COMMISSION OF INQUIRY
ON HORMONE RECEPTOR TESTING

BEFORE THE HONOURABLE JUSTICE CAMERON - COMMISSIONER

September 16, 2008

Appearances:

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Regional Integrated Health Authorities

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DR. KARA LAING - RESUMES THE STAND

THE COMMISSIONER:

Q. Please be seated. Now, Mr. Coffey, we'll try again.

COFFEY, Q.C.:

Q. Thank you, Commissioner. Yes, we have the signal, I believe, the recording is good.

DR. DAVID DABBS, EXAMINATION BY BERNARD COFFEY, Q.C. (CONTINUED)

COFFEY, Q.C.:

Q. Doctor, looking at P-0046 yesterday. And I think at page 5 of the exhibit. And, Doctor, we'd spoken of subspecialization, I believe. At paragraph 5 of Dr. Banerjee's report, this page refers to what he calls a disconnect between the laboratory program director, division manager, the clinical site chief and laboratory director in decision making and talks about the organizational chart indicating a complete separation of reporting structures in technical and clinical streams with no matrices--matrix, I'm sorry, cross reporting between technical and medical leadership. He talks about what he viewed as frustration and resentment on both sides, lack of communication, lack of accountability and

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lack of buy in. Doctor, I appreciate you, of course, haven't visited that lab. But I'm going to ask you about from your perspective the importance of communication and organizationinrelationto immunohistochemistry, pathology in general and IHC in particular.

DR. DABBS:

A. Yes. It's just in other areas of complex testing, it's critically important that the medical director knows what's going on in the laboratory and is able to communicate effectively among pathologists colleagues, as well as to the laboratory administrator, the person who is responsible for the technical staff in the hospital to assure that whenever issues or problems arise, that person inform-- they're brought to the attention of the medical director who can then act on them in communicating with the laboratory administrator so that that person can effectively find out what the specific issues are with technical procedures and the technical staff that are responsible for performing.

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COFFEY, Q.C.:

Q. And I believe yesterday you indicated that, at least in your institution, the immunohistochemistry, the person who's on the ground primarily responsible for it is a pathologist?

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. A medical -

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. - (unintelligible) a doctor. Doctor, while it's there on the screen in front of us, there's a reference to the Sakura Express. And Dr. Banerjee noted that in his view the implementation of it here locally had failed due to a lack of planning of work flow changes. The Commissioner has heard evidence on that. I just wanted to ask you about the Sakura Express itself. Have you had any experience with it?

DR. DABBS:

A. Yes, I did.

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COFFEY, Q.C.:

Q. And could you tell us, please, at least give the Commissioner the benefit of what your own thoughts on the Sakura Express?

DR. DABBS:

A. Sure. What I know about the Sakura express is twofold. I spent a few days in Miami where this device was actually put together and the prototype was, and I observed their work flow with this device. It's a microwave enhanced tissue processor and slides can be generated in under three hours from the time the specimen is received. It requires a great deal of special grossing techniques up front with tissues cut very, very thin, and that requires special tools. The second part is that I had the device actually at our institution for approximately two months. My main interest in this was if tissues could be processed with the molecular friendly fixative that is marketed along with this device. And what I did was I operated this device for approximately five weeks, comparing specimens that were fixed in formalin in the conventional fashion, along with this new

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fixative, specifically for hormone receptors and for HER2, analysis and I was not confident in the outcome, the results using this special fixative. So while that was my main interest in exploring the Sakura, I decided that this was not a device that could be used in that fashion because of the unreliable results that was given with this special fixative that was marketed by Sakura, so I had the device removed.

COFFEY, Q.C.:

Q. And when was that, Doctor, that experience?

DR. DABBS:

A. I don't remember the exact date, but it was more than two years ago.

COFFEY, Q.C.:

Q. Dr. Banerjee in paragraph 6 here notes, "Attendance by both medical and technical staff at various conferences with a focus on new technology should be encouraged. Consensus driven innovation should be the goal." Doctor, in the field of immunohistochemistry, in your view is it necessary that the medical and technical staff that are involved in immunohistochemistry

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would find it necessary to continuously upgrade their skills and their knowledge?

DR. DABBS:

A. Yes, it always is. Immunohistochemistry, like many other areas in medicine, is a constantly evolving discipline and there are a fair number of conferences that are available for medical and technical staff to attend. And in fact, the day that I flew up here, I had just given a small seminar at the National Society of Histotechnologists which has a great deal to do with immunohistochemistry, it happens to be held in Pittsburg this year.

