result there is an abundance of literature, would you agree, expressing concerns over the high rate of false, potentially false negative testing in ER/PR? Well let me rephrase the question -
DR. O'MALLEY:
A. Well I guess the date I showed you from the NEQAS program showed a quite high false positive--sorry, false negativity rates for those tumors that were low expressing.
MR. BROWNE:
Q. Right.
DR. O'MALLEY:
A. Yeah.
MR. BROWNE:
Q. And in terms of the, I guess the variability, there's been a number of suggestions in the literature what may be at the root cause of that variability, has there not?
DR. O'MALLEY:
A. That's correct, yes.
MR. BROWNE:
Q. And that includes choice of antibody, antigen

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retrieval controls and interpretation and then pre-analytical variables, those points?
DR. O'MALLEY:
A. Absolutely, absolutely correct.
MR. BROWNE:
Q. Now you mentioned, just again on the subject matter of interlab variability, the NEQAS program, which you have some familiarity and I think in one of your slides, as you mentioned here this morning in reference was the Rhodes article in 2000.
DR. O'MALLEY:
A. Uh-hm.
MR. BROWNE:
Q. Was there a second study that followed that again which, by NEQAS, which looked at tumors that were fixed and processed by the NEQAS labs and then participants, I guess, reviewed those results and then were scored on it? Are you familiar -
DR. O'MALLEY:
A. NEQAS have published many, many studies and I just can't recall off the top of my head all of those studies.
MR. BROWNE:
Q. Okay. In terms of some of their findings, was

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there--had there been any NEQAS publications which suggest that pre-analytical variables, such as tissue handling and fixation do not greatly affect ER/PR testing and that their focus tends to be the correlation which affects ER testing the most is antigen retrieval, has there been a -
DR. O'MALLEY:
A. Well, no, that's definitely not correct. In fact, there is good data in the literature looking at the pre-analytic component of the testing to show how important that is. There's a study by Goldstein -
MR. BROWNE:
Q. Yes.
DR. O'MALLEY:
A. - looking at different times and fixative and that study showed that if a tumor had been fixed for less than six hours in formalin, that the false negativity rate for ER and PR was very high.
MR. BROWNE:
Q. Now I'm focusing more on the NEQAS studies in terms of their findings tend to relate a correlation to antigen retrieval; whereas Dr. Goldstein's studies tend to place a lot of emphasis on fixation.
DR. O'MALLEY:

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A. Well I can't comment specifically on that NEQAS study because I just can't recall it.
MR. BROWNE:
Q. Can ER testing results, in terms of, I guess positivity rates and so on, be affected by the characteristics of a patient population? For instance, certain -
DR. O'MALLEY:
A. In terms of pre-post menopausal?
MR. BROWNE:
Q. Yes.
DR. O'MALLEY:
A. Status? Well we talked about that, that it's more likely that post menopausal woman with breast cancer would have an ER positive tumor.
MR. BROWNE:
Q. Okay, and just looking at, you mentioned Dr. Goldstein, the US experience, if I could just switch to that for a minute, I noticed among your curriculum vitae as well that you published another article with Professor--or Dr. Layfield, Lester Layfield?
DR. O'MALLEY:
A. Yes.

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MR. BROWNE:
Q. Has he done a number of studies involving various labs in terms of cut off values used across the United States?
DR. O'MALLEY:
A. I'm aware of one study. I was not involved in that study, where he did look at a very limited number of labs, looked at interlab variability with respect to ER testing and showed quite a significant discordance between the labs.
MR. BROWNE:
Q. And do you recall, again just to--maybe some times as you looked through this article, whether or not it included, I think some of the labs had cut offs anywhere between one percent and thirty percent?
DR. O'MALLEY:
A. I can't recall that paper, all of the details in that paper. Thirty percent would be a bit high, usually it's around ten percent, a few labs have used twenty percent.
MR. BROWNE:
Q. Now, you touched on the issue of fixation this morning in your presentation, can I ask whether long-term storage of unstained paraffin sections,

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can that alter the immunoreactivity of the ER?
DR. O'MALLEY:
A. Yes, that can alter the immunoreactivity, we've done our own studies on that, but ER actually is more robust than, for example, HER2, the antigenicity is lost much quicker for HER2 when a section is being cut and left at room temperature, than it is for ER, but it's certainly, it certainly is lost for both ER and PR, so we try and cut our sections, you know, freshly when they are being submitted for ER and PR testing and HER2 testing, and if they are cut and there's going to be some delay before performance of the test, then we refrigerate those cut slides.
MR. BROWNE:
Q. Has there been, you talked about, as I understand at Mount Sinai you use a combination of staining intensity and percentages to the Allred score, is that -
DR. O'MALLEY:
A. That's correct.
MR. BROWNE:
Q. Has there been a study which has sort of, other than Professor's Allred's work in this area, which has conventionally demonstrated a clinical importance of

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measuring staining intensity or heterogenicity?
DR. O'MALLEY:
A. No, actually, it really, it showed, I mean, the follow-up study by Ellege, for example, just reported on the percentage because they didn't--well it was a study performed by the same group of people, so they were using that data to support the dropping the evaluation of intensity. But, no, the vast majority of studies look just at the percentage.
MR. BROWNE:
Q. In percentages.
DR. O'MALLEY:
A. Rather than intensity, yes.
MR. BROWNE:
Q. Okay. Now as I understand, in terms of the evolution and Mr. Simmons asked you about the evolution of this test this morning, initially most of the studies focused on ER, it was much later in, I guess, the process that PR was looked at and validated independently, is that correct?
DR. O'MALLEY:
A. That is correct, yes.
MR. BROWNE:

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Q. And now I think, is it fair to say that the literature supports that PR status is independently associated with disease free survival and overall survival?
DR. O'MALLEY:
A. Yes, that study did show that, the study I believe by Moshin et al that you're referring to?
MR. BROWNE:
Q. Yes. And as a result for, I guess, from that one could suggest that ER positive and PR positive tumors have a better prognosis than ER positive and PR negative?
DR. O'MALLEY:
A. Yes.
MR. BROWNE:
Q. And then, I guess, in turn, PR positive and ER negative have better prognosis than ER negative and PR negative?
DR. O'MALLEY:
A. That is correct, yes.
MR. BROWNE:
Q. Okay. Now as well, we spoke or you spoke about the internal and external controls utilized by the pathologists this morning. Can an external control

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stain stronger than an internal control?
DR. O'MALLEY:
A. Yes, yes, I guess it could.
MR. BROWNE:
Q. And would that relate back to the type of tumor that's used in a number of labs? I know in your lab, you use, I think three different types, a negative, a moderate, and a high.
DR. O'MALLEY:
A. Um-hm.
MR. BROWNE:
Q. Are there a number of labs that use, for controls, simply high expressing tumors?
DR. O'MALLEY:
A. I believe so.
MR. BROWNE:
Q. And would that cause then probably a higher staining external versus if you had a low or moderate expressing internal, would that cause that result?
DR. O'MALLEY:
A. Well, what we're looking at for--we're not grading the intensity. It may lead to a variation in intensity, but what's more important is that there are positive tumor cells present or positive in

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terms of the internal control, positive normal epithelium.
MR. BROWNE:
Q. Okay, and again, Mr. Simmons asked you about positivity rates. Just generally, in the literature, what sort of--from about around about 2005-2007, there is a number of articles published on positivity rates around the world. What is generally an accepted positivity rate?
DR. O'MALLEY:
A. About 75 percent for ER, up to 80 percent in some studies.
MR. BROWNE:
Q. And as well, you were asked about--by Mr. Coffey this morning about certain tumors which are more predictive of, I guess, or there's an expectation that PR, or excuse me, ER positivity. One example was the classic, I think you described the classic ductal -
DR. O'MALLEY:
A. Infiltrating lobular.
MR. BROWNE:
Q. Infiltrating lobular. Is there such a, I guess, variation on that where you have an infiltrating

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ductal with a prominent lobular feature?
DR. O'MALLEY:
A. A lot of those will be positive, for sure.
MR. BROWNE:
Q. Are they the same as your classic?
DR. O'MALLEY:
A. No, in terms of -
MR. BROWNE:
Q. What would be the percentage differences?
DR. O'MALLEY:
A. In terms of prognosis, the prognosis isn't just quite as good for no special type with lobular features as it is for a classic or pure infiltrating lobular.
MR. BROWNE:
Q. And the frequencies, are they the same, in terms of when you talk about classic lobular, when you have an infiltrating ductal with lobular features?
DR. O'MALLEY:
A. Well, it'll be dependent on the grade of that tumor and so a ductal no special type with lobular features could be grade one to grade three, and that will obviously affect the ER status.
MR. BROWNE:

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Q. And then in terms of, just to go back on the internal control for a minute, and that's you mention the inclusion of normal breast epithelium as an internal control. While that's desirable, is it always possible in every case to get an internal control?
DR. O'MALLEY:
A. It's not always possible in every single case, but it is certainly highly desirable.
MR. BROWNE:
Q. What sort of instances can you think of where an internal control may not be--you may not be able to get an internal control?
DR. O'MALLEY:
A. Where we have a section right through the centre of the tumor. You're not going to have any normal tissue on that section.
MR. BROWNE:
Q. And finally, the last couple of questions, you mentioned Dr. Goldstein's work. Has he recently published an article about ER staining and antibody incubation and antigen retrieval?
DR. O'MALLEY:
A. He may have, but I haven't done a recent literature

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search of him.

MR. BROWNE:

Q. I think that may be all my questions for Dr. O'Malley. They are. Thank you very much.

DR. O'MALLEY:

A. You're welcome.

THE COMMISSIONER:

Q. Mr. Pritchett?

MR. PRITCHETT:

Q. We have no questions, Madam Commissioner.

DR. FRANCES O'MALLEY, EXAMINATION BY MS. JENNIFER NEWBURY

MS. NEWBURY:

Q. Good afternoon, Dr. O'Malley. My name is Jennifer Newbury and I represent the Canadian Cancer Society, Newfoundland and Labrador division. I just have a couple of topics for you this morning. First of all, I was interested in exploring with you a little bit how a pathology lab maintains best practices in the absence of national and international standards, and I take it that what you do in your lab and what your lab does is to conduct your own validation studies and conduct your own literature review, and I take it that you do have to conduct the literature review first as to, you know, make sure that you

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know what types of validation studies to conduct. Is that -

DR. O'MALLEY:

A. Well, what types of antibodies to use in validation studies, yes.

MS. NEWBURY:

Q. And that changes from time to time, I take it?

DR. O'MALLEY:

A. It does.

MS. NEWBURY:

Q. As new equipment and new antibodies become available, and that's based on research, I guess?

DR. O'MALLEY:

A. Yes, keeping abreast of what's happening.

MS. NEWBURY:

Q. Okay, and I'm just wondering, what sort of a time and resource commitment would there be for a lab to maintain those best practices, to keep pace with the literature, to conduct validation studies?

DR. O'MALLEY:

A. Trish Wegrynowski will be able to address the specific time, but it is time consuming. It absolutely is time consuming.

MS. NEWBURY:

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Q. Okay, and what part is more time consuming than the other? Can you say whether it's more the literature review or the validation studies itself?

DR. O'MALLEY:

A. Well, the literature review isn't that time consuming. It's the validation. It's all of those technical steps that are quite time consuming.

MS. NEWBURY:

Q. Okay, and in terms of your role as a pathologist and perhaps the role of pathologists in your lab generally, what sort of a time commitment would there be to keep pace with, you know, the types of antibodies available, the types of equipment that might be on the market? Just to give a picture for the Commissioner, you know, how many conferences might you go to a year or how many journals do you have to read, what sort of continuing education seminars might you have to attend in the course of a year, and is there much variation from year to year?

DR. O'MALLEY:

A. There definitely is variation from year to year and from person to person. I attend a lot of conferences, so I mean, I can't give you a specific number that would be appropriate for every lab.

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MS. NEWBURY:

Q. Okay. Is there a designation of an individual or a couple of individuals within a lab to take on that role in terms of keeping pace with research and new developments?

DR. O'MALLEY:

A. Well, in an academic setting, we're all expected to keep pace with current developments.

MS. NEWBURY:

Q. And how about in a lab that may not be affiliated with a teaching hospital or may not have the academic component, would you have any idea what might be involved in that situation?

DR. O'MALLEY:

A. Well, there still is a requirement to keep, you know, knowledgeable about what is happening and, in fact, the MOComp program demands that through the Royal College of Physicians and Surgeons, that one must keep up with current knowledge.

MS. NEWBURY:

Q. Okay, and that's a Canadian -

DR. O'MALLEY:

A. Yes, that's a national requirement.

MS. NEWBURY:

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Q. Okay, and within your lab, as a group, do you try to cover off all key conferences or all key areas? Is there any sort of formal structure in place or do you just go by your areas of interest?
DR. O'MALLEY:
A. We go generally by our areas of expertise.
MS. NEWBURY:
Q. Okay, and are most of the resources available in Canada for you to do this or do you often have to travel to other jurisdictions to maintain, I guess, your best knowledge or keeping pace with the new developments?
DR. O'MALLEY:
A. Often it requires travelling internationally.
MS. NEWBURY:
Q. Okay.
DR. O'MALLEY:
A. Mainly to the U.S.
MS. NEWBURY:
Q. Okay, and in terms of the absence of national and international standards for ER/PR testing, I take it this isn't unique for that particular type of testing?
DR. O'MALLEY:

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A. That's true.
MS. NEWBURY:
Q. Okay, and are there--would you say that there are many other types of laboratory testing that don't have national standards? I mean, how unusual is it?
DR. O'MALLEY:
A. Yes, yes.
MS. NEWBURY:
Q. There are many of them?
DR. O'MALLEY:
A. There are many, yes.
MS. NEWBURY:
Q. So it would be, I guess, typical for pathologists, for example, to keep pace with new developments and to keep pace with new types of testing procedures by attending these various conferences? You wouldn't just have to do it to learn about what's happening with ER/PR? You would be doing this in the normal course of your profession? Is that correct?
DR. O'MALLEY:
A. Yes, yes.
MS. NEWBURY:
Q. And do I assume that it would still be preferable to have national standards applicable to ER/PR?

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DR. O'MALLEY:
A. It would absolutely be preferable. I look forward to these being published.
MS. NEWBURY:
Q. Okay, and it seems that there is a fair bit of flexibility by labs in terms of choosing the types of procedures that they want to use, the types of equipment, the types of antibodies. Do you expect that the national standards would allow that flexibility? Would there be some -
DR. O'MALLEY:
A. Well, there needs to be that flexibility because each lab does function differently, but within that, there won't be flexibility around the validation process itself.
MS. NEWBURY:
Q. Okay, and how would that be implemented, do you expect?
DR. O'MALLEY:
A. Well, through this national committee that has been struck, I would think.
MS. NEWBURY:
Q. Okay. So the national standards committee, you expect, would focus on validation studies or would

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they also deal with the various types of equipment and testing?
DR. O'MALLEY:
A. I would think that they will cover, in a broad stroke, the pre-analytic, analytic and post-analytic aspects of the testing, but I wouldn't expect them to mandate that a specific machine should be used for performing immunohistochemistry. They won't get into that sort of minute detail.
MS. NEWBURY:
Q. Okay.
DR. O'MALLEY:
A. So as I say, that's really a decision that each lab must make.
MS. NEWBURY:
Q. Okay, and for labs to be able to make those decisions, to choose the type of antibody or the type of equipment, would it still be necessary for pathologists to, you know, maintain or keep pace with conferences and continuing education and journal resources?
DR. O'MALLEY:
A. Absolutely.
MS. NEWBURY:

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Q. You've spoken a bit about the national standards initiative and I think you mentioned it was an 18-lab study conducted in relation to that. Was the purpose of that study to get an overview of how labs are performing? Were labs randomly chosen for that particular study?

DR. O'MALLEY:

A. No, the labs were not randomly chosen. The labs that were--labs were invited to participate in that study and most of the labs actually had participated in the national HER2 program, development of those national guidelines. So they were hand-picked to--and most of them were very large labs and many of them functioned as reference labs.

MS. NEWBURY:

Q. Okay. So then was the purpose of the study to determine what level of concordance, whether or not you can have good concordance between labs for this particular type of testing?

DR. O'MALLEY:

A. Yes, it was a pilot study to see how the process could be implemented really.

MS. NEWBURY:

Q. Okay, and not to necessarily say that most labs, if

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you've picked them randomly, would necessarily perform at the same level? It wasn't that type of a study?

DR. O'MALLEY:

A. No, no, it wasn't. No, and in fact, it would be--I think this is the best case scenario. Those concordance rates were incredibly high.

MS. NEWBURY:

Q. Okay, and why would that be a best case scenario?

DR. O'MALLEY:

A. Well, because of the labs that were chosen, they all have a lot of experience. They're all very large labs.

MS. NEWBURY:

Q. And how then would that, those good results be available or translate to the smaller labs that are not considered to be reference labs? How would you be able to translate that ability?

DR. O'MALLEY:

A. Well, those labs should participate. Once this program is in place, is rolled out, then those labs should participate in the process and so any problems with a particular lab then will be identified early.

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MS. NEWBURY:

Q. Okay, and will there be a process in place then that these other labs can improve their procedures? Will there be resources available to, I guess, modify the test as need be to reach the same level of concordance as the larger reference labs?

DR. O'MALLEY:

A. I don't know, but I certainly hope so.

MS. NEWBURY:

Q. Okay. You were asked a couple of questions this morning that relate to, I guess, monitoring of trends in terms of the ER/PR results, and you've mentioned there's one of several types of cancer that are expected to be ER positive. That's the invasive lobular, the classic invasive lobular carcinoma, and I believe you also indicated that with increasing age or post-menopausal, you would expect a higher rate of ER positivity, and is that knowledge used to actually be an extra check on the results that you have?

DR. O'MALLEY:

A. Well, not really because there is variability. What is more an extra check is looking at the type and the grade of the tumor.

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MS. NEWBURY:

Q. Okay, so the type and the grade of the tumor.

DR. O'MALLEY:

A. Rather than on the menopausal status of the patient.

MS. NEWBURY:

Q. Okay, so that wouldn't be used as a check, but the type and grade of tumor would be?

DR. O'MALLEY:

A. Yes.

MS. NEWBURY:

Q. And I take it that was the reason, in the one case that you did have experience with, it was sent to four different labs. Was that because of a lack of confidence in the accuracy of the first couple of test results?

DR. O'MALLEY:

A. Well, it was just a concern because of the type of cancer. It was a classic infiltrating lobular cancer, so even though many of those labs had repeated the test and were quite happy with their controls, it was still a concern just because of the type of the cancer.

MS. NEWBURY:

Q. Okay, and are there any other trends, in terms of

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the ER/PR testing, that you can use to help, I guess, be an extra check in terms of the expectations that you would have for your ER/PR testing?