COFFEY, Q.C.:

Q. Doctor, now there's a reference here to pathology assistants. Are they utilized in the States now?

DR. DABBS:

A. Yes, to a great degree, especially at our institution.

COFFEY, Q.C.:

Q. Yes, okay. And their role there is what?

DR. DABBS:

A. Their role there is largely to oversee accessioning and grossing of the specimens and

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specimen preparation so that slides can be prepared from tissues. Some of the pathologist assistance are on the job trained, many of them are also school trained, they take masters degrees at various institutions, and they work together to assist the pathologists in preparing specimens to make slides.

COFFEY, Q.C.:

Q. Doctor, there are--we looked under "Recommendations", I'm not going to take you through all of those, but on the paragraph 3 on page 6 of the exhibit, Dr. Banerjee's noted that "Consideration should be given to switching into the rapid monoclonal antibody SP1 for ER IHC." Doctor, in terms of ER, the ER antibodies, I think you referred to this yesterday, you referred to the SF11, 1D5 and SP1?

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. Okay. Doctor, in your view, are either one or more of those acceptable or all of them?

DR. DABBS:

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A. Yes, they are.

COFFEY, Q.C.:

Q. They're all acceptable?

DR. DABBS:

A. They're all acceptable, yes.

COFFEY, Q.C.:

Q. I take it that whichever one a laboratory chooses to utilize, that they have to optimize for that?

DR. DABBS:

A. Correct.

COFFEY, Q.C.:

Q. Doctor, while we're on the subject, I'm going to go back to page 4 of the exhibit, which is under the heading, "Conclusions About the Reasons For Test Failure," paragraph 1 and 2. One refers to the DAKO system and two to the Ventana system. Now, we understand, from evidence the Commissioner has heard that the DAKO system is what--the DAKO autostainer is referred to, has been referred to here as a semi-automated platform and the Ventana is, that was being referred to here as an automated platform. I appreciate that they are relative terms. Doctor, do you have any

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views on the advantages or disadvantages of one, like a relatively semi-automated system such as the DAKO autostainer versus the Ventana system?

DR. DABBS:

A. I think the only significant difference is that the DAKO is not fully automated, and that's not an issue. That device is used throughout the States. It's a very robust device. I just obtained the new version, actually, of this device for my research laboratory. It's a totally open system so it has significant advantages over the Ventana system, which is really a closed system, the software for the Ventana system is a closed system. So in that regard if one wants to work up a variety of basically any antibody from scratch, the DAKO system would have an advantage because it's an open system and you're able to do that, whereas you're not able to do that with a Ventana system. But on the other hand, if you're doing predominantly clinical work and you want to have minimal technical input to it, it becomes useful in that regard because it's basically fully

automated, and with ready to use reagents and has a, you know, a slight advantage in that regard. So they're both robust, excellent systems. It's a matter of how are you going to use it.

COFFEY, Q.C.:

Q. Look, please, at--just a moment, please? It's Exhibit P-1850, I believe. No, sorry. It's Dr. Mullen's report. The copy I happen to have in front of me happens to be unnumbered, as it turns out. It's the April 14th report, 1840, maybe? I apologize, Commissioner. I'm just--I hadn't noticed it.

THE COMMISSIONER:

Q. I'm sure we'll find it.

COFFEY, Q.C.:

Q. Okay, it's dated April, 2008. It's 1840.

REGISTRAR:

Q. 1840?

COFFEY, Q.C.:

Q. I was right. Yes, thank you, Registrar. Doctor, this is a report dated April 14th, 2008. It was prepared by Dr. Brendan Mullen, who is the pathologist from Mount Sinai Hospital in Toronto, Canada. Doctor, have you

had a chance to have a look this report?

DR. DABBS:

A. Yes, I have.

COFFEY, Q.C.:

Q. And again, without kind of reading it out to you, I'm going to ask you perhaps using the mouse and the cursor on the screen, are there any things that you'd like to--or think are noteworthy, looking at it, in the context of what the Commissioner is dealing with here?

DR. DABBS:

A. Well, I was struck particularly by the "Summary of Observations." In fact, point No. 1 where Dr. Mullen describes poor fixation and processing that resulted, at least in part, in incomplete tissue sections. And some of that can result, as I mentioned before, from tissue that contains water, isn't properly dried off before the actual slide goes to immunohistochemistry. That's a risk for losing tissue during the process. The loss of internal structure of the nucleus in staining restricted to the periphery of the slide sounds like he's describing poor fixation whenever the nuclei don't look like they

should. It suggests that the fixation is responsible for that. And again, what he refers to as exploding sections resulting in loss of sections of the tissue, which in some instances apparently lost pieces of, portions of the actual tumour tissue that was to be assayed, again likely a result of inappropriate adherence to the slide, inappropriate drying that lead to that. And he refers to these hollow nuclei again. So it sounds like poor fixation and technique in preparing the slide for immunohistochemistry, at least in that part. The second, the absence of internal controls, he noted that many cases had no normal epithelium to be used as an internal control and where it--some was present, some of it apparently was lost because of this what he refers to as exploding tissue sections or loss of tissue due to inappropriate drying. Negative internal controls, he describes in many cases the internal control either did not stain or stained very weakly. Also, with the exception of a small minority of cases the ER internal control was significantly weaker. Again,

these are major red flags for improper technique that may be related to fixation, antibody concentration or even improper antigen retrieval leading all to, potentially point No. 3 there.

COFFEY, Q.C.:

Q. Doctor, he notice the difference, a difference in his view, looking at the original slides, at least quite a number of them, between the ER internal control and the PR internal control where it was there, the PR control generally stained better. Can you account for that?

DR. DABBS:

A. Well, it's difficult to account for that specifically. But again, we're dealing with two different titres, two different antibodies.

COFFEY, Q.C.:

Q. Okay.

DR. DABBS:

A. So again, a fair amount of the things that I've observed and what people have written seems to be related to perhaps proper antibody dilutions, at least in part. The stain

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deposit obscuring morphology, in many cases excess stain was present either on the surface or beneath the section, those are artifacts that can be associated with overheating or improper development of the chromogen solution. External controls he describes as being inconsistent, both between slides or within slides, in some cases positive cells were barely stained. Again, that's a hallmark that there's definitely something systemically wrong with the staining apparatus if your expected positive results are weak or not staining at all. And then lastly, the discrepancy between internal and external controls in only one of the two--in only one or two of the 539 cases he looked at was the staining of the internal control as strong as the corresponding external control. So again, there are multiple points here that all substantiate that the process was uneven and erratic and fraught with technical difficulties.

COFFEY, Q.C.:

Q. Doctor, the final point he makes is he says, "There were few cases," I'm sorry, there were

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very few cases in which there was a significant difference in my" he calls it "my observation compared to that recorded on the original report," which is a percentage, okay, on the original reports. "Some of my observations were higher than those recorded and some lower." I understand from the evidence he's given here is that, well, you know, he might have called something 20 and somebody else originally had called it 30 or vice versa.

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. Or 60 versus 70.

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. That sort of thing, 60 versus 65. Doctor, that sort of, you know, leaving aside the issue of whether or not the original slides should have been interpreted at all, okay, leave that aside for the moment, in relation to the issue, or this particular aspect of the matter which is an estimation of the portion

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of cells that have nuclei staining.

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. And Dr. Mullen said there was some difference but only a couple of cases, I said a couple, very few that there was significant difference. I wanted to ask you about that. The fact that he wouldn't come up with a whole lot of different figures for the proportions or percentage figures, does that surprise you or would you--and what I want to ask you about is, I suppose, inter-observer variability in that regard.

DR. DABBS:

A. Um-hm.

COFFEY, Q.C.:

Q. And, in fact, intra-observer variability and just generally what you know about variability in terms of interpretation, the interpretation end of this?

DR. DABBS:

A. Sure. When examining for proportion of number of cells that are present, the inter-observer variability tends to be lower than when one is

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looking at both percent of cells and the staining intensity. So it's not really surprising here that apparently what he's describing is that there is a low variability between what he observed and what the original observer catalogued in the report. And there were only just a very few or a handful of cases where there was a significant difference. And I think that's probably to be expected within acceptable parameters, so I think what he's describing here is that the interpretation was not an issue.

COFFEY, Q.C.:

Q. Now, whether or not it should have been interpreted and what should have or might have been done, having observed these kind of problems he's noted in the slides, that's a different issue.

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. But in terms of the actual percentage call, the fact that in 539, approximately 539 cases there would be a few cases in which there would be a significant difference in

interpretation, you wouldn't find that unusual?

DR. DABBS:

A. No, I wouldn't find that to be unusual. The only--the key item there, in my opinion, would be if something was interpreted as negative and in fact it was positive, but he's not describing that.