DR. O'MALLEY:

A. Trends beyond the type and the grade?

MS. NEWBURY:

Q. Yes, beyond the type and the grade.

DR. O'MALLEY:

A. No, I can't think of any additional steps.

MS. NEWBURY:

Q. Is gender ever an issue with -

DR. O'MALLEY:

A. No, male breast cancers are often ER positive.

MS. NEWBURY:

Q. Okay, and within your lab, is there any formal process in place to make sure that all of these trends are monitored on a regular basis or is it just left to the individual?

DR. O'MALLEY:

A. Yes, we have standard operating procedures.

MS. NEWBURY:

Q. Okay, and perhaps you can just explain how that works.

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DR. O'MALLEY:

A. Well, actually Trish will probably go into detail on those SOPs.

MS. NEWBURY:

Q. In terms of the monitoring, and so that would be left to technologists, as opposed to pathologists, in terms of monitoring?

DR. O'MALLEY:

A. Well, no, the pathologists oversee that.

MS. NEWBURY:

Q. Right, okay, but she'll know the details on the standard operating procedures?

DR. O'MALLEY:

A. Yes.

MS. NEWBURY:

Q. Okay. Great, thank you. Those are all the questions, I have. Thank you.

THE COMMISSIONER:

Q. Mr. Crosbie?

DR. FRANCES O'MALLEY, EXAMINATION BY CHESLEY CROSBIE, Q.C.

CROSBIE, Q.C.:

Q. Thank you, Commissioner. Thank you, Doctor, Ches Crosbie. You told us that you have at least weekly tumor boards or panels, you said board, I think?

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DR. O'MALLEY:

A. Yes.

CROSBIE, Q.C.:

Q. And this is an interdisciplinary team of oncologists, pathologists and others who--do they only look at difficult cases? Do they look at all cases routinely? How does that work?

DR. O'MALLEY:

A. We look at all invasive breast cancer cases, but we spend more time on the difficult cases. But we do bring--but each patient is discussed, yes.

CROSBIE, Q.C.:

Q. Is the oncologist, I'm assuming most or maybe all patients would have an oncologist. Is that fair?

DR. O'MALLEY:

A. Yes.

CROSBIE, Q.C.:

Q. Is the treating oncologist involved in these boards?

DR. O'MALLEY:

A. Yes, yes.

CROSBIE, Q.C.:

Q. So that's a feature of a board when you have an interdisciplinary look at a case that the treater is present?

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DR. O'MALLEY:

A. Yes.

CROSBIE, Q.C.:

Q. Does the decision making--perhaps I'm overstepping. Is it usual then that a consensus is arrived at that assists the treater in how to approach the case?

DR. O'MALLEY:

A. Yes.

CROSBIE, Q.C.:

Q. But these boards, they don't make actual treatment decisions. That's always a matter for the primary responsible physician who's treating, is it?

DR. O'MALLEY:

A. Well, actually, the boards do function in a consensus fashion and in the difficult cases where the treatment may not be straightforward, there may be options in terms of the chemotherapeutic regiment. So the medical oncologist will ask his or her colleagues for their opinions on which treatment, given the tumor type, size, all of the other prognostic factors that we look at, given those characteristics. So we actually do, as a group, reach a consensus at those meetings.

CROSBIE, Q.C.:

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Q. Is it recorded?
DR. O'MALLEY:
A. Yes, it is recorded.
CROSBIE, Q.C.:
Q. Would it be true to say, harkening back to the sign that Harry Truman was supposed to have on his desk, you know, the buck stops here, that ultimately that decision is between the treating--if that's the primary treater, the oncologist and the patient?
DR. O'MALLEY:
A. That is true. That is true, but often what happens is the medical oncologist will say "this is my recommendation and I have--we have discussed your case at tumor board and it's also the recommendation of the group," for example.
CROSBIE, Q.C.:
Q. I seem to have picked up somewhere along the way, and you did testify that PR status can be used independently of ER status, as an indication for hormone therapy?
DR. O'MALLEY:
A. That's correct.
CROSBIE, Q.C.:
Q. Is there some standard regarding that, like PR-40?

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DR. O'MALLEY:
A. I'm not sure exactly what you mean. You mean the cutoffs?
CROSBIE, Q.C.:
Q. Yes.
DR. O'MALLEY:
A. The cutoffs for PR are the same as ER, so in our lab, anyway, so one percent is accepted as a positive result for both ER and PR.
CROSBIE, Q.C.:
Q. Now what the treating oncologist chooses to do with the information in discussion with the patient, I guess we'd have to learn more from an oncologist about that?
DR. O'MALLEY:
A. Certainly.
CROSBIE, Q.C.:
Q. Do you know what the annual positivity/negativity ratio was for ER/PR testing at, well, I guess we have to look at it in--I guess we should talk ER and then PR, you'll have to tell me. Do you know what it was for last year at Mount Sinai, your institution?
DR. O'MALLEY:

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A. I believe it was around 75 percent, somewhere around there, 75 to 77 percent for ER and about 65 percent for PR.
CROSBIE, Q.C.:
Q. And for ER do you know what those numbers may have been for, say, the last five years?
DR. O'MALLEY:
A. I don't. I'd have to look at the data.
CROSBIE, Q.C.:
Q. Would you--I'm assuming it's no big imposition if I were to ask you this, but if it is, you can tell me, would you be able to look at your data going back to 1997, simply tell us per year at Mount Sinai what were the ratios for ER and PR?
DR. O'MALLEY:
A. Yes, it would take a bit of work. It's only in the last few years that it's become an automated process, but it could be, it could be retrieved.
CROSBIE, Q.C.:
Q. Okay. Well, I don't want to burden you, as I say. When did it become automated?
DR. O'MALLEY:
A. Just in the last few years.
CROSBIE, Q.C.:

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Q. Well, perhaps as far back as you have the automated data and can relatively easily access it? Sounds like it's several years for the data.
DR. O'MALLEY:
A. Since the synoptic reporting, that has made it easier to retrieve that data.
CROSBIE, Q.C.:
Q. So is that a reasonable question for me to ask of you?
DR. O'MALLEY:
A. To pull that data?
CROSBIE, Q.C.:
Q. Yes.
DR. O'MALLEY:
A. Certainly it is.
CROSBIE, Q.C.:
Q. Okay. And I guess you can send that along through the channels of communication you've been using with the Commission?
DR. O'MALLEY:
A. Yes.
CROSBIE, Q.C.:
Q. No one's -
DR. O'MALLEY:

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A. Yes.
CROSBIE, Q.C.:
Q. I think the answer is yes.
COMMISSIONER:
Q. On the understanding that what we're retrieving is the easily retrievable material on the automated system.
DR. O'MALLEY:
A. Okay, but that--yeah, okay.
COMMISSIONER:
Q. That's, as I understand, is what Mr. Crosbie is seeking. While I'm sure he'd love to have the other, he's not asking you to do major research for him.
CROSBIE, Q.C.:
Q. That's exactly right, Commissioner.
COMMISSIONER:
Q. Thank you.
CROSBIE, Q.C.:
Q. Can we bring up, Registrar, 0067, please? Scroll down to about the middle. And this letter, for your information, was written in 2005 by Dr. Cook, a pathologist here, to the VP medical services. And I'm looking in the paragraphs that--paragraph that

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commences, "May 17, 2005," and you go to the middle of that, you see the statement in the middle, "It is estimated that"?
DR. O'MALLEY:
A. Um-hm.
CROSBIE, Q.C.:
Q. "Approximately 50 to 85 percent of all breast cancers exhibit estrogen receptors." That's a sort of broad band. Would you accept that as a reasonable statement?
DR. O'MALLEY:
A. Yes, 50 percent is a little bit on the low side.
CROSBIE, Q.C.:
Q. If an institution were running a positivity rate for PR--for ER, rather, of 50 percent, would that raise any questions in your mind?
DR. O'MALLEY:
A. It would, it would, for sure. That's too low for an ER positivity rate.
CROSBIE, Q.C.:
Q. At what stages does it become too low?
DR. O'MALLEY:
A. Well, for ER I would be concerned at anything lower than 70 percent, certainly 65 percent.

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CROSBIE, Q.C.:
Q. Here in Newfoundland I understand we were in the habit of sending out slides for purpose of doing these reading of ER/PR positivity to smaller centres outside of St. John's, outside of the lab at the Health Sciences. Are there pitfalls in sending slides out to smaller centres where they might have only one or two pathologists?
DR. O'MALLEY:
A. Yes, yes. Certainly I can speak from the Her2 experience that, in fact, the guidelines recommend that to perform Her2 testing a minimum of 250 immuno tests per year should be--Her2, specifically, immuno tests should be performed in a lab, so it's certain accuracy is related to volume, for sure.
CROSBIE, Q.C.:
Q. That's what I was going to say, is there a relationship to volume?
DR. O'MALLEY:
A. Yes.
CROSBIE, Q.C.:
Q. Is there also a benefit to being in, you know, a lot of what pathologists do, I take it, involves things that are in a grey zone. Is that true?

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DR. O'MALLEY:
A. We wouldn't like to think that a lot of what we do is in a grey zone. I think we can -
CROSBIE, Q.C.:
Q. Some of it?
DR. O'MALLEY:
A. But some, yes, certainly some cases are very difficult to make a definitive diagnosis of invasive cancer, but the vast majority are easy to, it's easy to make that definitive call.
CROSBIE, Q.C.:
Q. Is it fair to infer there's a benefit to having colleagues available to consult with and share notes with?
DR. O'MALLEY:
A. Definitely.
CROSBIE, Q.C.:
Q. If you have any degree of uncertainty about how to make a call?
DR. O'MALLEY:
A. Yes, yes. And indeed, at Mount Sinai we often show cases to one another, consult with one another on difficult cases.
CROSBIE, Q.C.:

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Q. Can you expand a bit, please, on the concept of a reference lab, what characteristics would a reference lab have? You spoke of it in terms to Her2/neu and Mount Sinai functioning in that manner with regard to that test, but I assume it's a concept that has application with regard to other tests or processes, as well?

DR. O'MALLEY:

A. That's true. Again, the lab must--they're generally labs that deal with very large volumes of tests and they would have rigid quality control procedures in place, SOPs, they would have to fulfil many, many criteria to be assigned that, as a reference lab.

CROSBIE, Q.C.:

Q. So who is it that says you're a reference lab, is that a consensus kind of thing?

DR. O'MALLEY:

A. Well, in Ontario it was a decision made by the ministry, ministry of health and long-term care.

CROSBIE, Q.C.:

Q. And so you told us that your institution in relation to Her2/neu is "the" reference lab?

DR. O'MALLEY:

A. It's one. There are two references -

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CROSBIE, Q.C.:

Q. Two?

DR. O'MALLEY:

A. Two reference labs in Ontario and we are one of those labs.

CROSBIE, Q.C.:

Q. And that was determined by the ministry?

DR. O'MALLEY:

A. It was.

CROSBIE, Q.C.:

Q. What about for ER/PR testing?

DR. O'MALLEY:

A. As I say, we don't have either provincial or national standards for ER/PR testing. They are in process.

CROSBIE, Q.C.:

Q. Okay. So then that requires some kind of agreed generalizably--generally applicable standard for the concept of reference lab to make sense the way you're explaining it? There should be some consensus as to what standards are and then the reference lab is selected by somebody as representing the embodiment of that standard against which other labs are to be measured?

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DR. O'MALLEY:

A. Yes. Although I see that the program based on the pilot study from this national body, it would be more of a--it would be more like the NEQAS program.

CROSBIE, Q.C.:

Q. Well, what I get from that is there's external proficiency reviewing going on?

DR. O'MALLEY:

A. That's a quality assurance program.

CROSBIE, Q.C.:

Q. Um-hm. So is my statement roughly accurate, you need a body of agreed standards in order to have a reference lab?

DR. O'MALLEY:

A. Oh, definitely, yes.

CROSBIE, Q.C.:

Q. All right. To say that there's no generally agreed set of standards for, or, you know, national standards or even provincial standards for ER/PR testing, that's not to say that there are no standards at all?

DR. O'MALLEY:

A. Absolutely, absolutely.

CROSBIE, Q.C.:

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Q. In fact, every competent institution has its own set of standards, right?

DR. O'MALLEY:

A. That's very true.

CROSBIE, Q.C.:

Q. And you would normally expect to find those standards in something called a standard operating procedures manual?

DR. O'MALLEY:

A. Yes.

CROSBIE, Q.C.:

Q. That's where you'd find them, the institution's own standards?

DR. O'MALLEY:

A. Um-hm.

CROSBIE, Q.C.:

Q. Can you tell us a bit more about validation, for example, in relation to antibodies? Say you get a new antibody or batch of antibody, just relate it to that?

DR. O'MALLEY:

A. Well, what we do is we have--we know how a previous antibody have behaved in terms of the staining that it gave with previous cases, so we like to--we, when

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we're bringing in new antibody, we like to validate it on at last 100 previously stained cases. So the validation process involves assessing these previously stained tumors with the new antibody and looking at the concordance between the staining that had been previously obtained and with the staining that obtained with the new antibody. And Trish will be able to go into the details later in the week.

CROSBIE, Q.C.:

Q. I'm sure. Just trying to get the basic idea. You don't just take a new batch of antibody and run samples through and, you know, rely on your controls, for example, to tell you whether you getting problems with it, you do it, in effect, side by side, you retest other samples with a known outcome by a process that you trust, right?

DR. O'MALLEY:

A. Yes.

CROSBIE, Q.C.:

Q. And she can tell us more about that. At this point in time IHC external proficiency testing, would you say, recommended, highly recommended, optional?

DR. O'MALLEY:

A. I would say that it is mandatory and I would expect

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that the standards, the national standards will make that statement. Certainly for Her2 our guidelines, our national guidelines as well as the CAP ASCO guidelines say that external quality assurance be involved in an external quality assurance program is mandatory.

CROSBIE, Q.C.:

Q. What about for ER/PR, say, in 2005, how would you characterize it?

DR. O'MALLEY:

A. Well, again, I mean, it's highly recommended to--I mean, it hasn't been stated as mandatory because we don't have those national standards, but as I say, for most laboratories they should be involved in a quality assurance if they are performing these tests.

CROSBIE, Q.C.:

Q. What about in 1997?

DR. O'MALLEY:

A. The same, I would say the same statement applies.

CROSBIE, Q.C.:

Q. Is it within your knowledge that the institution here, as they began to send up samples to your institution for retesting, did it come to your

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knowledge that they had been actually testing for ER/PR status their DCIS cases?

DR. O'MALLEY:

A. I can't comment on that because I really wasn't directly involved in the retesting. Dr. Mullen will, I presume, be able to answer that question for you.

CROSBIE, Q.C.:

Q. You were asked about a section coming through without an internal control and your comment was it's highly desirable to have the internal control present, which is essentially a piece of normal tissue which accompanies the tumor slice?

DR. O'MALLEY:

A. Well, it's actually in the slice, it's actually part of the section. So you've got the tumor, as I showed -

CROSBIE, Q.C.:

Q. But it's not a separate piece of tissue, it -

DR. O'MALLEY:

A. It's not a separate piece, it's actually -

CROSBIE, Q.C.:

Q. It's a margin around the tumor?

DR. O'MALLEY:

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A. That's right, that's right.

CROSBIE, Q.C.:

Q. And what you're looking for there is you're looking to see a few dots in that normal tissue because ordinarily and even in postmenopausal women those receptors will be present if the tumor itself is positive, is that the general idea?

DR. O'MALLEY:

A. No. They will be--the whole point of that internal control is that they are positive independent of the ER and PR status of the tumor.

CROSBIE, Q.C.:

Q. Oh, okay. Excuse me.

DR. O'MALLEY:

A. Yes.

CROSBIE, Q.C.:

Q. So if you got a negative tumor plus positive receptors in the internal -

DR. O'MALLEY:

A. Normal -

CROSBIE, Q.C.:

Q. - control, you know something is wrong?

DR. O'MALLEY:

A. No, no. You know that the test has actually worked.

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The problem would be if the tumor was completely negative for ER and your internal controls in normal epithelium was negative, that would be a problem. That test should not be interpreted because the normal epithelium is negative, so one couldn't be sure that the test has worked in that particular slide.

CROSBIE, Q.C.:

Q. Yeah, I'm sorry, I had all this reversed. But the point I'm wanting to get around to is if indeed the slide had no normal tissue on it and the reading pathologist had any concern about that, he or she could ask for another slide?

DR. O'MALLEY:

A. Yes, yes.

CROSBIE, Q.C.:

Q. And a slide which did, was accompanied by normal tissue?

DR. O'MALLEY:

A. Yes. I mean, it's more difficult if the case is coming from outside, it's easier if the case is being--is in house because one can just quickly look at the other sections of tumor, but it's more tricky if the case is being sent from outside.

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COMMISSIONER:

Q. Is it also not more tricky if it's a biopsy that's been done and sometimes the little piece that's taken doesn't necessarily get a lot of normal tissue?

DR. O'MALLEY:

A. Yes, yes, absolutely, because often the core biopsy, the radiologist targets the centre of the tumor, so many times a core biopsy may not have normal tissue.

CROSBIE, Q.C.:

Q. You're not usually relying on a core biopsy for definitive treatment, though, are you?

DR. O'MALLEY:

A. Well, that's a good point. I mean, we are--the core--the function of the core biopsy to make a diagnosis of invasive breast cancer. We don't routinely do ER/PR on the core biopsy, we wait until we received the surgical, surgically excised specimen. We do it in some circumstances, but generally we want for the surgically excised specimen.

CROSBIE, Q.C.:

Q. And so, and this is my final question, which is just as well, although there may be more. What I want to ask you is if the pathologist is reading the internal and external controls, then the reliability of the specimen itself for giving you an accurate reading in relation to positivity, negativity, that should be in place, is that right? The controls ought to catch any problem in the preparation of that specimen up to that point?

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DR. O'MALLEY:

A. Oh, yeah. Yes, they should, they should. But -

CROSBIE, Q.C.:

Q. They really should?

DR. O'MALLEY:

A. - I mean, it takes--you know, it is dependent on having a senior experienced pathologist or technologist to oversee all of those technical steps that go into the test to ensure that the positive and negative controls behave as they should.

CROSBIE, Q.C.:

Q. So if we have a large or an inordinately large number of misreads, then we may want to have a look at what was going on to ensure the suitability of the controls and what was happening with the controls?

DR. O'MALLEY:

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A. I would expect that the controls are archived, the control sections are--to my understanding. I don't know how long they're archived for. Again, Trish will be able to answer that.