COFFEY, Q.C.:

Q. And in this context negative means zero, I take it?

DR. DABBS:

A. Negative means zero, yes.

COFFEY, Q.C.:

Q. Yeah, okay. And positive is anything, any percentage staining?

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. Doctor, there are some other subject matters that I wanted to ask you about, discreet onto themselves. One is the effect of--your understanding of the current view within pathology of the effect, if any, of refrigeration of--refrigeration of tumour

tissue on ER/PR testing. What's your understanding of the current view on that?

DR. DABBS:

A. Refrigeration of specimens, I think that--well, first of all there really isn't--there really to my knowledge aren't any studies that look at refrigerated tissue versus non or those that are immediately put into fixative regarding ER/PR or other testing. I think what I described yesterday from the consensus view of the committee was to get tissue as soon as possible in all instances under one hour into fixative, and if that means would the specimen be better off in the refrigerator for that period of time, one hour before formalin, I don't know that anyone has really looked at that specifically. So that remains to be an unknown. It probably would not have an adverse effect.

COFFEY, Q.C.:

Q. How would, Doctor, the cooling of formalin itself, like, for example, the fixative process and the chilling of formalin --

DR. DABBS:

A. Uh-hm.

COFFEY, Q.C.:

Q. Does that have--do you know if there's any studies at least that you're aware of in relation to that?

DR. DABBS:

A. I'm not aware of chilled formalin, but we do know that warm formalin will penetrate tissues better than room temperature formalin, and that's been the idea behind enhanced heating for tissue processors, enhancing the fixation process.

COFFEY, Q.C.:

Q. Doctor, so ideally then, from your perspective in terms of a tissue sample when it's either taken out using a needle or excised with a scalpel, what should be done with it, a breast tissue sample in this context?

DR. DABBS:

A. The--well, I think if biopsies are performed in a clinic or in a radiology suite that those people need to be instructed that as soon as the tissue is available, it should go into a container of formalin and sent immediately to the laboratory. Tissues coming from the operating rooms, the operating room personnel

need to be instructed to send the tissue fresh immediately to the interoperative consult area so that the tissue can be--the margins typically are inked in six different colours for purposes of orientation for the final report. The tissue is sliced extremely thin, as thin as possible, and then we typically report on the margins, how close they are, and things like that. We then get that into fixative immediately and also at the same time procure fresh tissue for tumour bank for potential research. That's what we do at our institution. So these cases, everyone is aware of the importance of getting to the specimens as soon as possible, and I think one hour is actually fairly liberal. In an institution where communication is optimal, it should be within minutes and not, you know, as long as an hour.

THE COMMISSIONER:

Q. Dr. Dabbs, actually that was something I had noted from your slide presentation yesterday, one of the recommendations was that breast resection specimens must be sectioned fresh as soon as possible, fresh meaning not having

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gone in--before they go into formalin?
DR. DABBS:
A. Correct.
THE COMMISSIONER:
Q. So in your institution, is there a space near the operating room in which this is done before it gets transported to the lab or does it go directly from the operating room to a lab section where that's done?
DR. DABBS:
A. Yes, we have--like, many hospitals have an area. It might not necessarily be next to the ORs, but we do have a room next to the ORs which is a place where we do interoperative consultations on frozen sections.
THE COMMISSIONER:
Q. Uh-hm.
DR. DABBS:
A. So it's a small laboratory area where we receive these, and we have a bench there where we can place the specimen, ink it, and then section it thin like that. Tumour procurement takes it's--tumour procurement takes its bit of tissue if there's adequate tissue and then this goes into fixative, and it's then

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processed and the time in formalin is recorded. So this is done at our institution in a room. It's a modest--very modest size adjacent to the ORs. We actually--our laboratory, the main laboratory, is one floor up and probably maybe a tenth or two tenths of a mile away. So it's a slight hike down to that room where we get called every time for interoperative consultation, and I think many institutions are similar to that. Some laboratories have the luxury of actually having the entire laboratory on the same floor as the operating room and that's an ideal situation, but it's by no means the norm.
THE COMMISSIONER:
Q. And would it be the norm--I mean, obviously this is the recommendation of the group here about cutting fresh. Are there studies which deal with comparison between having a cutting of fresh as opposed to cutting after the breast tissue would have been in formalin for a period of time and transported to a lab?
DR. DABBS:
A. Well, we do know from specimens in general that if material is placed into formalin