CROSBIE, Q.C.:

Q. But that might be a possible source of trouble?

DR. O'MALLEY:

A. To pull those -

CROSBIE, Q.C.:

Q. Issues with controls -

DR. O'MALLEY:

A. - external controls?

CROSBIE, Q.C.:

Q. If you're getting a lot of reversals when another institution is reading your slides for you?

DR. O'MALLEY:

A. I'm not entirely sure that I'm getting what you're asking, I'm clear about what you're asking.

CROSBIE, Q.C.:

Q. Well, for example, we heard from a gentleman by the name of Dr. Ejeckam who--have you heard that name in -

DR. O'MALLEY:

A. I have heard that name. I don't know that

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individual.
CROSBIE, Q.C.:
Q. He had involvement back in 2003 where he suspended testing for five or six weeks and he intervened and in a troubleshooting capacity, it's fair to say, and Dr. Ejeckam did emphasise that to him the internal control is critical, but in general having workable controls was very important for ensuring that you got a valid reading on the patient's tissue sample. And everything I just said is a reasonable statement, is it?
DR. O'MALLEY:
A. Well, they're vital, yes.
CROSBIE, Q.C.:
Q. So if it turns out that an institution was not getting reliable reading of the patient's tissue sample, stands to reason we should look for problems with the controls?
DR. O'MALLEY:
A. Definitely, yes.
CROSBIE, Q.C.:
Q. That's all I wanted to bring out. Thank you.
COMMISSIONER:
Q. Mr. Pike, do you have any questions?

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MR. PIKE:
Q. No questions, thank you.
COMMISSIONER:
Q. Mr. Clements?
MR. CLEMENTS:
Q. No questions.
COMMISSIONER:
Q. Do you have anything arising, Ms. Coffey?
DR. FRANCES O'MALLEY, RE-EXAMINATION BY BERNARD COFFEY, Q.C.
COFFEY, Q.C.:
Q. Yes, just a couple of questions, if I could, Doctor. Doctor, just if you could for the Commissioner, just to elaborate a little bit on an answer you just gave Mr. Crosbie. You indicated that, well, if it's an in-house case and when you look at a slide and there's not enough tissue there, from your perspective, to consider it as an internal control, what--if it's an in-house case, what's the advantage of it being an in-house case, what do you then actually do?
DR. O'MALLEY:
A. Well, if the other blocks from that tumor are readily accessible, we can just go into the lab and pull those sections and review them very, very

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quickly and choose a more suitable block, if need be.
COFFEY, Q.C.:
Q. Yeah. Look at the HNE (phonetic) slide for a particular block?
DR. O'MALLEY:
A. Look at the HNE slide.
COFFEY, Q.C.:
Q. And get one with tumor and normal tissue and say, well, I want ER on that one?
DR. O'MALLEY:
A. Exactly.
COFFEY, Q.C.:
Q. Okay. I just want to clarify that. And, of course, if it's not an in-house case, you might not have all the blocks, I take it?
DR. O'MALLEY:
A. We often don't. In fact, many of the labs that send us cases, just send us one block of tumor.
COFFEY, Q.C.:
Q. In terms of the block itself that's to be utilized, you know, for the ER test or PR test, who chooses the block, who identifies which block?
DR. O'MALLEY:

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A. From externally or internally?
COFFEY, Q.C.:
Q. Well for the internal control, who would -
DR. O'MALLEY:
A. Oh, for the internal controller, the case that's actually assessed?
COFFEY, Q.C.:
Q. Well, for example, if you're going to do--you're called upon, you go back tomorrow, you're at work and you're doing your case and you have to choose which block to do the ER test on, is it your choice as to which block to choose?
DR. O'MALLEY:
A. Yes, it's the pathologist responsible for that particular case -
COFFEY, Q.C.:
Q. Okay.
DR. O'MALLEY:
A. - decides on which block is assessed.
COFFEY, Q.C.:
Q. That's one. Could you tell us please too, because Mr. Browne, I think, asked you about abstract versus published. You started -
DR. O'MALLEY:

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A. It's a published abstract, but it hasn't been published--the entire article hasn't been published. So, I was just making a distinction between a published abstract and the actual peer reviewed paper, publication of the paper.

COFFEY, Q.C.:

Q. So, in the context, when it were, like, abstract is used there, for example, in your CV, that indicates that it hasn't been peer reviewed?

DR. O'MALLEY:

A. Oh no, no, no, it has. Those abstracts are peer reviewed to undergo publication and presentation at the particular conference that it is being sent to. No, they have been absolutely peer reviewed. It's just that all of the--it's so--an abstract is basically just a synopsis of the data and then the paper contains all of the details.

COFFEY, Q.C.:

Q. Sure. Doctor, I think Mr. Simmons asked you about reactivity and long term storage of paraffin blocks.

DR. O'MALLEY:

A. Um-hm.

COFFEY, Q.C.:

Q. And then your answer was framed in terms of well, if

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we have--if a slide is prepared in the sense of a very thin slice is taken off the paraffin block and it's put on the slide, that it's not desirable to leave the slide lying around unrefrigerated.

DR. O'MALLEY:

A. That is correct.

COFFEY, Q.C.:

Q. Because it can have a negative effect on the ability when it's processed -

DR. O'MALLEY:

A. The accuracy of the test.

COFFEY, Q.C.:

Q. What about the block itself, like paraffin blocks themselves in the whole, how about them?

DR. O'MALLEY:

A. No, they can be stored for many, many years and antigenicity can still be retained many, many years later.

COFFEY, Q.C.:

Q. Okay. And there was as well--Mr. Simmons asked you some questions about had you testified to the effect that what HER2/neu, there are national guidelines -

DR. O'MALLEY:

A. Yes.

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COFFEY, Q.C.:

Q. - standards, I think is the word you used, for the HER2/neu tests. And you've indicated that it's only now that ER/PR national standards, you anticipate, will hopefully be in place shortly. Do I understand that correctly?

DR. O'MALLEY:

A. That is correct.

COFFEY, Q.C.:

Q. But HER2./neu compared to ER/PR, HER2/neu is relatively new compared to ER/PR, IHC tests.

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. Can you tell the Commissioner, as a practising pathologist, why it is that HER2/neu has national standards now as opposed to ER/PR which has existed for, I gather, more than a decade.

DR. O'MALLEY:

A. A lot had to do with the cost of the drug that's used in HER2 positive tumors, Trastuzumab or Herceptin, it costs about $45,000.00 per patient per year of treatment. So, there are major cost implications in the case of a false positive result,

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ie., a patient's tumor is called HER2 positive, when indeed it's not positive. So, that patient has undergone significant--has been treated with a very, very expensive drug that is not going to benefit the patient. So, it was really the cost of that drug that drove the issue for bringing in standards sooner in the setting of HER2, than for ER and PR. The endocrine drugs are a lot cheaper.

COFFEY, Q.C.:

Q. Okay. And finally then, Doctor, Mr. Simmons asked you about the, or referred you to the fact that there are different antibodies which have different specificities and different sensitivities known and, of course, there are different detection systems and different antibodies used by different laboratories and different detection systems used by different laboratories and each lab has to decide for itself, what's the appropriate mix and procedures. Okay. In relation to that, if whatever the particular lab decides to choose, which antibody to choose, decides to use for ER/PR and which detection systems or system it finally decides upon, from your perspective, if the lab in doing so appropriately optimizes the process and carefully follows the

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procedures it has established, worked out for itself and established, should the ER and PR results be accurate?

DR. O'MALLEY:

A. I would think so.

COFFEY, Q.C.:

Q. Okay. And therefore, usable clinically for treatment -

DR. O'MALLEY:

A. Yes.

COFFEY, Q.C.:

Q. Thank you, Commissioner.

EXAMINATION PER CURIAM

THE COMMISSIONER:

Q. Thank you, Mr. Coffey. Doctor O'Malley, occasionally people refer to something called a false negative. Is it expected that there would be a certain number of false negative in ER testing?

DR. O'MALLEY:

A. Well, ideally, we want to--the whole point of optimization is to significantly decrease the possibility of either a false negative or a false positive.

THE COMMISSIONER:

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Q. But is it more likely or less likely that--is it more or less likely that you would have a false positive, for example, than a false negative?

DR. O'MALLEY:

A. Well again, that depends on all of the factors that we've talked about. If a tumor has been sub-optimally fixed, if it hasn't been handled in the manner that I spoke about, then the chances of having a false negative result are high. On the other hand, if an antibody is highly, highly sensitive and used in conjunction with a highly sensitive detection system, this particularly pertains to the situation of HER2, then there's a greater chance of a false positive result.

THE COMMISSIONER:

Q. Well, if one were looking at the results of a particular laboratory or laboratories, indeed, across the whole country, is there a commonly accepted number in North America, for example, would you say--you know, I would expect that two percent, three percent, five percent, ten percent of those test results would be false results.

DR. O'MALLEY:

A. Well, again -

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THE COMMISSIONER:

Q. I know you would hope that it wouldn't be.

DR. O'MALLEY:

A. Exactly, exactly, but even less than five percent would be a concern.

THE COMMISSIONER:

Q. Okay. Thank you very much.

DR. O'MALLEY:

A. Well, I should say even less than ten percent. Less than five percent may happen, because when we look at that external quality assurance in inter-observer variability, if we get 95 percent concordance, that is acceptable.

THE COMMISSIONER:

Q. And do I take it then that where you think that differences--you see, to me, what you might call a false negative might arise for a different purpose, and I frankly, I'm not quite sure, how does one figure out that there is a false negative, by the way? Is it just that two or three tests down the road somebody finds a different result, so -

DR. O'MALLEY:

A. Something would have to prompt that.

THE COMMISSIONER:

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Q. Okay.

DR. O'MALLEY:

A. Yes, because we wouldn't be reporting it out if we thought that there was a chance that it could be falsely negative.

THE COMMISSIONER:

Q. Okay, and it seems to me that there is a difference in the circumstance where you have the difficult case and you might have a reasonable difference of view between pathologists as to how you should interpret something, and a case where sort of one pathologist might view it one way and then there's the other ten in the room who says no, that's not what it is at all. It's something entirely different.

DR. O'MALLEY:

A. Well, no, in a situation of--we could look at two different situations. There's the diagnostic dilemma or there's the difficulty in scoring in ER cases. So it's the latter, I think, that you're asking?

THE COMMISSIONER:

Q. Yes. Well, in this case, although my mind sometimes drifts to the other, I confess.

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DR. O'MALLEY:
A. Yes. Well, I mean, in that situation, it's just really a matter of what is the percentage. There might be some variability in what one pathologist assesses as the percentage positive tumor cells versus another, but that really is only relevant for cases, one of which I showed, where the degree of positivity is at the low end. For the vast majority of cases, and speaking specifically about ER, they're either completely negative or highly--or very strongly positive. So it's only about six percent or so, certainly less than ten percent, where the degree of positivity is around that borderline level where there might be a little bit of variability in terms of interpreting.
THE COMMISSIONER:
Q. Okay. So that should not be a major problem?
DR. O'MALLEY:
A. It should not be a major problem.
THE COMMISSIONER:
Q. Okay. Mr. Crosbie, you're -
CROSBIE, Q.C.:
Q. Commissioner, with great respect, your question about rates of false negatives is a very contentious

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issue, which you've raised now -
THE COMMISSIONER:
Q. Well, we have it in the literature that there is such a thing. So are you saying that there's a problem with my question or you want to ask a follow up one?
CROSBIE, Q.C.:
Q. The problem is that it would make some of the other lawyers in the room want to explore the topic further. Now that may not be necessary, but she made a very quick comment on it, and it's a very key issue for some of us.
THE COMMISSIONER:
Q. In another setting or in this one?
CROSBIE, Q.C.:
Q. I believe in this setting, yes. I can only assume that when we talk of false negative rates, there will be other individuals from your institution, like Dr. Pritzker, who would be able to address that this afternoon. Is that so?
DR. O'MALLEY:
A. You can certainly bring it up with him, yes.
CROSBIE, Q.C.:
Q. Yes.

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COFFEY, Q.C.:
Q. And well, actually, Dr. Mullen.
DR. O'MALLEY:
A. And Dr. Mullen.
THE COMMISSIONER:
Q. Dr. Mullen, yes. Frankly, I started down this road just for an explanation of what it was and how one figured out what it was. But I perhaps got diverted. Are you content then with the idea that there will be others, Mr. Crosbie, or are you suggesting there is another question or two you want to ask of this witness?
CROSBIE, Q.C.:
Q. No, I'm content.
THE COMMISSIONER:
Q. All right. Well, on that basis then, only left for me to thank you very much for coming all this way and for giving us what I, at least, have found an extremely interesting morning. Thank you.
DR. O'MALLEY:
A. Thank you.
THE COMMISSIONER:
Q. We'll adjourn until--we're a little late today. Let's make it 2:20.

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(LUNCH BREAK)
THE COMMISSIONER:
Q. Please be seated. Mr. Coffey.
COFFEY, Q.C.:
Q. Thank you, Commissioner. The next witness is Dr. Kenneth Pritzker.
DR. KENNETH PRITZKER (AFFIRMED) EXAMINATION BY BERNARD COFFEY, Q.C.
REGISTRAR:
Q. Would you please state and spell your complete name for the Commission.
DR. PRITZKER:
A. My name is Kenneth Phillip Henry Pritzker. K-E-N-N-E-T-H P-H-I-L-L-I-P H-E-N-R-Y P-R-I-T-Z-K-E-R.
REGISTRAR:
Q. Thank you.
COFFEY, Q.C.:
Q. Dr. Pritzker, can you give the Commissioner please a brief overview of your education and your professional background. And I emphasis "brief" because in your case, I think it goes on for some period of time.
DR. PRITZKER:
A. Sure. I graduated in medicine at the University of

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Toronto in 1967 and at the same time I received a Bachelor of Science in medicine in Pharmacology. After that I did a rotating internship and a year of internal medicine, followed by pathology studies at McGill University. And in 1972 I became a fellow of the Royal College of Physicians/Surgeons of Canada in Pathology and commenced work at Mount Sinai Hospital, had an appointment at Mount Sinai Hospital in Toronto.

CROSBIE, Q.C.:

Q. Will we be seeing an exhibit, Mr. Coffey?

COFFEY, Q.C.:

Q. Yes, I'll be doing that in a second. Go ahead, sorry, Doctor.

DR. PRITZKER:

A. I've been at Mount Sinai--Mount Sinai has been my base for my entire career and in the early years, I was a general pathologist, but I had a special interest in bones and joints and developed a research group interested in diseases such as osteoarthritis and osteoporosis. And in 1986 I became chief of the department in Mount Sinai and I have had that role since that time. Over the years and since the start of my career, I've been involved

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with various specialities, societies, local, provincial, national and international in pathology. And I guess, one of the highlights was presidency of the Canadian Association of Pathologists which was in the early 1980s.

COFFEY, Q.C.:

Q. Commissioner, if I could please, I have some exhibits I'm going to ask to be entered. They would be exhibits P-1706 through P-1717 inclusive and P-1726.

THE COMMISSIONER:

Q. Entered.

EXHIBITS P-1706 THROUGH P-1717 INCLUSIVE, ENTERED AND MARKED EXHIBIT P-1726 ENTERED AND MARKED.

COFFEY, Q.C.:

Q. Registrar, could you bring up, please, Exhibit P-1726? Doctor, this is a document entitled curriculum vitae for Kenneth Phillip Henry Pritzker. I take it that that is your CV?

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. And on my account, it goes on for 109 pages, looking at the numbering system here. Doctor, could you

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tell the Commissioner, please, as you indicated, you were, as you put it, a practising pathologist in the sense of on a day-to-day basis for years.

DR. PRITZKER:

A. I still am.

COFFEY, Q.C.:

Q. And I was going to ask you about that. Are you still -

DR. PRITZKER:

A. Yes, I am.

COFFEY, Q.C.:

Q. Okay. And you are also, though, since about 1986, did I get that right, and what is your job title there?

DR. PRITZKER:

A. At the present time, my job title is Pathologist in Chief and I'm also Director of the Department of Pathology and Laboratory Medicine.

COFFEY, Q.C.:

Q. And as a practical matter, in those roles, what does each of those roles mean?

DR. PRITZKER:

A. Well, Pathologist in Chief is responsible for the medical aspects of the department including the

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quality and the quantity and the nature of all services. And in the context of our hospital which is a teaching hospital, it's only the services, but it's also the academic output, the teaching and the research. So, my overall responsibility that that's of high grade and adequate quantity. The directorship indicates I'm responsible for the support infrastructure which is really the technical operations as well. I'm responsible for that in reporting to the president for the entire outcome of the department.

COFFEY, Q.C.:

Q. And so in that capacity, I take it in the former capacity you have physicians report to you?

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. And in the latter capacity what type of other occupations report to you?

DR. PRITZKER:

A. Well, it's technologists, technicians, clerical staff, principally.

COFFEY, Q.C.:

Q. Anybody who works in the department, I take it?

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DR. PRITZKER:
A. That's correct.
COFFEY, Q.C.:
Q. Doctor, and you've indicated, as well, though, you're still a practising pathologist and have remained so. What does--what type of pathology do you practice?
DR. PRITZKER:
A. Well, my special interest is in diseases of bones and joints, and because of all the other responsibilities I have, I confine my practice, at this time, to that subject. It's things such as bone and tumors of bone and soft tissue and it's also the examination of specimens that have various forms of arthritis.
COFFEY, Q.C.:
Q. And, Doctor, are you still yourself involved in academic publications?
DR. PRITZKER:
A. Yes.
COFFEY, Q.C.:
Q. And, Doctor, could perhaps describe--first of all I'll ask you, Mount Sinai Hospital, is it--you've indicated it's associated--it's a teaching hospital,

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it's associated with which university?
DR. PRITZKER:
A. The University of Toronto.
COFFEY, Q.C.:
Q. And are there any other--as a relationship, then, with UFT's medical school, does it have, Mount Sinai, have a relationship or participate with any other groups within Ontario?
DR. PRITZKER:
A. Oh, yes, we do. But there are--and beyond Ontario. But these are informal relationship which would be developed on a departmental basis or even on an individual basis.
COFFEY, Q.C.:
Q. And within the pathology and laboratory medicine program at Mount Sinai, could you tell us, please, how it's structured perhaps in terms of, you know, the relationship between the physicians, the pathologists and the technologists and technicians and the administrative staff, how is that all laid out, perhaps?
DR. PRITZKER:
A. Okay. The first thing you should be aware is it's quite a large operation. There are a total of about

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300 people on staff, plus about 100 students on site at any one time. And it's also quite a varied operation. We would have somewhere around 30 different centres of activity, technical centres of activity. So it's clear that in order to operate such a centre, it has to be, the organization has to be reasonable complex. Now, what we have is a site of organization in which there sections, medical sections which would be for a particular subject, such as surgical pathology, cytology, biochemistry and within those sections there may be folks who have specific responsibilities, medical responsibilities for the oversight related to particular subjects which require it, such as immunohistochemistry, that was--and on a technical side we have units and, we call it units to define it, these centres, and they may have, a unit might be--an example of a unit would be histology and an area of focused activity within that unit might be the immunohistochemistry, it would be immunohistochemistry. So if we look at it at the local base, the local centre of activity, we would have a technical person who would be the lead and we would have a medical person that would be at the

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lead, and they would be expected to work together to produce the results and to have oversight and supervision of the activity. In organization chart terms the technical person reports upwards to their supervisor, who reports upwards to the administrative director and the medical person usually would report to me directly or they may report to another physician, depending on the circumstance. The--if and when there are issues, and there always issues, as you can expect in a complex operation, one that requires deliberation. It's expected that the medical people involved and the technical people involved and sometimes with other resource people, some staff people, the quality individual or whoever, would study the problem and recommend to the administrative director or myself solutions. And what would happen then is we would have a discussion around that report, often with the folks and determine a course of action. That's a microcosm of how the place works.
COFFEY, Q.C.:
Q. Now, just to take the IHC -
DR. PRITZKER:
A. Yes.