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without sectioning and having the entire tissue exposed to the formalin, that fixation will not begin--will not be optimal because penetration of the tissue from the outside is slow, it's about one millimetre per hour.
THE COMMISSIONER:
Q. Uh-hm.
DR. DABBS:
A. So maximum in a portion of unfixed tissue, if you let it even sit overnight, it'll penetrate maybe four or five millimetres maximum. So if you section that tissue the next morning, the entire aspect of it will be raw. It will be - it will give very unsatisfying histologic stains and that's not to mention the fact that if you're ever going to do any complex testing, it would be futile. The tissue would be, in effect, liquifacted and unusable for that. Now if you're asking if you take that specimen, put it in a bucket of formalin without sectioning it and then section it within one hour, that would probably be okay as well.
THE COMMISSIONER:
Q. Right.

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DR. DABBS:
A. But the key thing is exposure of the tumour tissue as soon as possible in formalin, and in essence, it's also conceivable if you're dealing with a remote location, to have an assistant cut into that, take a thin piece of tumour, several thin pieces of tumour, put them in a tissue cassette and put them in the same bucket with the formalin. That way you're getting the tumour fixed while it's on its way to the lab. That's doable as well. One can always deal with the inking after the fact. So that's possible.
THE COMMISSIONER:
Q. So--okay, I just want to make sure that I understand. So for those--because you raised two different things. One is really if you're in a hospital where there is a lab relatively close by, I understand you to say that if you can't cut it fresh, the optimum thing would be to put it in formalin, get it to the lab, and still have it sliced.
DR. DABBS:
A. Yes.
THE COMMISSIONER:

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Q. Within about an hour?
DR. DABBS:
A. Yes.
THE COMMISSIONER:
Q. If you are--if you happen, as we have in this province, to be in a remote location where, in fact, the lab may not be in the same institution where the tissue sample is taken, then that presents other kinds of problems, and one of the potential ways of dealing with that would be to have placed in the same bucket a slice which had been taken, as I understand?
DR. DABBS:
A. Yes, of the tumour.
THE COMMISSIONER:
Q. And then transported, so that it is, in fact, in the formalin doing its thing in terms of fixation while it's being transported to the lab, which may be some distance away?
DR. DABBS:
A. Correct.
THE COMMISSIONER:
Q. Are there other ways of dealing with the question of having to transport because

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sometimes you might be transporting across town, but there's at least--there are at least two institutions which from the evidence I've heard within this province where the transportation may take some time. In one case, perhaps 24 to 48 hours.
DR. DABBS:
A. Uh-hm.
THE COMMISSIONER:
Q. So would that same method be a way of dealing with it or are there other ways of dealing with it?
DR. DABBS:
A. I think the transportation issues can also be dealt with on an individualized basis, and by that I mean at these hospitals where the surgery is being performed, there's probably at least someone from the laboratory who I think could be trained to section the tissue, cut it with a knife into one centimetre or less thick sections, put it in a bucket of significant size with formalin, and then the transportation could occur. They wouldn't have to actually cut into any tumour and specifically put it into, you know, specially

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marked cassettes. They could simply cut the tissue with a broad knife into one centimetre or less sections, put it in formalin, and have it transported, and if it takes, you know, 48 hours to get to the destination, then the laboratory director just needs to be able to validate that their assay they're using, the ER/PR or HER2, or whatever, works under those conditions of fixation beyond 48 hours. Now, for example, if you recall from the recommendations, it said up to 72 hours. Well, for our laboratory at Magee, what I did is I validated it for 96 hours to make sure that if there's any issues with transportation, especially in the unlikely event that something got to the laboratory late on a Friday, and it happened to be a long three day weekend, to take into account for that. One of the things that I did not mention, but you will, is that overfixation for formalin is almost never an issue. It can be--the assay can be altered with antigen retrieval, and that's what antigen retrieval does, it levels the playing field for specimens that have been fixed for however

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long. It's underfixation that you cannot repair. So the key thing is to get the specimen into formalin as soon as possible and once that's done, then just, you know, adjust your assay if you have to adjust your antigen retrieval a little bit and your optimization process then for specimens like that, and that's why we keep track of how long specimens are in formalin, so that if you--you know that you're getting specimens from hospital "B" and they typically don't get to the lab for 48 hours, and then it takes another 24 hours to process, then you look at those assays and compare them to your standard operating procedure, and if your results look fine, then you don't have to do anything, but if signals are appearing weak with your controls from that tissue, then you can up your antigen retrieval and that way whenever you receive specimens from hospitals out in a remote area, you know that once you've received them that your machine, you're going to program it on a different protocol to take into account the fact that it was fixed longer.
COFFEY, Q.C.:

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Q. So you have to adjust how the particular tissue sample is handled or processed overall to the ER/PR process, bearing in mind how it's being handled before you received it?
DR. DABBS:
A. Correct, exactly, and like I say, the wonderful thing about formalin fixation is it's very forgiving. Overfixing will never destroy a specimen, but underfixing will destroy it. So that's the importance of getting it in formalin up front as soon as possible. As I mentioned, 96 hours, I see no change whatsoever in our ER/PR or HER2 at our institution, and so on our path reports, it says that our fixation time is between 8 and 96 hours.
COFFEY, Q.C.:
Q. Now, Doctor, to make sure I understand it, you pointed out making cuts in the tissue at one centimetre distances or less if possible, I take it that that means, in effect, that if that's done all the way through the tissue, and it's one centimetre, say, the cuts are at that distance, that spacing, that any piece of tissue within the specimen is within a half a

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centimetre of fluid to start - of formalin to start?
DR. DABBS:
A. Yes.
COFFEY, Q.C.:
Q. And your penetration rate is one millimetre per hour?
DR. DABBS:
A. Yes.
COFFEY, Q.C.:
Q. So within five hours at least there's some formalin in every part of the tissue should have been in contact with formalin?
DR. DABBS:
A. Yes.
COFFEY, Q.C.:
Q. That, I take it, is the way it works in terms of the actual mechanics of it?
DR. DABBS:
A. Yes.
COFFEY, Q.C.:
Q. And, though, just as you pointed out yesterday, the fact that formalin has arrived on a particular piece of tissue doesn't necessarily end the matter, it has to continue

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to be exposed to formalin?
DR. DABBS:
A. Correct.
COFFEY, Q.C.:
Q. In order for the fixation process to do what it's supposed to?
DR. DABBS:
A. Uh-hm.
COFFEY, Q.C.:
Q. And that, I take it, is why it's important to have the tissue slices as narrow as possible?
DR. DABBS:
A. Yes, and I think that one centimetre is actually quite generous. I think - I'm usually pretty successful in getting it at half centimetre or less. It takes a thin knife, a very sharp instrument, to do that for larger specimens, but it is entirely doable.
COFFEY, Q.C.:
Q. And that, I take it--so there's particular types of knives that one would use to do it.
DR. DABBS:
A. Uh-hm.
COFFEY, Q.C.:
Q. And I take it, it requires experience in

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manual dexterity?
DR. DABBS:
A. Yes, it does.
COFFEY, Q.C.:
Q. Doctor, I haven't raised this with anyone else, and I haven't raised it with you as of yet, but I'll ask you, is there to your knowledge any devise or thought given to actually creating a device, a mechanical device, that would compensate for any lack of ability on the part of the person who--lack of ability to slice very thinly by the person who is actually doing the processing of the tissue?
DR. DABBS:
A. What I can tell you is that because the Sakura tissue processor requires extremely thin slices, and we're talking two millimetres, they did develop some tools for that. It's specifically designed for that processor. It's very labour intensive, but there you're talking about cutting sections for a cassette. Actual devices for cutting gross specimens, the only kind of device that I'm aware of is one that is used by neuropathologists for

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slicing autopsy brains. Basically, if you can picture a plexiglass board that has two raised rails of approximately, let's say, ten centimetres apart, okay, once you section the brain in half and you put one half face down, and you slide your knife using those rails as a guide, you get something like five millimetre sections, okay, and then you lay them all out. That's how the neuropathologists do their examination for autopsies of the brain. Nothing like that exists for the breast. Some people have devised other whole breast section methods which involves slicing on an electric device, sort of analogous to what you see in a deli, okay, but there's nothing that's really been recommended or is in general use or even marketed for that purpose for the breast.

COFFEY, Q.C.:

Q. Doctor, the Commissioner has heard references to the idea of reprocessing of tissue, I mean, after it's been--after it has arrived in a block, paraffin block, and at times, at least certainly in one of the hospitals involved in this matter there was a certain amount of

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reprocessing of tissue that occurred. Are you familiar with the idea of reprocessing of tissue?