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COFFEY, Q.C.:
Q. - activity, that exists within which unit? The -
DR. PRITZKER:
A. So, the IHC, immunohistochemistry exists within the centre, the unit of histology. And Trish Wegrynowski is our lead technologist there and Dr. Robert Riddell is the lead physician for the immunohistochemistry.
COFFEY, Q.C.:
Q. And the lead physician for immunohistochemistry, for IHC, what is--it's Doctor, I'm sorry, Doctor?
DR. PRITZKER:
A. Dr. Robert Riddell.
COFFEY, Q.C.:
Q. Riddell. What is, in that context, Dr. Riddell's responsibilities are what?
DR. PRITZKER:
A. It's primarily strategic in terms of reporting. His role would be to tell us normally what they're doing each, for each period of time. But we have many requests to expand the service; he would be part of the process, he would be leading the process, he would evaluate that. If there was financial resource implications beyond what they could do,

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that would come to us, but the administrative director and myself. Similarly if there is changes of technology, that would also come up that way. From time to time, it's in every area of the laboratory there are quality issues, these issues are addressed usually internally with reporting through a quality group which we have, which, in fact, has representation from all of the areas and has a fulltime coordinator, but there may be a resource issue or there may be a sensitivity issue that there's a problem needs to be addressed in a very timely fashion and at that point we would become aware of it.
COFFEY, Q.C.:
Q. Now, I'm going to come back to the quality group and ask you how that kind of fits into the overall scheme of things.
DR. PRITZKER:
A. Okay.
COFFEY, Q.C.:
Q. But in terms of Ms. Wegrynowski, she reports to whom in that scheme?
DR. PRITZKER:
A. She reports to the charge technologist for

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histology, a person by the name of Cindy Dunn.
COFFEY, Q.C.:
Q. Okay. And Ms. Dunn reports to?
DR. PRITZKER:
A. The administrative director.
COFFEY, Q.C.:
Q. Who reports -
DR. PRITZKER:
A. Who is Mr. Vince D'Mello.
COFFEY, Q.C.:
Q. And reports, her reports -
DR. PRITZKER:
A. And Mr. Vince D'mello works with me.
COFFEY, Q.C.:
Q. Ultimately?
DR. PRITZKER:
A. Yeah.
COFFEY, Q.C.:
Q. Okay, so that's--you were aware that that kind of lines of authority in a flow chart sense would meet?
DR. PRITZKER:
A. That's correct.
COFFEY, Q.C.:
Q. Okay.

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DR. PRITZKER:
A. And those are delineated in our organizational charts.
COFFEY, Q.C.:
Q. Doctor, the quality group you referred to, where do they come--what relationship do they have to this?
DR. PRITZKER:
A. Well, they are not specifically related to immunohistochemistry -
COFFEY, Q.C.:
Q. Yes, I appreciate that.
DR. PRITZKER:
A. They apply to all the processes in the laboratory. And once again we have a physician, in our place it's Dr. Bernard Fernandez, and we have quality officer, Mr. Gaman Modi, who are responsible for organizing the quality program. It's these folks who organize and work with all of the other groups. It's a large, it's a large and revolving exercise to ensure that the standard operating protocols are in place, that we have the quality--the proficiency testing that we prepare and, for accreditation, that we address any deficiencies that we find, this kind of thing. It's not only internal, both these folks

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work externally, as well, in the hospital and elsewhere as part of their duties.

COFFEY, Q.C.:

Q. And I take it they're charged with, in one sense, kind of an oversight, make sure that -

DR. PRITZKER:

A. That's right.

COFFEY, Q.C.:

Q. - everybody is doing what is required -

DR. PRITZKER:

A. That's right.

COFFEY, Q.C.:

Q. In terms of quality, quality -

DR. PRITZKER:

A. It's not only that the pieces are in place, it's not only that you have a standard operating protocol, but actually, the standard operating protocols are used and used as stated.

COFFEY, Q.C.:

Q. And, Doctor, from your perspective, your vantage point, how much interaction is there, for example, between the IHC technologists and the pathologists who utilize that service and what sort of interaction occurs?

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DR. PRITZKER:

A. Well, it's daily and it's active. So I've described partially the high-level interaction, but on a daily interaction the pathologists are responsible for all the work which comes from each pathologist, because they use that as the basis to render their opinion and their judgment. So if there is an issue, and there often is, with a particular set of materials, it's common to go to the immunohistochemistry laboratory and discuss this with the technologist, to ask for a repeat, if necessary, this kind of thing. So this is not always done by a walk through, sometimes it's done by a phone call or other means, but there's a steady parade of physicians interacting with the technologists in the immunohistochemistry laboratory each day. When I'm on service, I do my turn there, too.

COFFEY, Q.C.:

Q. And, Doctor, we have, Commissioner has heard not a lot yet and she will hear a lot more, I anticipate, about this sort of matter, but--and, for example, when Dr. O'Malley was here this morning and she made reference in passing to, more than in passing, in fact, a fixation, fixation as being a concern at

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times. And just from her comments I understood that the fixation process begins really with excision of the tissue and that would be in the OR, in the main?

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. And what, if any, is the relationship between, like, the laboratory people, you on the bench, as it were, at times, because you say you take your turn looking at slides even today, and ensuring that fixation protocols exist and are actually followed in the OR, who takes care of that and what liaison, if any, is there, or oversight?

DR. PRITZKER:

A. Right. We do, we provide the fixative and we provide the protocols for the fixation conditions.

COFFEY, Q.C.:

Q. And that's "we" in this context is?

DR. PRITZKER:

A. We, being the department.

COFFEY, Q.C.:

Q. Department, your department?

DR. PRITZKER:

A. Not myself personally.

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COFFEY, Q.C.:

Q. Your department?

DR. PRITZKER:

A. Yeah, our department.

COFFEY, Q.C.:

Q. Okay.

DR. PRITZKER:

A. And our department would work with the nurses, predominantly, who are in the operating room who are--the nursing administration in the operating room to ensure that the materials are delivered, that the materials are appropriate and so on, the fixative is appropriate and so on.

COFFEY, Q.C.:

Q. The fixative is appropriate and I take it in terms of then it has to be moved from the OR, the tissue sample, to the laboratory to be processed?

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. And that would be moved, I take it, by porters or the equivalent?

DR. PRITZKER:

A. That's correct.

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COFFEY, Q.C.:
Q. And so in terms of just making sure that the whole process works in a timely fashion, who's responsible for that?
DR. PRITZKER:
A. Well, again, we have a list of what is being operating on, what to expect. We have people whose job title is pathologist assistant, these are technologists who have a special interest in receiving the materials and assessing the material for sampling. And we try to make sure that everything that we expect to get is received and is received in a timely fashion. I should say that the routine is to place something in the fixative immediately after excision unless there is special direction to forward it to the lab immediately for examination.
COFFEY, Q.C.:
Q. And now, you referred just now to pathology assistants?
DR. PRITZKER:
A. Um-hm.
COFFEY, Q.C.:
Q. How long have they existed at Mount Sinai?

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DR. PRITZKER:
A. Oh, I think we started over ten years ago, somewhere in that neighbourhood.
COFFEY, Q.C.:
Q. And you indicated that at least back in 1980s, I believe, you were the president of the Canadian Association of Pathologists at one point in your career?
DR. PRITZKER:
A. That's correct.
COFFEY, Q.C.:
Q. And I take it since then, though, you have routine contacts with your colleagues across the country?
DR. PRITZKER:
A. Yes.
COFFEY, Q.C.:
Q. And elsewhere?
DR. PRITZKER:
A. Yes.
COFFEY, Q.C.:
Q. What, if anything, is your understanding about pathology assistants and I got--you said Mount Sinai began it about a decade or more ago. How about elsewhere in the country and how has it progressed?

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DR. PRITZKER:
A. Well, the pathology assistants have been a topic for at least 30 years, but over the last ten years it's become very necessary to have these individuals as the workload has gone up. This is something very similar to other kinds of professionals who've developed assist positions, and the most important aspect about this is their formal training and ultimately their accreditation. So what has happened is that in the past it was quite a loose group of people in the sense, or quite a varied group of people in the sense that they came from many different kinds of backgrounds in the hospitals. We deliberately chose to have medical laboratory technologists because they have an independent professional status, though they don't have a college of their own, and because these individuals have a basic background which enables the training. I'm very pleased to say that the Canadian Association of Pathologists has fostered the concept of pathologists assistants that a year ago--actually, it was two years ago here in Newfoundland they established a section of pathologists assistants. And that the group in the

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Toronto area, Ontario, is self organizing and they've had two annual meetings so far attracting over 80 people. So actually, the group itself is ahead of the educational bodies and the regulatory bodies in terms of getting itself together, and that's quite a good thing.
COFFEY, Q.C.:
Q. And within, again, the laboratory at Mount Sinai ultimately, I take it, the pathologists assistants report in that structure, organizational structure eventually to you?
DR. PRITZKER:
A. That's correct, that's correct.
COFFEY, Q.C.:
Q. And, Doctor, I'm going to ask you about how Mount Sinai became to be involved in the activities that have ended up with you sitting here. If I could, please, Registrar, Exhibit P-0543? Now, Doctor, this is an office copy of a letter dated, it's from Dr. Donald Cook dated August 2nd, 2005 to yourself in your professional capacity at Mount Sinai. And he just writes, "As discussed in our telephone conversation, I am currently putting a hold on the reporting of all estrogen and progesterone receptors

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from our laboratory medicine program in St. John's hospitals, Eastern Health for all virgin and newly diagnosed patients with breast cancer. I certainly appreciate your laboratory's assistance in performing immunohistochemical staining along with interpretative results on these cases. I anticipate we may be dealing with anywhere from 30 to 40 cases per month, possibly over a three-month period. We will correlate Mount Sinai's results with our own to further help us validate our Ventana automated system. I will be in contact with Maria Mandes at your laboratory regarding this. We will, of course, reimburse Mount Sinai for all costs incurred. Thank you for your help at this difficult time." Before I go on, Maria Mandes is whom?

DR. PRITZKER:

A. Maria Mandes is our manager of research services in our laboratory. These are services which we perform for the pharmaceutical and device industries and we keep this separate from our routine services for a number of reasons, one is that the--these services have their own rhythm, they tend to be custom. They are extremely high quality in the sense that the documentation exceeds what would go on in a

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conventional hospital setting and the documentation and the practices meet a standard called Good Laboratory Practices, which is set up by the FDA and it's independently audited. Those practices essentially are ones which demand extraordinarily extensive documentation and, of course, adherence to the documentation in terms of the operation of the work that goes on there. So we asked Maria to do this because our laboratory was fully--our regular laboratory was fully occupied with work. Our research and innovation laboratory was fully occupied with work, but it was possible to be able to shift some of the work which we already had in order to do this work. It was also a review which we could do on a batch basis, which the research laboratory lended itself to do.

COFFEY, Q.C.:

Q. The idea of processing a lot of samples, kind of in bulk as it were.

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. It's set up more for that, a particular type of sample?

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DR. PRITZKER:

A. That's right, it could deal with things that are offline in a batch basis.

COFFEY, Q.C.:

Q. And now could you tell then, the Commissioner, what you recall about how you got yourself involved in this?

DR. PRITZKER:

A. Well, the documentation, the e-mails are in the exhibits, but essentially, first I received a phone call from Don Cook requesting assistance and we receive, from time to time, but quite often, a number of calls asking for assistance of one type or another and we try to accommodate, even though there's usually very little capacity in our system, and as you can see from the exhibit, the request was for a limited number of cases and for a limited time period. So we did offer our help and then we determined how we could get this done.

COFFEY, Q.C.:

Q. I take it this initially here is referring to maybe dealing with anywhere from 30 to 40 cases per month, possibly over a three-month period. I take it that refers to current cases, 30 to 40, about one a day?

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DR. PRITZKER:

A. That's correct, and but we did expect to receive the material in batches of five or six at a time, something like this.

COFFEY, Q.C.:

Q. Now sir, what then happened?

DR. PRITZKER:

A. Well, this is 2005, as I recall, the actual work started somewhere in November of 2006, in terms of--not in terms of this, but in terms of the look back stuff. So for the period of 2005 to that period, the work was being performed and there was really no difficulty or strain on the part of our laboratory.

COFFEY, Q.C.:

Q. Just in terms of that, Doctor, I'm just going to ask you, because I understand, in fact, the look back started in '05 actually, in September. So this is August of--I think we just looked at August of '05.

DR. PRITZKER:

A. Right.

COFFEY, Q.C.:

Q. So you just said '06. I'm just wondering -

DR. PRITZKER:

A. Well, I believe it was '06 where the big work was

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done, but -

COFFEY, Q.C.:

Q. Well, I'll take you then to some of the documents, Doctor.

DR. PRITZKER:

A. Yes.

COFFEY, Q.C.:

Q. Now just in terms of that, just so the Commissioner has some sense of what, you know, how much involvement you, yourself, would have in this, when you were first asked by Dr. Cook, like "can you help?" who if anyone internally did you check with first?

DR. PRITZKER:

A. Well, we were--this was a request to perform services because there was some question about whether the interpretation and whether the staining had been correct in the original place. So the first thing which we did was, in our discussions, was to determine what we would have to do to assure that our staining was completely at the leading edge of standards, and so we reviewed what we were doing. Those standards have changed and evolved over the years. Fortunate to have people such as Dr.

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O'Malley and others who are experts in what standards should be present. So we did that. We reviewed our standard operating protocols. The next question was how were we going to get this work done, and so we had to line up both the technical work and the professional work involved, and we basically asked Maria, who's expert at organizing technical work, to lead that and to work with Cindy Dunn and Trish to ensure that the processes which we were doing were identical to those which would be going on in the routine laboratory.

I did this with Dr. Mullen, who is my associate, as he is a very active, very experienced surgical pathologist, does participate in the breast pathology and is quite expert in processes, in terms of organizational processes to get work done. So those were the people we talked with, as well as with Frances O'Malley, of course.

COFFEY, Q.C.:

Q. And if we could, please, Exhibit P-1706? Now Doctor, these are two e-mails, one of August 10th--well, both of them are August 10th, 2005, one just internal to Eastern Health, but the one below, it's from yourself, August 10, 2005, 4:12 p.m. to Dr.

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Donald Cook. The subject is ER and PR consultation, immunohistochemistry, and you said "Don, this is to ask your advice about billing for our services," and you go on to talk about that, and you say "you may be happy with this arrangement, however, particularly if you never see the dollars or the budget, however, this arrangement is not specific to pathology services, nor was it designed for 'look backs' such as the studies to be performed on ER or PR negative tissues. The alternative is for Mount Sinai Hospital to bill you directly, and one suggestion is to bill in usual way for active consultations and to bill you directly for the services associated with review of the negatives. Please advice. Thanks, Ken."

So I take it that this was, of course, dealing with Dr. Cook to straighten out, well, somebody's got to pay--you know, in terms of how it will be billed for.

DR. PRITZKER:

A. That's right.

COFFEY, Q.C.:

Q. Somebody has to pay for it, and you were suggesting here that for active consultations, I take it which

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would be generally the current cases ongoing?

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. You would bill through the usual OHIP/MCP whatever?

DR. PRITZKER:

A. That's correct. That is the means in place for interprovincial payments for direct patient services. It was never designed for laboratory services, but it's the way we've been doing things.

COFFEY, Q.C.:

Q. And in the alternate, and is also though to bill Eastern Health directly for the services associated with the review of the negatives, like the past cases?

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. Okay, if we could, please, Exhibit P-0567? And Doctor, this is an e-mail from Donald Cook, Dr. Cook to yourself, Thursday, August 11th 2005. The subject is ER and PR consultations. He writes "Hi, Ken. Regards to billing, your suggestion is good. You can bill for active consultation and bill me

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directly for the services employed in the review of the negative ERs. I'm hoping to send our reviews for the years 2003 and 2002 as soon as we can compile these cases, hopefully by the end of next week. We will submit the other years following these. I will contact Maria when we are ready to send these cases for your help. Once again, thanks for all your help." Signed Don.

And then to give yourself some sense of at least what the documentation that I'm going to be showing you suggests, if you'll look, please, at Exhibit P-1707? This is an e-mail, Doctor, from Nancy Good to Dr. Brendan Mullen. The subject is ER/PR list. It's sent September 13th, 2005 and Ms. Good writes "Hi, Dr. Mullen. Here is the list of all the patients we have received blocks from so far. The ones highlighted in blue have been stained," and I'm not going to take you through them, pages in the attachment, but there are ten pages listing patients, specimen numbers, I take it, prepared for Dr. Mullen as of September 13th. Doctor, who is Nancy Good?

DR. PRITZKER:

A. Nancy Good is a technologist, quite an experienced

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technologist, who was working in immunohistochemistry at the time.

COFFEY, Q.C.:

Q. And what was her involvement in this, do you know, your understanding?

DR. PRITZKER:

A. I don't know all the details actually. It looks, from the e-mails, that she was one of the people, maybe the main person, who was responsible for, on a technical side, keeping all things in order. She was--actually, Nancy is in the--was in the histology laboratory. She was so very experienced technologist, she was also working with Maria Mandes on the research things. So this hybrid aspect that we needed some of the resource from the main histology laboratory and we needed some of the resource from the research laboratory, which involved Nancy.

COFFEY, Q.C.:

Q. And just then when you say you wouldn't know all the details of this, and that was really a point I wanted to make with you is that it would be Dr. Mullen and Nancy Good and Maria Mandes who would, in fact, be, from your perspective, by that point in

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time -

DR. PRITZKER:

A. Absolutely.

COFFEY, Q.C.:

Q. - charged with actually getting it done?

DR. PRITZKER:

A. That kind of detail.

COFFEY, Q.C.:

Q. You having agreed, on behalf of the hospital, to have the hospital participate and do it and made the arrangements, it would be left to Dr. Mullen and company to -

DR. PRITZKER:

A. That's right. The set up of these spreadsheets and so on was something which I'm sure that Maria and Brendan did and as part of a way of keeping track of all this material.

COFFEY, Q.C.:

Q. If we could, please, Registrar, just again to give the Commissioner some sense of what stage the review retesting process was at various points in time, Exhibit P-1708, please? And Dr. Pritzker, this is an e-mail from Nancy Good, Thursday, October 20th, 2005. It's to Dr. Cook, but it's copied to Dr.