DR. DABBS:

A. Reprocessing of tissue is a phenomenon that is in general common knowledge, yes.

COFFEY, Q.C.:

Q. And in what circumstances is it used and what effect, if any, could it have on ER and PR results?

DR. DABBS:

A. I think the reason why tissue is reprocessed is because whenever a paraffin block gets to the histotechnologist to slice in their microtome, they find that they cannot cut it and get a good section. Usually what that means is the centre of the specimen falls out and you end up if they cut that, they get a big hole in the centre of the specimen, and there could be several reasons for that. If the tissue is not properly fixed, then tissue will be soft as opposed to being hardened by the fixative. That can be one potential cause. Another could be insufficient dehydration through the tissue processor. If

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there's something wrong with the alcohols, let's suppose that the alcohols are not frequently changed, alcohols can accumulate water just by sitting, alcohols if they're not changed can form esters within the container, so you're not getting a good dehydration and if you don't remove all the water from the tissue, it will not dehydrate, and so it will be relatively wet and soft and that's another reason why the histotechnologist would not be able to make a good section from that. So it could be fixation, it could be inappropriate dehydration. Another would be if the section is cut too thick when it's put into a cassette, what happens there is when the lid goes on the cassette, the tissue gets compressed because it's too thick and it will not infiltrate with paraffin well at the last step, and so that will appear, to the histotechnologist, to be a soft area that they can't cut. It sort of would be like trying to cut, you know, lard. It just doesn't cut. It just sort of spreads. So those are the three, I think, most common reasons why tissue would need to be reprocessed.

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Now the question is does reprocessing per se affect immunohistochemistry? And my answer to that would be that there are no studies that I'm aware of that have looked at that per se. However, what I can say is if the tissue is not properly fixed upfront, it doesn't matter what you do to it, it's not going to harm it any further, and the same goes if the tissue is properly fixed, no matter what you do to it in reprocessing, when you look at what the actual steps are in reprocessing, it's not going to affect the tissue as long as it's been properly fixed. But if it's not been properly fixed, you're still going to get a poor result for a complex test like ER/PR regardless of tissue processing, reprocessing.

COFFEY, Q.C.:

Q. So that, from your perspective, the reprocessing process itself won't remedy any damage, I'll use that word, in the sense of due to fixation problems that has already occurred?

DR. DABBS:

A. Correct.

COFFEY, Q.C.:

Q. But also, if there--it won't cause any damage to fixation that has properly occurred?

DR. DABBS:

A. Correct, because the steps that occur during tissue reprocessing really have already been done and to do them again, in the mode that's been recommended, no extreme temperatures, etcetera, will not harm the tissue and I think it's also important for the laboratory to monitor how often tissues are reprocessed because I think that's a quality measure. If you're having a lot of tissues reprocessed, it suggests that something is going wrong that could be anywhere from the person who's cutting the initial sections to the tissue processors, and you know, people who are involved with that. So that's distinctly a quality measure is to find out how frequent are tissues being reprocessed.

COFFEY, Q.C.:

Q. Doctor, and I take it, if there is any significant amount of reprocessing going on or being required to go on in the laboratory, from your perspective, there should be inquiries made about why that would be so?

DR. DABBS:

A. Yes, and by keeping track of this, you're basically looking at the people involved who are involved with processing, grossing, cutting, processing of tissue, and this is really the only way to get a grip or a complete handle on quality, so that you can go back and see, okay, what areas in the process need to be altered so that we can minimize or decrease the tissues that are being reprocessed, because tissue should not have to be reprocessed.

COFFEY, Q.C.:

Q. Doctor, just on the point of dealing with the idea of tissue taken in hospitals that are somewhat remote from the site where they're going to be processed into blocks. Doctor, you've referred to someone could be trained on site, wherever the surgery is occurring, to properly section the specimen. Doctor, you've also referred to, though in your own institution, that core biopsy are utilized generally or at least initially for ER/PR testing?

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. Would you have any thoughts on, at least in these--for example, and I'll refer to it as relatively remote institution, that's an hour by vehicle away from the centre where the blocks are going to be processed, or the tissue is going to be processed into blocks, or for that matter, 24 hours away, okay, in some instances in this province. Would there be any advantage to utilizing, at least initially, core biopsy process, because I take it the specimen is so much smaller than a mastectomy specimen?