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Mullen, Maria Mandes and yourself. The subject is ER/PR blocks, and the attachment is block discrepancies.xls. Ms. Good writes "Hi, Dr. Cook. Maria would like to know if we will be receiving any more blocks for retesting and if so, approximately how many more? Everything has been logged into our database (we have approximately 547 patients) although some don't have an RS number yet. Please find the attached list of block discrepancies and other notes. If you have any questions, please give me a call." So I take it you'd be copied on this, Doctor, at that point in time, just simply to keep you in the loop, as it were?

DR. PRITZKER:

A. That's right. That's our practice is to try to keep everybody involved by e-mail. RS stands for research service number.

COFFEY, Q.C.:

Q. Yes, and I take it by this--that suggested, I take it, that by that point in time, there were about 547 retests in the queue as it were or some, I understand, had already been reported, but in total received up to then.

If we could, please, Exhibit 1703? Doctor,

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this is a series of e-mails. The earliest in time is October 20th, 2005 at 2:38 p.m. It's from George Tilley to Dr. Robert Bell, and he refers, the contents of it, a conversation Mr. Tilley apparently had with Dr. Bell. Do you know Dr. Robert Bell?

DR. PRITZKER:

A. Very well.

COFFEY, Q.C.:

Q. Okay. Who is he?

DR. PRITZKER:

A. Robert Bell is currently the president and chief executive officer of the University Health Network, but before he had that--before he took on that position, he was head of surgical oncology and he was also the lead sarcoma surgeon in Toronto. So he was a--he's a colleague of mine, who we worked very closely together over many, many years, on the sarcoma service.

COFFEY, Q.C.:

Q. University Health Network, Doctor, could you tell the Commissioner what is that?

DR. PRITZKER:

A. University Health Network is a corporate entity which incorporates three hospitals, the Toronto

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General Hospital, the Toronto Western Hospital, and the Princess Margaret Hospital. They have three different functions, but they have one corporate governance and administration.

COFFEY, Q.C.:

Q. And here in this context, the bottom of the first page of the exhibit, there's a reference to "our laboratory clinical chief," that would be Don Cook, in this context, "will be contacting the two individuals you referenced to also see what insight they can offer in terms of national follow," and when we look up above there, sir, at October 23rd, 2005, Dr. Bell has sent or sends an e-mail responding to Mr. Tilley and copies it to Bruce Youngson and Dr. Frances O'Malley, and the Commissioner met Dr. O'Malley this morning, but who's Dr. Bruce Youngson, do you know?

DR. PRITZKER:

A. Dr. Bruce Youngson is a breast pathologist at University Health Network and he's a professional colleague of Frances O'Malley's.

COFFEY, Q.C.:

Q. And this, I take it, on October 24th 2005, that October 23rd e-mail was forwarded by Dr. O'Malley to

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yourself for your information, I take it.

DR. PRITZKER:

A. Right.

COFFEY, Q.C.:

Q. With a view, I take it, because she was referenced in it.

DR. PRITZKER:

A. She was referenced and she was aware that it might have downstream implications for us, and that I should be alerted to that.

COFFEY, Q.C.:

Q. If we could, please, Exhibit P-1306? Now Dr. Pritzker, this is an e-mail from George Tilley, October 20th, 2005, to yourself. Subject is ER/PR testing. He writes "Hi, Ken. Just wanted to thank you again for talking with me this morning. I appreciated the opportunity to talk through this difficult issue with you and get your advice. There appears to be a growing body of evidence and opinion that there are many questions inherent with this ER/PR test. Even for me as a non-clinician, it raises eyebrows. As a member of the Board of Canadian Patient Safety Institute, I wanted to ensure that if there were"--I'm sorry, "if there are

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learnings from our experience, we will share it. Having said that, I understand that Ontario already has a comprehensive accreditation program in place for its labs. Our clinical"--I'm sorry, "our laboratory clinical chief will be contacting the Canadian Association of Pathologist and others that we may subsequently identify. It appears that there is a gap in terms of a national entity who can take the lead with this issue. So we are likely to have a shotgun approach"--I'm sorry, "to take a shotgun approach to the follow up and hope that there is someone who can keep it moving." Signed George. Do you recall speaking with Mr. Tilley?

DR. PRITZKER:

A. Yes, I do.

COFFEY, Q.C.:

Q. Could you tell the Commissioner, please, about that?

DR. PRITZKER:

A. Yes, well Mr. Tilley phoned me and outlined the problems as he saw it and actually informed me of the depth of the problems, at least, on a greater insight as to what we were dealing with that it was a much larger issue than we had appreciated before. And he did ask questions and inquired of whether I

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had suggestions for how to enhance quality in a system. The accreditation program that he refers to is the Ontario Laboratory Accreditation Program which was instituted about nine years ago as an outgrowth of how to, how to ensure quality in the laboratory settings and it was modelled after the College of American Pathologists Program, it has a slightly different emphasis, much more emphasis on the technical aspects than the College of American Pathologists Program. We participate in both of these, and he did ask about national activities and I'm sure I explained to him, which he already knew very well, that the--in Canada our health systems are operated as provincial systems, so all of the operations are provincially based, that the various kinds of national organizations and the Federal government have responsibilities for setting standards, but have no capacity for or have very limited capacity, I would say, for ensuring those standards, that responsibility is the responsibility of a Provincial governments and the societies and organizations and is done differently in each province.

COFFEY, Q.C.:

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Q. And you did just, several minutes ago, refer to some initiative, I gather, that started in Newfoundland about, oh at least it was a meeting, I take it here in Newfoundland, several, two or three--two and a half years ago?

DR. PRITZKER:

A. The initiative that I referred to is the pathologist's assistant initiative.

COFFEY, Q.C.:

Q. Yes, okay.

DR. PRITZKER:

A. As would be an example of fostering a group of health professionals that--emerging group of health professionals that are needed for the kinds of things which we do. The Canadian Association of Pathologists has also been very active over the years in advocating standards for many things, one notably is the storage--guidelines for the storage of slides and blocks and reports, but many other kinds of guidelines over the years as well.

COFFEY, Q.C.:

Q. Now -

THE COMMISSIONER:

Q. Can I just interrupt for a second while this is in

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my mind?

COFFEY, Q.C.:

Q. Sure.

THE COMMISSIONER:

Q. The activities that the Canadian Association of Pathologists in, as you describe it, I think, promoting standards.

DR. PRITZKER:

A. Uh-hm.

THE COMMISSIONER:

Q. Then I'm assuming that's just what it is, it's just a group of people who are interested who will say "we suggest" and that's as far as the power goes?

DR. PRITZKER:

A. Yes, that is as far as the power goes, for example in the kinds of recommendations that they make, it's quite a persuasive power because it represents the consensus of the leadership of Canadian pathologists and it's usually developed reflecting the consensus of pathologists worldwide. So when these recommendations come along, they've got a very substantive basis, but the actual implementation of those recommendations are either at a provincial level or even at a local level if there's not a

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specific provincial directive and very seldom is there a provincial directive.

THE COMMISSIONER:

Q. When you say "provincial directive" you mean as in provincial government directive of some kind?

DR. PRITZKER:

A. That's correct.

THE COMMISSIONER:

Q. Thank you.

COFFEY, Q.C.:

Q. Exhibit P-0386 please? Now, Doctor, I'm just going to put this in context, that e-mail from Mr. Tilley of October 20th is at the bottom of the first page of this exhibit. On October 26th, 2005, you apparently forwarded that on to--that e-mail, to Dr. Brendan Mullen and Dr. Donald Cook, subject is "ER/PR testing" and you write, "Brendan and Don, there may be an opportunity here, pathologists advocacy and patient safety initiatives. May assist finding resources for pathology labs, even restoring the autopsy to prominence, worth thinking about. Signed KP." Doctor, in this context what does that e-mail refer to and what are you contemplating?

DR. PRITZKER:

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A. Well I think no matter what the laboratory is in this country over the last, well maybe even for much longer than ten years, the resources have not kept pace with the needs and the demands that have been placed upon us. There is also whatever guidelines and reasonable advice we can provide on quality, I think virtually every laboratory has had to make choices because of budget constraints and we would try to make those choices as wisely as we can and to make sure that everything we do is safe and well done, but I think we're saying that you--that there is a resource issue, amongst other things, and that as professionals, we should be taking advantage of every opportunity when a problem has been identified to responsibly respond and use the difficulty to try to redress the problem and obtain the resources so that we can get solutions to put these kinds of problems in the past.

COFFEY, Q.C.:

Q. If we could, please, exhibit P-0682, Doctor, these are two e-mails of November 16th, 2005, the first of them at 3:32 p.m., it's from Dr. Cook to yourself and he writes, "Hi, Ken, I would like to thank you and your department for your ongoing efforts in

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helping us deal with this very difficult situation. We are getting a lot of pressure for faster reporting of the retro cases. In speaking to the 'powers that be' I have repeated to them that Mount Sinai is operating at full capacity and that resources are limited. This appears to be the general state of laboratory medicine today in Canada. There is very little flexibility in the system, especially when it comes to our pathology manpower situation and the shortages we are experiencing. If there is any way Mount Sinai can speed up the process, I would certainly appreciate it. In the meantime the issue if 'national standards for immunohistochemistry testing' will be on the agenda for our next executive meeting of the Canadian Association of Pathologists in late November. There may be a good opportunity to make this a national issue to bring to the Federal Minister of Health, along with the need for additional human and financial resources for our labs. Issues surrounding patient safety and national standards for all aspects of laboratory medicine. I will keep you posted on any developments. Many thanks. Signed Don Cook." And

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then the same day you responded to Dr. Cook at 6:54 p.m. saying, "Don, we have done 200 with 500 to go. As we were at capacity, we had just received a batch stainer which I'm told can go live next week, then the pressures will be on us for interpretation. We will try to get this stuff out as soon as we can. I had a good chat with Bev earlier in the afternoon. Cheers, Ken." So in mid November then, what was the state of affairs, Doctor?

DR. PRITZKER:

A. Okay, so it is 2:05, I appreciate being reminded. At this time we were undergoing a consideration of upgrading the technology in the immunohistochemistry laboratory and we were undergoing an expansion of our research services laboratory, and we were under a great deal of strain because not only were we at full capacity in our regular laboratory, we were close to full capacity in our research laboratory and we were trying to make efforts to expand both. So that was the scene. The batch stainer for immunohistochemistry works exactly the same way, it's actually manufactured, I believe, by the same company, as the other automated stainer, the ones in the routine laboratory are designed to have each

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slide stained with a different immunohistochemical stain; the batch stainer is designed so that you can put through many slides for the same stain.

COFFEY, Q.C.:

Q. If we could, please, exhibit P-1710?

DR. PRITZKER:

A. So Judith John is our--was, she just left, our communications and marketing individual and Jeannine Banack is the vice-president at the time who related to the laboratory and obviously when there are--when there is news that affects us, it's important to communicate that to the administrative folks in our environment, so that's what this letter is about.

COFFEY, Q.C.:

Q. And that says as of December 4th, 2005.

DR. PRITZKER:

A. Yeah.

COFFEY, Q.C.:

Q. It's an internal e-mail. And just one or two points in it I wanted to refer you to, the second last paragraph reads, "The amount of work involved"--and that's the work, the current cases for Newfoundland and the retesting--"the amount of work involved is very large and is a great burden for us, as we were

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pushing capacity with our existing work; however, we agreed to take this on as it was important to Newfoundland to have confidence in the repeated results and for Mount Sinai Hospital, this was a national service to assist patient care. Naturally the patients and the politicians in Newfoundland are anxious to have these studies completed as soon as possible. We are too, but realistically this will take a few months until everything is completed. Our peers in Newfoundland understand this well and are appreciative; however the pressures from the press and public continue. Signed Ken." So, Doctor, as of the beginning of December, 2005, I take it your earlier e-mail referred to this batch stainer and Mount Sinai had gathered, like the machinery resource that it needed to increase its capacity and I take it it was a matter of getting it, bringing that on line, getting slides produced and then allowing Dr. Mullen the opportunity to actually review the many, many slides?

DR. PRITZKER:

A. Yes, and we'd like you to take note of the date, it's December 4th, so that within two weeks, somewhere December 15th, the laboratory ordinarily

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starts to ramp down for two weeks to give people a break, but in this particular case we kept this process going through the entire season and I must say, at a personal cost of our folks who had to work through that period, but it was done.

COFFEY, Q.C.:

Q. If we could, please, exhibit P-1342? Doctor, this is two e-mails, but the one at the top of the page here from yourself, December 20th, 2005, 5 p.m. to Dr. Cook, copied to Dr. Mullen, Maria Mandes and Dr. Williams, you write and it's an update on ER/PR, "Don, as of today everything is tracking towards a successful completion at end of January, 2006. All the best for the holidays and the New Year. Signed Ken."

DR. PRITZKER:

A. Uh-hm.

COFFEY, Q.C.:

Q. So that is consistent with your memory that this was going on through -

DR. PRITZKER:

A. That's right and that's what was happening.

COFFEY, Q.C.:

Q. If we could please, exhibit P-1075? Again, there

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are a couple of e-mails here of January 9th, 2006, we're into. The first is from Dr. Cook to Brendan Mullen, effectively asking on behalf of the vice-president of Medical Services here in St. John's as to when they might expect to receive further results and Dr. Mullen, on January 9th, at 4:30 p.m., responded to Dr. Cook, but also copied you, saying "Yes, they will all be reported by the end of January. When do you plan to re-institute the ER/PR, HER2 assessment for the current cases? Signed Brendan Mullen." So I take it by that point and we'll hear more from Dr. Mullen on this, but it was anticipated, I take it at that point in time that Dr. Mullen would finish up his review of the retests by the end of January.

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. And there was at least thought being given by him and Mount Sinai at large that St. John's might be or asking when St. John's would be in a position to take on their own current work again.

DR. PRITZKER:

A. That's correct.

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COFFEY, Q.C.:

Q. And in that context, Doctor, well I'll ask you this, does Mount Sinai have enough work to do without doing Newfoundland's work?

DR. PRITZKER:

A. Well our challenge is on a continuing basis is to meet the demands of the work that's thrust upon us and we tend to be a place that gets asked to do things when other people can't cope or don't have the resources, and if we can't do it, there isn't another place where it's easy to get it done, so we try to accommodate what we can do and we try to grow our operation so we can sustain these kind of things, but it's a continuing exercise, I must tell you.

COFFEY, Q.C.:

Q. If we could, please, exhibit P-1711? Doctor, this is an e-mail from Brendan Mullen, Dr. Mullen of January 20th, 2006, it's to Dr. Cook but it's copied to yourself and others and Dr. Mullen writes, "Attached please find the ER/PR results for the Newfoundland and Labrador retrospective review. The initial report of the ER/PR results has been revised for seven cases due to restaining of the material

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when the initial specimen was negative and the internal controls were either negative or absent." And he names--he identifies those cases by number and continues "When you have the opportunity to review the results, I would like to discuss some of the technical difficulties we encounter with processing and staining of specimens. Some of the same issues are present in the current Newfoundland and Labrador material." And I'll be asking Dr. Mullen about that latter statement, but I take it then by the January 20th, 2006 from Mount Sinai's perspective, the end was in sight in terms of the retesting?

DR. PRITZKER:

A. Yes.

COFFEY, Q.C.:

Q. And this is your advice. Doctor, there is an exhibit I would like to refer you to, it's P-1713. I appreciate this is--it's an e-mail of May 16th, 2007 from yourself to Joseph Mapa?

DR. PRITZKER:

A. Yes, Joseph Mapa is the president of Mount Sinai, probably the most informed CEO about laboratories in the country because he and I had been working

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together on this for a very long time and again, that was--and Mr. Stationwala is the current VP who relates to laboratories.

COFFEY, Q.C.:

Q. And here, the text reads, "Breast cancer diagnostics, the media, TV, radio and newspapers have been discussing Newfoundland problem of unreliable results for breast cancer diagnostics with adverse patient consequences. Lab is blamed but it is also clear that lab was severely under resourced, consequences of 'picking on labs' for cost savings happens everywhere in Canada. A race to the bottom in cost without understanding patient care consequences. For this stuff, PLM was referenced lab to compare with original Newfoundland results. So far Mount Sinai hospital has received good press. Signed Ken." Now this, Doctor, would be just after this broke in the media nationally on May 15th.

DR. PRITZKER:

A. Uh-hm.

COFFEY, Q.C.:

Q. You were writing, I take it, to let your president know internally that if Mount Sinai's name came up,

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as it were, in the context it did, to give him at least a heads up this was doing on. You do, though, refer here to--and you've got it in quotes "picking on labs for cost savings". Doctor, you've got a long career and what did you observe over the years in terms of that?

DR. PRITZKER:

A. The laboratories are obviously a vital and central portion of health care, but they're also one which is one step removed from the patients, so whenever they--whenever there is pressures on a health care system, the word goes out that it should be clinical care that should be preserved and that everything else should be truncated. And unfortunately the laboratory--it becomes interpreted that the laboratories should be one of those areas for "cost savings". There is also in Canada a private laboratory industry which, by and large, works in ambulatory care, not in hospital care, which has a whole different rhythm to it. They, naturally, proclaim that they're great and that the hospital laboratories are extraordinarily expensive, but in fact that's not the case, the hospital laboratories are doing different things under very different

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conditions, even if they're doing some of the same tests, they're doing it under very different conditions. It's one thing to provide a test on a batch basis, it's another thing to provide a test in five minutes, this type of thing. So where this is a private e-mail, perhaps, as part of my efforts to share information and view points with the administrative leadership of Mount Sinai, but I would stand by the statement.

COFFEY, Q.C.:

Q. Yes, and that's why, in fact, I gathered, that's why I raised it because at exhibit P-1714 please? This is an e-mail, Dr. Pritzker from yourself, May 19th, 2007 to the same individuals. I'm not going to take you through it, it's just, I gather it's more, the same sentiment, just more elaborated upon.

DR. PRITZKER:

A. That's correct and I haven't seen the details beyond the screen there, haven't looked at that for some time, but I can say that the efforts by our staff were no less than extraordinary, it was really quite complex, there was a very, very large amount of work and it was done as best we could and I think as far as I could see, it was a model of its type and I

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really would--wasn't aware of where else there was a precedent at that time.

COFFEY, Q.C.:

Q. And if we could, please, exhibit P-0978? Doctor, this is a letter of July 19th, 2007, it's from a Robert Thompson, the Deputy Minister of Health in Newfoundland at the time, addressed to yourself and he writes, "I'm writing in follow up to your conversation on Tuesday, July 17th with Mr. Don MacDonald of the Newfoundland and Labrador Centre for Health Information. As Mr. MacDonald noted, the Department of Health and Community Services is carrying out a review of events surrounding ER/PR testing of breast cancer patients in Newfoundland and Labrador." And he goes on at some length and concluding with "Specifically I am requesting the following data fields for the period of January 1, '97 to December 31, 2005." And he has fifteen different types of data specified, so he's looking for, I take it, information at that point. If we can look, please, at exhibit P-0990? And this is a letter on Mount Sinai Hospital letterhead, Pathology and Laboratory Medicine. It's August 3rd, 2007, to Mr. Thompson, it's from yourself and it--you write,

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"Dear Mr. Thompson, thank you for your letter of July 19th, 2007 enclosed. Mount Sinai Hospital will be pleased to provide the information requested in database format to the Government of Newfoundland and Labrador in the very near future." So I take it that even after the retesting was all done, when the government approached Mount Sinai in the summer of '07, you undertook to provide the data requested?

DR. PRITZKER:

A. Yes, I want to comment on this.

COFFEY, Q.C.:

Q. Yes.

DR. PRITZKER:

A. The request was for extremely sensitive data which is very patient specific and so what we did was we actually validated all of the people who were asking this were the people who were supposed to be asking for this, that the data would be kept confidential, that the--and that no patient specific data would be revealed and we received those assurances, we validated those assurances and we then undertook to transmit the data in the most confidential way that we were advised could be done.

COFFEY, Q.C.:

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Q. And in terms of that, and I did skip over a couple of lines, in exhibit P-0990? Page 3, in fact, that's the letter from Mr. Thompson of--if I could, Doctor, of July 19th, 2007. He concluded by saying, "I assure you that any data provided by Mount Sinai Hospital to the Centre for Health Information on behalf of the Department of Health will be held in the strictest confidence and will only be used by the Department of Health in carrying out the aforementioned review." So there was certainly that assurance given.

THE COMMISSIONER:

Q. Mr. Coffey, when you find a convenient place, we'll take the afternoon break.

COFFEY, Q.C.:

Q. Doctor, one question I did have in the exhibit we looked at just several minutes ago, you did refer to the idea that the problem in Newfoundland is perhaps due to or at least the laboratory in Newfoundland was perhaps under resourced. What was your source of that knowledge? What led you to believe that?

DR. PRITZKER:

A. The source of that knowledge was, I guess, periodic discussions which I had had with Don Cook and with

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probably others that were more informal, of what the resources were like compared to resources enjoyed by other hospitals which we knew.

COFFEY, Q.C.:

Q. And had you met Dr. Cook before this particular matter?

DR. PRITZKER:

A. Yes.

COFFEY, Q.C.:

Q. How long have you known Dr. Cook?

DR. PRITZKER:

A. It goes back some way.

COFFEY, Q.C.:

Q. Okay.

DR. PRITZKER:

A. I know him as a professional colleague at national meetings and this kind of thing.

COFFEY, Q.C.:

Q. If we could break, Commissioner, thank you.

THE COMMISSIONER:

Q. Take the afternoon break.

(RECESS)

THE COMMISSIONER:

Q. Please be seated. Mr. Coffey.

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COFFEY, Q.C.:

Q. Thank you, Commissioner. Doctor, one final question, national--for example, national standards for laboratory medicine, or standards applied nationally, what sorts or organization or organizations would be required to be engaged in order to formulate such standards?

DR. PRITZKER:

A. Well, it starts with the professional societies, not just the physicians but the other professional societies. There are regulatory groups, such as the Royal College of Physicians and Surgeons of Canada, but really that's a regulatory group for examination standards and continuing education standards. In order to have standards that are implementable, both provincial advocacy groups, provincial medical societies, technology organizations and provincial regulatory groups, such as the, in Ontario it would be the College of Physicians and Surgeons of Ontario, might need to be involved. In Ontario, in a lab field, there are two organizations, one is the Ontario Laboratory Accreditation, which is mandatory and is really run as a joint effort by the Ontario Medical Association and the Ministry of Health and

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Long-term Care and also the sort of long-standing program, the Quality Management Laboratory Services, which involves proficiency testing and other kinds of audits. So it's actually quite a large set of groupings to promote standards. I would say though that it's not--we're not looking at national standards. It should be the same standard wherever these procedures are done, in whatever country it's done, whatever jurisdiction it's done, and we need to not invent our own wheel with respect to the standards, but to work together to be part of really it's an international effort and increasingly, that seemed to be so.

COFFEY, Q.C.:

Q. And where laboratory medicine is concerned, and in particular, immunohistochemistry, IHC, I take it, are they almost there or just beginning?

DR. PRITZKER:

A. Well, in all of the technological developments, it's rare you get to the end. It's a continuing evolution. It turns out that staining itself, specific staining, is an art form that's been very useful and it's been a substrate part of our infrastructure for about 150 years, and it's

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gradually becoming a science or the science is gradually becoming incorporated into it and it's gradually going from a qualitative science to a quantitative science, and we're just really at the beginning of the quantitative aspects of it.

COFFEY, Q.C.:

Q. I take it that translates into we still have -

DR. PRITZKER:

A. We have a long way -

COFFEY, Q.C.:

Q. - you're never ultimately -

DR. PRITZKER:

A. We have a way to go. We have a way to go here, but it's compounded by the fact that it's not something that's totally new. It's something that's been with us for some time and those processes, to remodel those processes and to move those processes forward is actually more work than something which would come about as a brand new advance.

COFFEY, Q.C.:

Q. Thank you, Commissioner, they're the questions I have. Other counsel might have some questions for you, Doctor. Thank you.

THE COMMISSIONER:

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Q. Mr. Pritchard?

MR. PRITCHARD:

Q. Commissioner, I have no questions for this witness. Thank you, Dr. Pritzker.

THE COMMISSIONER:

Q. Mr. Simmons?

DR. KENNETH PRITZKER, EXAMINATION BY MR. DANIEL SIMMONS

MR. SIMMONS:

Q. Thank you, Commissioner. Good afternoon, Dr. Pritzker. I'm Dan Simmons. I'm the counsel for Eastern Health. Thank you very much for making the trip to share your knowledge on this subject with us. You, I understand, have been involved in pathology laboratory medicine since before immunohistochemistry was a regular and standard part of the testing processes, I believe?

DR. PRITZKER:

A. That's correct.

MR. SIMMONS:

Q. Can you give us maybe some overview of how immunohistochemistry has grown over the time that you've been involved in laboratory medicine, and some appreciation maybe of whether the complexity of the tests have increased and what maybe the

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significant changes or challenges have been with IHC testing, as you've seen it over the years? Big question.

DR. PRITZKER:

A. Sure. Well, when I began pathology, and that's close to 40 years ago, there were antibodies that were used to stain tissues to determine the presence of particular substances. They were florescent and there were very few of them, maybe three or four that were in common use. The change to a method which could use a bright field microscope, an ordinary microscope, started to occur in the mid 1970s and I recall was initially one stain, and it was a stain that could be used to assist the pathologist to provide some information about what type of tissue, what type of cells was there, but was not related in any way to a therapy that was being offered.

Somewhere in the early 1980s or around 1980, there was the beginning of automation and year by year, the numbers of these tests increased, and by the 1990s, the automation was quite extensive and there was conversion of methods that had been previously done by chemistry techniques, such as the

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ligand assay for the estrogen receptor and progesterone receptor to immunohistochemical techniques. So it was growing and growing.

I can say that at the present time, in our laboratory, we have about 150 antibodies, which estrogen receptor and progesterone receptor are only two. That our volumes are increasing disproportionate to the number of specimens and to the growth in other work in our laboratory. So it's a very, very substantial thing and growing and continuing to grow. It's also, with--perhaps it's about five to seven years that there's been attention to trying to determine these assays with some increasing quantitation. I believe that Dr. O'Malley explained to you that the current standard is zero or one plus, two plus, three plus. Those are reasonable ways of dividing off the results. They compare reasonably well whether you put some numbers on the one plus, two plus or three plus or whether this is done by the subjective judgment of a pathologist or qualified delegate, but it's not good enough--well, it's not optimal, because there's still a greater range of prognosis within each of those categories than might be warranted if we had

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better ways of quantitation. There's a great deal of effort going on, in our place, but also in other places around the world, to try to achieve this.

MR. SIMMONS:

Q. So in relation to the ER/PR test specifically, which you're speaking of now, I understand, although the test is, I think, quite useful, I understand to be quite useful as it's currently applied, I gather you'd be suggesting that there's still much room for improvement in how you quantify the results of the test and use it in the clinical environment?

DR. PRITZKER:

A. That's correct. In many different kinds of processes in medicine, there are things which we would like to be able to do and which people are working to try to achieve.

MR. SIMMONS:

Q. You mentioned earlier some of your observations regarding when times are tight in health care and resources are scarce, it's the direct patient care that gets the emphasis and services like laboratory are often put in the second rank, where resources are applied. I'm paraphrasing. You expressed it much more eloquently. Am I right in recalling that

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it was during the 1990s, the late 1990s, that health care in Canada went through a period of restraint, starting with the Federal Government and restraint in the money that the Federal Government was putting into health care, transferring to the provinces for that purpose. Recall that as being around that time period?

DR. PRITZKER:

A. I certainly did.

MR. SIMMONS:

Q. Does that coincide reasonably well with some of this period in the growth of complexity and numbers of tests and the demands on the immunohistochemistry services in Canada?

DR. PRITZKER:

A. First, I would like to say that the pathology lab medicine services are direct patient care.

MR. SIMMONS:

Q. Yes.

DR. PRITZKER:

A. They're not always recognized that way, but they are direct patient care, and I would like to emphasize that to you and to others. There was a constraint that started in probably the late 80s, early 90s,

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that related to patient care in a very--that resulted in a very substantial squeeze on laboratory services, which that was never really the subject of largesse. So we were always marginal. So we had the squeeze at the same time as where we've experienced throughout my career, a continuing growth in terms of the advocacy and demand for laboratory services and this growth is accelerating actually. Laboratory services are becoming more relevant to health care than ever and so it's a greater challenge for us to obtain the resources to get this work done well.

MR. SIMMONS:

Q. I expect you'd agree with me that Mount Sinai is regarded as a leader in Canada in areas such a immunohistochemical testing and laboratory services.

DR. PRITZKER:

A. We try.

MR. SIMMONS:

Q. Through those time periods where resources have been scarce and demands have been growing, how has Mount Sinai coped with those pressures and maintained its quality of service in the immunohistochemistry area?

DR. PRITZKER:

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A. Well, we have had some special opportunity and the special opportunity for us came about that independently of the services which we provided for patients, we've been providing services for industry, same kinds of services. So it's basically been a process of mixing and matching those resources that have enabled us to be able to cope with this.

MR. SIMMONS:

Q. So the services provided through your research laboratory then, if I understand correctly, may have provided some financial supplement to the services that you provided to your clinical lab and from what Dr. O'Malley has told us, also meant that you had to apply very stringent standards in the research lab performance of this testing.

DR. PRITZKER:

A. That's correct. That is one of the key factors. The other is that we deliberately set out to recruit individuals who would be leaders in their fields. They develop their own research and they also develop their own connectivity to other leaders in the field. So we basically have early warning, if you will, certainly knowledge of what's out there,

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what's coming down the pipe and so on.

MR. SIMMONS:

Q. We've heard quite a bit in the media, certainly here, and I think somewhat nationally in recent months about a national shortage of pathologists, difficulties recruiting and here in Newfoundland certainly in retaining. What has your experience been at your institution with recruitment and retention of pathologists and finding enough qualified people to meet the requirements that you have?

DR. PRITZKER:

A. Well, it's exceptional. We have--first, there was a time in the mid 90s where they virtually cut off the training of laboratory physicians, and making it very difficult for anybody to recruit, because the supply had been cut off. That was a unwise decision, but that was the health planners' decision. It wasn't ours. At Mount Sinai, we have to recruit not only people who are competent, but people who have got a special interest in a subject and people who are interested in the academic side, the research and teaching. So it's a very specialized pool. To do so, basically we've had to

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do long range planning and we've managed that reasonably successfully. I think our faculty is quite good and knowledge of it is quite good. But it takes some time to recruit folks. We've been fortunate in our place, with all the difficulties, to provide an environment to retain these folks and the folks that have moved on from us have actually moved to positions where we couldn't hold them because they were going to a senior leadership position somewhere or something like this.

MR. SIMMONS:

Q. Are there any particular advantages to being able to retain pathologists in your service for a longer period of time, versus having them move on and be replaced by others?

DR. PRITZKER:

A. Yes, there's huge advantages, not only for pathologists, but for other staff. Also, just while my mind's on it, say that the shortage is beyond pathologists. It's also technologists.

MR. SIMMONS:

Q. Yes.

DR. PRITZKER:

A. And you should be aware of that. The advantage is

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that it takes time to build and operate a culture where people are talking together and understanding each other and so continuity within the department, continuity between the professionals on the lab side and the clinical people is extremely important in building quality of care.

MR. SIMMONS:

Q. Okay. How do these things, your Mount Sinai's ability to cope with financial pressures in the IHC lab, the recruitment and retention of pathologists and technologists, in your observations, how do those compare with what you've seen in other institutions in Ontario or in Canada and their ability to cope with those kinds of pressures?

DR. PRITZKER:

A. Well, it's fair to say that we've done better in terms of coping than our peer institutions, but we're also the only laboratory that was not subject to any mergers, amalgamations, or other kinds of disruptions over that period. We're the only--I wouldn't call it survivors, but the only people who managed to emerge from this without any interruption to our programs.

MR. SIMMONS:

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Q. And I gather you perceive that as having been an advantage not to have had to participate in mergers and amalgamations?

DR. PRITZKER:

A. Yes, it was actually quite difficult to achieve, but it was a very major advantage.

MR. SIMMONS:

Q. Right, and what are your observations about what disadvantages there may have been to others who had to go through mergers and amalgamations in this period?

DR. PRITZKER:

A. Well, there was inevitable discontinuity of organization.

MR. SIMMONS:

Q. Um-hm.

DR. PRITZKER:

A. I can't speak to specific situations because I wasn't inside them, but I can--we can see from the Ontario experience where they had a wholesale change of services about circa year 2000 that there was a period of time, two or three or four years where there were a lot of difficulties in just obvious communication because people either had just arrived

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or they were just departing or they weren't there, and that was reflected in the kinds of work that was referred to us, for example. But I can also say that as those organizations rebuilt themselves, so the last couple of years, for example, they're becoming stronger and stronger and it's going--but there is an opportunity cost, there has been an opportunity cost related to the quality, related to all of the various kinds of mergers and reorganizations. And unfortunately, there hasn't been very much in the way of achievement in what was set out to be done, which was cost savings, if one looks very hard at this. That's not to say that reorganization shouldn't ever happen but they have to done with care.

MR. SIMMONS:

Q. You've mentioned that in Ontario there is a program for laboratory, I think it's accreditation, that's the QMPLS program?

DR. PRITZKER:

A. That's more proficiency testing. The accreditation is a separate body.

MR. SIMMONS:

Q. Okay. So there is accreditation for laboratory

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services in Ontario?

DR. PRITZKER:

A. That's correct.

MR. SIMMONS:

Q. And that's a provincial accreditation?

DR. PRITZKER:

A. That's correct.

MR. SIMMONS:

Q. Are you familiar with the, I'm sure you are, with the Canadian Council on Health Services Accreditation, CCHSA?

DR. PRITZKER:

A. That's right, they're now Accreditation Canada, I believe.

MR. SIMMONS:

Q. Oh, okay.

DR. PRITZKER:

A. They've changed the name once again.

MR. SIMMONS:

Q. Okay. Can you tell me, if you can, what kind of role the accreditation services provided by CCHSA plays in looking at laboratory services if, in fact, it does at all?

DR. PRITZKER:

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A. Sure. That's evolving. In the past they would accredit hospitals on a periodic basis, usually every, at one point it was every four years, but say every three years, and it was a comprehensive accreditation of which the laboratories were a very small part.

MR. SIMMONS:

Q. Um-hm.

DR. PRITZKER:

A. And what they were looking for in the past was that the standards were there. They were looking to see that the standards were actually implemented on the ground.

MR. SIMMONS:

Q. Um-hm.

DR. PRITZKER:

A. That's all changed. And in the current, past two years, they've become, that particular organization has changed its philosophy completely, and as I understand it, the accreditation process now is one which involves tracers of activity. So the auditors would come in and they would say, well, I want to look at this, and then they would go up and down that process to see that it was being done as it was

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said to be done.

MR. SIMMONS:

Q. Um-hm.

DR. PRITZKER:

A. That's a much more hands-on, real-time exercise and one which is, in my view, much more beneficial for quality processes. It's also a process which is similar to the good laboratory practices process which we have been experiencing in our place for many years.

MR. SIMMONS:

Q. Right, okay. You've told us that in your laboratory you have, I guess what we could call dedicated people whose job it is to promote quality initiatives within your laboratory services. And how long have you had that, those positions in place, that program?

DR. PRITZKER:

A. We put this in place at the time of the crunch of services where we--in 1993. So we had to shrink the laboratory, it was mandated that we do this, and we decided that if we were going to do this, we were going to, within the budget that was remaining, put in sufficient funding to have high quality and to

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have a quality program and then we had a few other things which we wanted to do, and we did all that.

MR. SIMMONS:

Q. At that time when you were shrinking the laboratory program, was there any consideration given to putting the responsibility for quality initiatives on those people who were managing the daily activities of the lab versus creating the separate positions?

DR. PRITZKER:

A. Well, it's both.

MR. SIMMONS:

Q. Yes.

DR. PRITZKER:

A. The individual was, the best way to describe it is a coach.

MR. SIMMONS:

Q. Yes.

DR. PRITZKER:

A. Okay. And the quality is part of the responsibility of all of the folks in the laboratory irrespective of their qualifications. And our desire at that time was to standardize protocols across sections of the laboratory to ensure that the operations were

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according to the protocols and there were two ideas behind it, one idea, of course, was to raise the quality and partly as it differentiated and partly because that's what should be done, and also if we could put a system of quality across the entire laboratory and do it in a uniform way, our overheads would be, would decrease. Ultimately once you achieve quality, that's the cheapest way to go.

MR. SIMMONS:

Q. Okay. You were asked, I think, if you are aware of any other situation analogous to what happened here in Newfoundland where the hospital here asked your institution to do a retest for a seven-year period, a look back. I believe I understood you to say that you weren't aware of anything like that having been done previously?

DR. PRITZKER:

A. That's correct.

MR. SIMMONS:

Q. So to your--had you been asked back in--maybe you were, back in 2005 by anyone from Newfoundland is there anyone we can go to whose got some experience with this to give us some help as to how to handle this large retesting issue, would you have been

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aware of anyone who had had any kind of experience like that?

DR. PRITZKER:

A. Well, certainly if had been or we had thought of it, we would have mentioned those folks, it was--we want to try and have the work done, any work done in the place where it's most appropriate.

MR. SIMMONS:

Q. Yes.

DR. PRITZKER:

A. Yeah.

MR. SIMMONS:

Q. I was thinking more in lines of advice about how to manage the issue, someone who would give them something like that for -

DR. PRITZKER:

A. Again, again if there is any--if we had thought of it or we could have thought of where to go, we would have asked for the advice ourselves.

MR. SIMMONS:

Q. Oh, yes, I'm sorry, I misunderstood.

DR. PRITZKER:

A. Or we would have directed the folks in Newfoundland to those people.

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MR. SIMMONS:

Q. So there was no where you knew to refer?

DR. PRITZKER:

A. No. We did, we did discuss this, as well, we did do a small literature search to see whether there had been case studies that could be helpful to us, but we didn't find very much.

MR. SIMMONS:

Q. Um-hm, okay. And finally, I wonder if you want, it's up to you, I'm interested in knowing if you have any views on where the delivery of complex lab services is going or should be going in Canada, because the complexity has been increasing, the demands have been increasing, is there a direction that you foresee that's a preferable way to manage these issues in the country in the future?

DR. PRITZKER:

A. Well, this a question which, of course, we could spend a lot of time on and which we've had a lot of thought about and talked over the years about. The lab services are complex services, no question about that. And part of the complexity involves the intimate interaction with both the clinical folks and the support folks, so that it's not possible to

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have one large regional laboratory, sort of one restaurant in town.

MR. SIMMONS:

Q. Um-hm.

DR. PRITZKER:

A. Because if you do this, then the interaction with--it's very difficult to maintain the interaction on the clinical side. It's also not possible to do every test in every laboratory.

MR. SIMMONS:

Q. Um-hm.

DR. PRITZKER:

A. And the traditional--the traditional way of operating regional labs and in Canada the historical way was to have one, in the small provinces, one laboratory in each province which would do high-end tests and the small laboratories would refer to that. It was basically a mountain and a plane model. The--we can't do, it's not a sustainable model because we need to have the expertise everywhere, so we need to migrate to a networked model. We need to be able to have a model in which the centres such as ours engage in peer review just as other laboratories do for all our services. And

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this creates some difficulties because if you're the only place in the province or the only place in the country, where do you get that peer review? Well, the answer is you get that peer review from a peer laboratory anywhere else in the world that was willing to work with you. And in our case we've done this with a few laboratories. The--strongly, I'm strongly in favour of this model of essentially capacitating the groups in the field, okay, that are out in the regions because it is important to be able to have local presence of the expertise that can work with the clinical peers, but that expertise has to be supported and supported on a peer basis by access to resources and assistants and interaction with more academic centres is the traditional term for it. We're now in a position--we weren't in a position that this could be done easily a decade ago, but we are in a position now that this could be done because we have the means of communication. This process today is being watched, I don't know how far away, but it's certainly available anywhere in the world, right now.

MR. SIMMONS:

Q. Um-hm.

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DR. PRITZKER:
A. And so is any of our expertise. So we need to learn how to exchange expertise amongst ourselves in new ways and I think this is imminently feasible.
MR. SIMMONS:
Q. Thank you, very much, Dr. Pritzker. I don't have any other questions for you.
COMMISSIONER:
Q. Thank you, Mr. Simmons. Mr. Browne?
DR. KENNETH PRITZKER, EXAMINATION BY MR. PETER BROWNE
MR. BROWNE:
Q. Thank you, Commissioner. Good afternoon, Dr. Pritzker. I did mention to you over the break that I may be introducing some articles. I think you have copies, you've just been given copies by the Registrar. But before I refer to them, I just want to follow up on a--there's two areas that I actually wanted to sort of canvas with you, Doctor, and the first relates to a question by my colleague, Mr. Simmons, concerning, I guess, the financial crisis facing labs in the early 1990s, and you explained how your institution dealt with that. And just to sort of tie that in with the whole evolution, the Romanov report dealt with, I guess, some of the

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problems that developed with the under funding of the health care system as a result of that time period. And am I correct in understanding that the Canadian Association of Pathologists, in fact, made a submission to the Romanov Report with regard to the effect of, I guess, these financial constraints on the lab system, and if so, are you aware of that?
DR. PRITZKER:
A. I believe they did, but I don't recall the details of what was said.
MR. BROWNE:
Q. Are you aware whether, in fact, it made its way into the Romanov Report in any consideration?
DR. PRITZKER:
A. I'm not aware of that detail and I'm not aware of either the status of either the Romanov Report or the Kirby Report on the impact of health care in this country.
MR. BROWNE:
Q. Thank you. The second area and I'll refer to those now, Registrar, if we could have entered, please, Exhibit 1727, Commissioner, please, and 1767?
COMMISSIONER:
Q. Entered.

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EXHIBIT P-1727 ENTERED INTO EVIDENCE.
EXHIBIT P-1767 ENTERED INTO EVIDENCE.
MR. BROWNE:
Q. Thank you. Doctor, this is, and this sort of follows on the last question you were asked by Mr. Coffey about--and you commented there's a need for international standardization in the area of immunohistochemistry. Did I understand that correctly?
DR. PRITZKER:
A. Yes.
MR. BROWNE:
Q. And, in fact, the article that I have here and hopefully will just walk through it in a minute, is from the Applied, or the Applied Immunohistochemistry and Morphology, the June, 2007 article. The individuals that are listed here, would you consider these leaders, I guess, in the field of immunohistochemistry, this Dr. Goldstein, Dr. Taylor among several individuals?
DR. PRITZKER:
A. Yes, I certainly know Doctors Taylor, Hewitt, Goldstein and they are, yes.
MR. BROWNE:

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Q. And this article is entitled "Recommendations for Improved Standardization of Immunohistochemisty" and is coming out in June of 2007.
CROSBIE, Q.C.:
Q. Can we see it?
MR. BROWNE:
Q. Sorry.
REGISTRAR:
Q. Which number is that?
MR. BROWNE:
Q. Oh, I'm -
THE COMMISSIONER:
Q. On my list is 1767.
MR. BROWNE:
Q. 1767, I don't have that. I apologize. Okay, sorry. And if we could just follow down here back to--we'll just see now, that's--it came out in June of 2007 and as you've acknowledged, several of these individuals--as a matter of fact, they're members of the ad hoc committee on immunohistochemistry standardization. Is this a committee--we've heard several committees from the United States referenced by Dr. O'Malley this morning, is this CAP or another committee?

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DR. PRITZKER:
A. I'm not sure who this particular committee reports. It says, in fact, it's an ad hoc committee. So, my guess is that it's a group of leaders in the immunohistochemistry field and I'm not sure of the journal, but I suspect that the journal is supported by this particular interest group in terms of -
MR. BROWNE:
Q. In effect -
DR. PRITZKER:
A. - (unintelligible) article, things like this.
MR. BROWNE:
Q. If we jump ahead to the end, Doctor, which is a good observation, you'll see and that's at page 130, acknowledgments that the ad hoc committee--sorry, let's go back here -
DR. PRITZKER:
A. It's the DAKO Corporation.
MR. BROWNE:
Q. The DAKO Corporation, correct.
DR. PRITZKER:
A. DAKO is one of the larger suppliers around the world of immunohistochemical reagents. It's reasonably standard practice for large corporations to provide

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grants in aid to professional groups to try to work towards developing standards.
MR. BROWNE:
Q. Okay. And in fact, if we look at what's in that acknowledgment section for a moment, it says that this meeting was held in, these recommendations in the body of this article flow from a meeting in August of 2006 in Santa Barbara which seems to suggest that this was the first ever international course on immunohistochemistry molecular morphology
DR. PRITZKER:
A. Well, it would not be the first course on immunohistochemistry, far from it, right, or it would be--these individuals together or separately have, I know Dr. Taylor for sure, has provided courses in other venues that would relate to how to do immunohistochemisty towards standardization. What this represented was a group of experts meeting perhaps for the first time in this context to try to address the issue of standardization. And what they appear to have done or what they have done and I have read this article before, was they collated the literature and put in order many of the considerations that are required, that they feel are

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required for quality immunohistochemistry. All of this is dependent on the current state of immunohistochemistry reagents.
MR. BROWNE:
Q. Right.
DR. PRITZKER:
A. That's a very important statement. As the reagents improve, then the kinds of things that would have to do, the numbers of checks and balances, the quality, all kinds of things like this might change as the reagents become more robust.
MR. BROWNE:
Q. Okay.
DR. PRITZKER:
A. The reagents are quite robust now, but as you can see from this ten pages or so, there's a large number of very specialized conditions that are required to achieve an excellent result. The object of the exercise would be to achieve the standardization and also to reduce the number of preconditions in order to achieve that quality.
MR. BROWNE:
Q. And if we could, if we look at the first page, Doctor, you'll see the first paragraph, third line

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there says, "recognized over a decade ago that IHC assay standardization was vital for reproducible and reliable results". Do you see that sentence? If you drop down, it says in the second paragraph on the right hand column there, it says, "despite the improvements of reagents automation", excuse me, "authors of the years have consistently noted inconsistent quality of IHC assays". So, I guess what the authors are saying is that even in 2007, there's still inconsistency noted despite all these articles and -
DR. PRITZKER:
A. That's correct and where it says that prior consensus conferences identified the likely causative factors, that was actually published and it was published in year 2000, that's reference 14.
MR. BROWNE:
Q. But despite that, these authors recognizes there's still -
DR. PRITZKER:
A. Still problems.
MR. BROWNE:
Q. - problems. And, in fact, just to go over to the next page, if we could, page 125, you'll see, the

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right hand column again, the first full paragraph beginning with, and I'll just--just bear with me. Okay, I'm on the right page and I'll put my cursor there. You'll see, actually, I have the cursor there, "given the increasing role IHC assays play as a predictive marker of oncology therapeutic agent response, faster turnaround time and laboratory costs containment should not be priorized as goals ahead of the laboratory procedures required for reliable, accurate and reproduced by IHC assays". So, this again comes back to the point, I think you've been making throughout your testimony here today, that there has to be recognition that these things do, cost containment measures and so on will have an effect on the end product.

DR. PRITZKER:

A. Yes, the costs, whatever they are, are very small fraction of the costs for patient care that result. And if the patient care proceeds without the quality laboratory result, essentially it's an appropriate utilization of services. And with the predictive markers, these are ones which, on the basis of the task, a therapeutic decision is made, the potential for cost savings and the potential for decreased

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patient risk by high quality laboratory testing is extreme. We're talking about yes or no to therapy which is potentially in the tens of thousands of dollars per patient and has, and therapy, which has its risks which--so, the therapy shouldn't be offered to patients that have a small chance or no chance of benefitting from that therapy.

So, all of this is relatively new, the realization of this is relatively new. Even though the HER2/neu marker has been around for some time, the realization that it does have this kind of cost benefit impact is new and the idea that the test must be done at recognized high quality is relatively new.

MR. BROWNE:

Q. We heard from Doctor O'Malley this morning, Doctor, that in fact, sort of the whole role out has been turned on its head, for instance. HER2/neu has come out and there are standards in place as it is coming out, whereas that wasn't the case for IHC and ER/PR, these standards are now only starting to become developed, isn't that the case?

DR. PRITZKER:

A. Yes, there's the evolution of this is quite

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interesting. The estrogen receptor, progesterone receptor story is one that evolved over 40 years. The Her2/neu story is one that has evolved over somewhere about 15 to 20 years, actually, since the beginning of it. I'm now involved in the next one, which is K-ras testing, which has evolved over six months. So the pace of pressure on us to evolved testing is increasing very dramatically and it's actually happening faster than any part of the system can absorb at the moment, but it is there and from a patient standpoint it's a very good thing. We're now having more and more powerful diagnostics which affect therapeutics. This trend is going to increase and the rate of ascent of this trend is going to increase for the foreseeable future.

MR. BROWNE:

Q. Doctor, just moving ahead on this article, as a matter of fact, what I've attached, as well, is an interview which came out as a result. Now, Doctor, just on that point, to go back to your answer, while I might find this, is any of this sort of change in approach due to cause and effect given what has happened with ER/PR that it's recognized that we now need to come at this in a different perspective and

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develop these standards much more early on in the process?

DR. PRITZKER:

A. Absolutely.

MR. BROWNE:

Q. Okay.

DR. PRITZKER:

A. You know, traditionally the way the testing goes from the research laboratory to the service laboratory is to adopt and refine a research-based test. Increasingly that's not the case. What's happening in most recent times is that a test is offered on a service basis or would be offered on a service basis after the reagent has been perfected and validated sufficient for national regulatory authorities such as Health Canada and the FDA in the United States. And increasingly it would be a standard analyte specific reagent, the standard reagent for the test that was manufactured would be very consistent rather than in the remote past where some of these things would be made in a adjacent research laboratory.

MR. BROWNE:

Q. Now, Doctor, what I have on the screen here now, is

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at 1767, page 11, is, in fact, a question and answer session with the same authors. And I just want to sort of go over a couple of points, the first, and it's in relation to the recommendations that these authors made. And you just note here in bold type that the authors seem to suggest that right now we're stuck with formaldehyde, that's the best alternative we have for fixation and there's--it's because especially in relation to immunohistochemistry it's the most proven fixative in terms of the assay results. Do you agree with the authors in respect to that observation?

DR. PRITZKER:

A. Well, I would say the statement in bold is a provocative statement. The, I guess it's at the back here, so I can actually read it. It's a provocative statement in that, in fact, formalin is quite safe used in appropriate ways. It's a natural product that is present in our environment. Obviously if it is used in an uncontrolled setting, it does cause irritation and so on, but we have occupational standards which are applied that ensure that in Canada, at least, that the environment is quite safe. We actually monitor formalin in our

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laboratories. So it is, well, so it is safe and it is a--it is cheap and it is effective. And there are, from time to time, novel ways of trying to fix, fix tissues. And what we're trying to say is, when we say fix tissues, is preserve the capacity to identify the molecules, in the case of immunohistochemistry, that's what we're trying to do. So there are ways of doing it, methods such as freezing, which has its own difficulties, microwaving is another technology. So I do expect the technologists to change and to evolve, but I don't see replacement of formalin fixation in the very near future.

MR. BROWNE:

Q. And if we just carry on further down, there's another comment there you'll see in the centre of the page, "So far no one has enforced any rule about fixation and no one has really tried." So I guess is there, again, another provocative statement, from your perspective?

DR. PRITZKER:

A. I think so, I think it is provocative. Most laboratories are very well aware of the properties of formalin and other fixatives, particularly

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alcohol fixatives and we are aware that the capacity to fix tissues decreases, for example, with time as they--as the materials become exposed to air. We're aware of, we're aware of some of the other difficulties that you need certain volumes of fixative to the amount of tissue that the, cutting the tissue in thin enough slices to get penetration in fixation is important and all that kind of thing. That's wide--that's in textbooks that histology technologists know and pathologists know and most laboratories apply that knowledge with care.

MR. BROWNE:

Q. Okay. Now, further on down, and maybe these are all provocative statements, Doctor, you'll see in the left-hand corner, at least on my screen, a question with regard to quality assurance standards and referenced by several--answers by several of the pathologists. And there's a reference by--or an answer by Dr. Yaziji, "The best quality control method standardizing IHC are across the Atlantic and north of the border. There is ample data to suggest that CAP proficiency testing doesn't come close to the European and Canadian systems." Are you able to comment on that statement?

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DR. PRITZKER:

A. Well, okay. So remember, this is -

MR. BROWNE:

Q. This sounds like an open mic session with these -

DR. PRITZKER:

A. This is an open mic session in a non-peer review publication that's trying to generate interest in the standardization of immunohistochemistry, and I think it has to be taken in that context. The quality control methods and quality assurance methods that are used by the College of American Pathologists are used by our laboratory and other laboratories which has CAP inspections and has had inspections locally and by--we participate in some European groups, as well. They all have different flavours, but the quality of--and they're already useful or we wouldn't be participating in them. But none of them assure the quality in the laboratory by themselves. The assurance of quality in laboratories is the implementation of quality in the laboratory and so what is needed then is the capacity to have a really a peer review sampling of what is actually going on in the laboratory, a peer review first within the laboratory so that there's

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transparency of the quality processes within the laboratory by folks who are both involved in a particular process and the folks who are distanced from a particular process but are involved in quality. And second, peer review from these other kinds of exercises and a variety of them. I think blanket statements are unwarranted, they are very good laboratories in many different countries, including the United States, including Europe and including Asia and I've visited many of those laboratories on the ground and I know what they do and I've learned from them and so have my colleagues. So it's not a simple thing and it's not a matter of "policing", there's too many things to do and in terms of what needs to be done to ensure quality, so it's really a culmination of a mindset and a mindset that ensures that what we say we are doing with quality is actually done.

MR. BROWNE:

Q. Now, Doctor, I think within the body of either this article or the previous one, there is some suggestion by these authors that while that is the case, it is involved on an individual lab basis and hence the problem and the need, I guess, for

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standardizing and more importantly sharing this information among the colleagues. You'll see in the last comment there, I'm just pointing out with the cursor about the question to each of the panel members about the fact that significant changes have happened over the years at a very fast pace and I think it's up at the top here as well, sorry, "there are major developments going on in the field and it is impossible to keep up with all aspects of scientific and technological developments" and that's Doctor Badve and then you'll see Doctor Taylor who says here, it requires a coordinated and global response, which I think you've mentioned as well earlier I think in answer to Mr. Simmons' question. So I think despite all the controversy around these statements, would you agree with the last sort of observation of the pathologists?

DR. PRITZKER:

A. Well certainly we do need to have ongoing continuing efforts towards both modularization and standardization of health care, including laboratory services, including the technical aspects of the lab services and including, really essentially including immunohistochemistry. It's, the state of health

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care that these efforts which, while they may in some places be locally based, provincially based or nationally based, are in fact international. They are occurring in many aspects of health care at the moment, not just the laboratories, as you're aware, and they are a very good thing, and most of us or I would say many, many people have--are participating in various initiatives and learning the principles of how you develop this kind of consensus. I also have to say that developing consensus and standardization is not a simple thing.

MR. BROWNE:

Q. Right.

DR. PRITZKER:

A. It really isn't.

MR. BROWNE:

Q. Could you explain that to the Commissioner, how that sort of approach developed, please?

DR. PRITZKER:

A. Sure. Well it's obviously needed because you have to have one standard--it's desirable to have one standard of communication and you have to have a best practice environment. It has to be in such a way that it's not so rigid that everyone is doing

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exactly the same thing because everybody could be lemmings over the cliff type of approach. And what happens at the beginning of these processes and I have been involved in these processes is that people come with very different protocols, each one thinking that theirs is the best, and absolutely convinced. And first there's a discussion as to what are we looking for anyway, right, and then there's a discussion of how--what are the options to achieve it and a review of how each of the different protocols has achieved it. The next step after that is to devise a standard which can be adhered to by most competent organizations who are doing the process. If one has a process that can only be done in lab A and no place else in the world, it's not a standard because lab A can't do all the work. So these or clinic A can't do all work if it's a clinical standard, so it is--there is a evolution of these processes and typically from a first meeting to the first set of standards is somewhere between two and four years. You might be able to shrink that a bit, but that's the conversation time that it requires to evolve these standards.

MR. BROWNE:

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Q. That's all the questions I have. Thank you very much, Doctor. Thank you, Commissioner.
THE COMMISSIONER:
Q. Thank you, Mr. Browne. Mr. Pritchard?
MR. PRITCHARD:
Q. No questions, Commissioner.
THE COMMISSIONER:
Q. Ms. Newbury?
MS. NEWBURY:
Q. I just have a couple.
DR. KENNETH PRITZKER, EXAMINATION BY MS. JENNIFER NEWBURY
MS. NEWBURY:
Q. Good afternoon, Dr. Pritzker, Jennifer Newbury for the Canadian Cancer Society, Newfoundland and Labrador Division. I just want to ask you a couple of questions. First of all, you mentioned that there were some capacity issues I guess it was straining the limits of the capacity for Mount Sinai in assisting Newfoundland in the retesting, as well as the current testing. And I'm just wondering in light of that, do you know why your lab would be chosen given those concerns that you had regarding capacity?
DR. PRITZKER:

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A. Well I understand from conversations other labs were asked as well, they--I think our lab was asked because we have a reputation for trying to help other labs, that's probably why we were asked.
MS. NEWBURY:
Q. Okay, so there were other labs that could have done it from an experience, I guess, or reputation point of view, but were these other labs also experiencing capacity issues?
DR. PRITZKER:
A. I can't comment on that, I would doubt that there would be any laboratory in Canada that would have had spare capacity.
MS. NEWBURY:
Q. Okay. And you were also asked a bit about the look back, I guess, or the retrospective review and the fact that you weren't able to find any research regarding a retrospective study, did I understand your evidence correctly on that, you were looking how press correspond -
DR. PRITZKER:
A. We did look, I can't say we looked extensively, we looked at what was easily available to us or what we thought was easily available to us for similar

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situations.
MS. NEWBURY:
Q. Okay, and you weren't able to find anything--I just want to understand -
DR. PRITZKER:
A. No, we didn't, it wasn't relevant to what we chose to do.
MS. NEWBURY:
Q. So does that mean that retrospective reviews don't take place or they don't take place with regard to ER/PR testing or is it something about the magnitude of the review, the number of years, the number of patients?
DR. PRITZKER:
A. It was certainly not common to have a large scale review of any type of testing, it's been a common and we've had experience in our own lab to do retrospective peer review of certain testing because there were questions asked and we wanted to satisfy folks that things were done as well as they could have been.
MS. NEWBURY:
Q. Okay, so retrospective reviews are done, but they're not of the same scope? I'm just trying to

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understand -
DR. PRITZKER:
A. Yes, so it's quite typically they're--for subspecialized testing, and this commonly goes on in laboratories around the world, there may be a question that, okay, so there's been a change in what you've been doing and is this change a result of the patient population or is it a result of your intrinsic quality in something you don't recognize and so the idea would be to take out a sample and to do this, to compare the sample with a peer laboratory, and most of the time it's a local laboratory but sometimes it's, in our case it's been international and it goes both ways, we don't do it just, send our samples to X, it's Y sends their samples to us as well. It's symmetrical.
MS. NEWBURY:
Q. And are there any procedures or protocols in place once you become aware of a potential issue in terms of how or whether you're required to conduct a retrospective review?
DR. PRITZKER:
A. No, the decision to do these things is the choice of the--at the present time is a choice of the

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laboratory director and this is done on the recommendation of staff and the various other kinds of pressures. You must be aware that retrospective reviews incur a very substantial sort of cost and in a typical laboratory setting, those costs would have to be absorbed by the operating budget of the laboratory, so for the most part we emphasize that we use these, you know, in a limited way and as a tool, find out what we have to find out and then spend most of our resource improving the system or moving on to the next demand for the resource I would say.

MS. NEWBURY:

Q. Okay, so cost then would be a factor weighing against a retrospective review or perhaps the size of the retrospective review -

DR. PRITZKER:

A. Well it's also my experience that in the, for the average set of problems which we have done these small reviews, essentially we can affirm what we already know and we're just providing some additional reassurance to folks that things were done well. So the idea, there isn't enough resource to do all these things, to have very extensive

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retrospective reviews all the time and I don't feel it's a cost-effective resource unless there's a particular problem has been identified. It's much better to use the scarce resources to develop quality on an ongoing basis and develop the new things which we are asked to do.

MS. NEWBURY:

Q. Uh-hm. Would the possible advantages to patients be a factor in deciding whether or not to conduct a retrospective review when you feel there might be a potential problem?

DR. PRITZKER:

A. Well that's what provokes the question of whether you should do a review or what action you should take is that some results, whether they're a small number or a moderate number, are discordant with what someone's perception of what the results should be.

MS. NEWBURY:

Q. Uh-hm.

DR. PRITZKER:

A. And further, when we look back on all of the materials that we have that state what we did and what quality and so on, we could not find the source

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of error that would give rise to this, so then the question is do we have it right or don't we have it right, and the way of doing that is to compare it further with another group and the reason why we do it reciprocally is because, you know, you have to be sure, you have to have some mechanism to ensure that the other group has got it right too, okay, so it's a question of sending things out to a consultant, how many consultants do you--to send the things out to. You need an objective way of assessing the advice that you are given and the materials you are given.

MS. NEWBURY:

Q. Okay, so then are retrospective reviews conducted in situations, not just when there might be a problem but just for random purposes, I guess, for quality -

DR. PRITZKER:

A. No, it's not random, it's usually on a--it's usually when a problem is perceived and where the source of the problem is not perceived, and it turns out that more often than not there is variation in--there may be variation in patient results, but there may and there have been in our experience variations in reagent manufacture which were not discovered by the

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company themselves.

MS. NEWBURY:

Q. Uh-hm.

DR. PRITZKER:

A. And they're very appreciative when that's found and with all of the, you know, we do somewhere in the order of 2500 different kinds of tests, so the chances of something happening somewhere along the line with something is pretty frequent, and so we do--we are aware of these things and we are trying to find ways of identifying the problem and solving the problems.

MS. NEWBURY:

Q. Okay, and would your standard quality procedures that you have in a lab, would that be a way of perhaps minimizing the need to conduct a retrospective study in the future? Is that how you would possibly pick up -

DR. PRITZKER:

A. That's where we go first, of course, and one of the things which we're always on the look out for are ways in which we can retrospectively and prospectively survey our material so that we can better identify deviations from quality. That's a

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work in progress, I would say the quality in most laboratories is very high and uses industry standard processes, but I would also say that the volume of testing, the sheer volume of testing and the emerging capacity to understand the deviations from the quality by computational techniques, has promised to improve quality still further.

MS. NEWBURY:

Q. Thank you, those are all the questions I have.

THE COMMISSIONER:

Q. Mr. Crosbie, do you have any questions for this witness?

CROSBIE, Q.C.:

Q. I do.

THE COMMISSIONER:

Q. Now we're nearing the end of the day, so can I--but I understand our witness has a flight to catch, so I'm going to ask the indulgence of counsel and suggest we press on.

CROSBIE, Q.C.:

Q. I'm hoping this is only five minutes worth.

THE COMMISSIONER:

Q. All right. If that's the case, then why don't we do it now. I was going to propose if you were going to

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be any length of time, we take a short break, but if we're talking five minutes, let's press on.

DR. KENNETH, PRITZKER, EXAMINATION BY CHESLEY CROSBIE, Q.C.

CROSBIE, Q.C.:

Q. That's, I think, all it is. In the materials we've had, we've heard that Eastern Health, and seen in documentation, had the idea that the look back was going to take maybe four weeks, six weeks originally back in the early fall period of 2005. Where would they get that idea from? Did that come from you?

DR. PRITZKER:

A. No, it didn't. The first materials, as you can see from the exhibit that was presented here, was 30 to 40 cases a week for three months.

CROSBIE, Q.C.:

Q. That wasn't a look back though.

DR. PRITZKER:

A. No.

CROSBIE, Q.C.:

Q. That was the ongoing -

DR. PRITZKER:

A. That was the ongoing one, and so the first that we had an idea that this was a larger exercise was somewhere in mid fall when they actually gave us the

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numbers and we started to scope out what was required to get it done.

CROSBIE, Q.C.:

Q. Did you actually give them an estimate about how long it was going to take?

DR. PRITZKER:

A. Yes, we did.

CROSBIE, Q.C.:

Q. And can you tell us when that was and whether it was in writing?

DR. PRITZKER:

A. Well, I do know that I was informed--I believe I was informed of what it was going to take somewhere in early November, it may have been before, and I recall this because it would be a very substantial-- it was a very substantial issue for us to do this in finite time. We had to reorganize a lot of resources to get this done. So I remember the scale of the problem was large. I don't remember communicating myself in writing to Newfoundland about the exact detail, but I do believe the detail was communicated by Dr. Mullen and Ms. Mandes.

CROSBIE, Q.C.:

Q. By, I'm sorry?

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DR. PRITZKER:

A. By Maria Mandes, who would be the coordinator of that project.

CROSBIE, Q.C.:

Q. Okay. Would six or eight weeks, once the scope and number of the specimens to be reviewed was known, ever be a reasonable estimate for your lab to make?

DR. PRITZKER:

A. I'm sorry, I don't understand the question.

CROSBIE, Q.C.:

Q. Would you ever have thought that this was going to take six to eight weeks once you knew the number of slides you were going to have to reexamine?

DR. PRITZKER:

A. Well, once we knew what we had to examine, we knew what time it was going to take us, and we -

CROSBIE, Q.C.:

Q. But was that six to eight weeks, when you knew that?

DR. PRITZKER:

A. That the work itself would take six to eight weeks?

CROSBIE, Q.C.:

Q. Yes.

DR. PRITZKER:

A. I believe that the original estimate was much longer

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than that, and we tried to truncate it to whatever time we could. We're now talking to--we're now somewhere in November, I believe, early November perhaps, of '05 and they wanted it before the holiday. Newfoundland wanted it before the holiday. We couldn't provide that and we felt it was going to go--I can remember conversations, it would go into March or whatever, and we tried to figure out ways in which we could supply this work faster and by the end of July--end of January, I'm sorry, end of January, we had completed the work. The memo was dated January the 20th and the work was substantially complete.

CROSBIE, Q.C.:

Q. Do I have the idea you had people working overtime on this outside normal working hours?

DR. PRITZKER:

A. That's correct.

CROSBIE, Q.C.:

Q. Weekends and evenings?

DR. PRITZKER:

A. That's correct, over the Christmas holidays.

CROSBIE, Q.C.:

Q. And over the Christmas holidays. Can you tell us

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what the unit price per, however you describe this, slide I suppose ended up being?

DR. PRITZKER:

A. Actually, I can't. I don't have that immediately available to me, but that information is available, but I don't have it at the top of my head.

CROSBIE, Q.C.:

Q. Presumably Eastern Health knows that too.

DR. PRITZKER:

A. Yes.

CROSBIE, Q.C.:

Q. Can you tell us what the gross cost to Eastern Health was?

DR. PRITZKER:

A. I can't tell you that either off the top of my head.

CROSBIE, Q.C.:

Q. It was billed -

DR. PRITZKER:

A. There was a costing and there was a billing, but I would have to ask for that information.

CROSBIE, Q.C.:

Q. This was billed directly to the Health Care Corporation here, was it?

DR. PRITZKER:

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A. Yes.

CROSBIE, Q.C.:

Q. Not to the Government?

DR. PRITZKER:

A. The retrospective stuff was billed to the Health Care Corporation.

CROSBIE, Q.C.:

Q. Okay. Have you spent all the money already?

DR. PRITZKER:

A. As you know, we're continuing to do testing. The testing was--the services were performed at that time we did them and they were billed appropriately and what we did was to ensure that the costing and the billing was on a formula that favoured the health care system, which is quite a bit lower than our usual and customary price for this.

CROSBIE, Q.C.:

Q. Lower than your price for -

DR. PRITZKER:

A. Pharma.

CROSBIE, Q.C.:

Q. Pardon?

DR. PRITZKER:

A. Lower than our price to the pharmaceutical companies

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and this kind of thing.

CROSBIE, Q.C.:

Q. Lower than your price for the ongoing work, not the look back work, but the work you were picking up over a few months?

DR. PRITZKER:

A. I can't compare it. The work that was done on the look back was done on a, here's a whole group of things, and a whole group of results, rather than on a here's a case coming in here, here and here. So that those are two different kinds of conditions.

CROSBIE, Q.C.:

Q. Was the look back price established by negotiation, bid or a combination or how?

DR. PRITZKER:

A. It was basically done by--it was done by negotiation, but we offered them a price. We offered Newfoundland, the health authority a price and they accepted it.

CROSBIE, Q.C.:

Q. Do you know if there were any competitors for the work?

DR. PRITZKER:

A. I wasn't aware of anything else at the time. We

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were not bidding on a competitive basis. We were offering to do the work because we were asked to and it was urgent and I wasn't aware--I wasn't even aware until a few weeks ago that they had approached other and had been turned down, and I wasn't aware that this was a competitive, industrial bid. I don't think we would have approached it in a way had we known that. This work produced great strain in our laboratory and we did this because we felt that it was very important for patient care, and that we recognized that there were few other places in our country, at least, that could even attempt to do this work.

CROSBIE, Q.C.:

Q. That leaves my last question. There would be labs one could find in the United States who, for the right price, would do this as well.

DR. PRITZKER:

A. That's correct, presumably.

CROSBIE, Q.C.:

Q. Reputable labs?

DR. PRITZKER:

A. Yes.

CROSBIE, Q.C.:

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Q. Thank you.

THE COMMISSIONER:

Q. Mr. Pike?

MR. PIKE:

Q. No questions, thank you.

THE COMMISSIONER:

Q. Mr. Clements?

MR. CLEMENTS:

Q. No, thank you.

THE COMMISSIONER:

Q. Mr. Coffey, anything arising?

DR. KENNETH PRITZKER, RE-EXAMINATION BY BERNARD COFFEY, Q.C.

COFFEY, Q.C.:

Q. I just have one point, Commissioner, thank you. If we could, please, Exhibit P-1676? I'm sorry, 1767, I apologize, 1767. This is that article that Mr. Browne referred you to, Doctor. Just on the first page of the exhibit, the right-hand side, first full paragraph. I think he read you the first sentence or so, but I just want to refer you to a couple of lines from it and ask for your views on what's stated here.

It reads "despite the improvements or reagents and automation, authors over the years have

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consistently noted the inconsistent quality of IHC assays," and then the footnote 6 through 11, and you can take your time and have a look at those if you like, they are and cover everything from Seidal et al's article, 2001, Interpretation and Quantification of Immunostains; Wick's, O'Leary, Maxwell, footnote 9, DeLellis and Taylor, C.R. Taylor, footnote 11. Okay?

DR. PRITZKER:

A. Yes.

COFFEY, Q.C.:

Q. And then he goes on to write, the authors go on to say, "unlike previous IHC epochs, most of the causative responsibility lies with the individual laboratory performing the IHC and specifically the lack of standardization and attention to quality assurance programs" and there, at footnotes 12 and 13, which is the study in 2004 by Varma et al and Rhodes. Well, Rhodes publishes a number of papers, but this is a paper in particular in 2003, Quality Assurance in Immunohistochemistry.

And then he goes on to say "prior consensus conferences identified the likely causative factors" and they are at Table 1, which is if you turn the

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page you'll see those, Table 1 on the next page, footnote 14, which is again a paper by Taylor in 2000 entitled The Total Test Approach to Standardization of Immunohistochemistry, and then finally "recent studies suggest that these problems are widespread and not insignificant," and that's footnotes 15 through 17. The footnote 15 is Perez et al's study published in 2006, and then a Rhodes paper in 2001 at footnote 16 and a Rhodes paper at footnote 17 in 2000.

The point being, Doctor, that--and finally, toward the end of that first paragraph or full paragraph, it reads "unfortunately, laboratories often do not appreciate the negative impact on their specimens and the validity of IHC performed on them created by diverging away from these recommendations," and they have this list of recommendations.

And what I wanted to ask you about in relation to this, Doctor, was this: really, effectively, I'll ask you about the second sentence, "unlike previous IHC epochs, most of the causative responsibility rests with the individual laboratory performing the IHC and specifically the lack of

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standardization and attention to quality assurance programs." So if one takes their starting premise, which is there's a problem or problems do exist in various places concerning IHC tests, these authors do posit that, at least in their views, most of the causative responsibility rests with the individual lab performing the test. Would that be--if there are problems, ultimately -

DR. PRITZKER:

A. Well, the responsibility for performing all tests is that of the individual laboratories. That's a true statement, and that's a statement that is true irrespective of how many standards there are and of how many regulations there are. It relates to the implementation of the standards.

Why hasn't there been a standardization? I mean, that's a question that hasn't been addressed today or this afternoon, but I think you can see that in the Table 1. There are close to 20 different areas where the tests could vary, and within that, there are a number of different choices as well. So that reflects the complexity of the immunohistochemistry technology, which all of us would like to have much simpler, but that's--it

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reflects that technology. And then over the past decade, especially, there have been two things. One, there have been advances in the technology, not only more assays and development of the platforms and more sensitivity, but also a greater realization of what the difficulties actually are in doing this technique. So it's a greater recognition by those who are in the field and doing this, and so it was the state of the art. We're now talking about a paper that's only a year ago. It was state of the art is one which standardization isn't there yet, where there is a cry to have the field move towards standardization. This is only one of several papers that have said this kind of thing in this time range, and I think this reflects the state of the art of immunohistochemistry at that time.

One can discuss the details, whether it should be this way or that way, but in fact, each of the technical details will evolve as we learn more and learn how to take all these variables and make them less variable.

COFFEY, Q.C.:

Q. And I take it ultimately, and if you disagree, please say so, ultimately the responsibility rests with the individual laboratory?

DR. PRITZKER:

A. That's correct.

COFFEY, Q.C.:

Q. From your perspective. Thank you. Those are the questions I have, Commissioner. Thank you.

THE COMMISSIONER:

Q. Thank you very much. Dr. Pritzker, I very much appreciate your having come from Ontario to assist us in the process of trying to learn more and more about this interesting subject of yours and hopefully along the way that learning process will take place. I'll keep trying.

DR. PRITZKER:

A. Thank you.

THE COMMISSIONER:

Q. Counsel, please do not turn off your computers. I'm advised by the administrative office that there will be someone arriving shortly with new exhibits and updates for you. Thank you once again. We'll meet in the morning at 9:30.

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CERTIFICATE

I, Judy Moss, hereby certify that the foregoing is a true and correct transcript in the matter of the Commission of Inquiry on Hormone Receptor Testing, heard on the 23rd day of June, A.D., 2008 before the Honourable Justice Margaret A. Cameron, Commissioner, at the Commission of Inquiry, St. John's, Newfoundland and Labrador and was transcribed by me to the best of my ability by means of a sound apparatus.

Dated at St. John's, Newfoundland and Labrador this 23rd day of June, A.D., 2008

Judy Moss

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