DR. DABBS:

A. Yes, and I think that core biopsies, I think the vast majority of institutions in the States use core biopsies as the initial testing mode for hormone receptors and HER2 analysis. I think they do that for several reasons. Historically, they know that they got better results from core biopsies because they generally were better fixed specimens, but also, I think the demands of patients and oncologists who want to have results, you

know, soon, so that in some instances actually patients are treated before definitive surgery. So it's important to get a good result and get it in a timely fashion, and so there's a great deal of timeliness as well about patients who are anxious and doctors who want to begin treatment, either with hormonal manipulation or even chemotherapy. So that's sort of a mini history, if you will, of the reasons why core biopsies, and I would say that if you're dealing with patients in remote areas, probably the best way would be to do the hormone receptors and HER2 on a core biopsy. That requires a small container that tissue can be put right into formalin and shipped here, and if it takes longer, then it shouldn't be an issue.

COFFEY, Q.C.:

Q. Doctor, slides, the ER and PR slides, okay, if they're--once they're prepared and examined by a pathologist, does long term storage have any effect on the slides, to your knowledge, in particular with IHC?

DR. DABBS:

A. Sure. Long term storage should not have any

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effect on immunohistochemistry result per se. Other things can happen to slides. They can become a little bit dehydrated. Bubbles can appear under the cover slip, but that's nothing. That can be fixed very easily just by recover slipping. But the test result per se for immunohistochemistry should not be altered over time.

COFFEY, Q.C.:

Q. How about long term storage of blocks before a particular ER or PR test is done?

DR. DABBS:

A. Yes, in general, if the specimen is well fixed and held and stored in an area where the paraffin is not going to be melt down, in an air conditioned facility, I think that one can expect that immunoreactivity will be maintained for quite a long time. I mean, immunohistochemistry has been performed on archive specimens that have been hundreds of years old and you know, it's quite doable. Storage per se will not result in destruction of immunostaining.

COFFEY, Q.C.:

Q. Doctor, you referred to metrics. I take it

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they're used in your own laboratory. You use them?

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. From your perspective, what role should they play and how important are they? And could you explain to the Commissioner really what metrics you mean by metrics?

DR. DABBS:

A. Sure. The metrics that we monitor, we have a person who is dedicated in the laboratory to quality assurance and so she will keep track of all of our pathology reports that have predictive and prognostic markers. I've especially given her the charge of keeping track of ER/PR and HER2 results, as well as fluorescence in situ hybridization test for HER2. So what she does is she will abstract this information from pathology reports from our computer system and send me quality reports, and the quarterly reports basically are spreadsheets, Excel sheets, that will give me information on, for example, for hormone receptor, the overall number of cases that are

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ER positive, the percent of cases, of those cases that are ER positive and PR positive, the percent that are ER positive and PR negative, the percent that are ER negative and PR positive and the percent that are ER negative and PR negative. She will give me information on the percent of cases that are HER2 three plus, the percent of cases that are HER2 two plus and the percent of cases of those that whenever the FISH is performed, the percent of those that are actually amplified, the percent of cases that are HER2 one plus and percent that are zero. So that what that does for me is it tells me, it gives me a view, if you will, at 35,000 feet of how are we doing with our percentages in each of these categories, and as I watch them over time, provided that I haven't changed anything in the system or tissue processor or immunohistochemistry, they should be fairly steady. There should be no wild fluctuations, and that is, in fact, the case.

I can tell you that there was once one-- there was some information in the literature suggesting that patients who are ER negative

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PR positive, that the reason why that category exists is because those specimens were not properly fixed and were false negatives, and so what I did, I took advantage of the fact that we went to this controlled timed fixation at our institution January 1 of 2007. So what I did, at that point, I decided to monitor our results over the next six months and compare it to the prior two years specifically for that category, ER negative PR positive group. The ER negative PR positive group, prior to controlled fixation, for 24 months, was 5.7 and 5.6 percent, and for the first six months of controlled fixation, according to the recommended guidelines, it was 5.7 percent, which clearly demonstrated to me that it was not an artifact of fixation, and we presented that information at our national meeting in December last March.

However, it--and so that was one example of how I could look at the metrics and say "I've changed fixation. What effect is this going to have?" and I took advantage of the fact that looking at this and finally disputed the argument or--well, the argument that it's

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poor fixation results in that ER negative PR positive group. It does not. It's independent of fixation, and that percent in that category was unchanged for that entire 30-month period.

More recently, we changed our antibody clones to the rabbit monoclonals, the SP1 and the 1E2. They're both rabbit monoclonals. And what I noticed, and I just got these metrics about two weeks ago, in comparing the ER negative PR positive, which as I mentioned was about 5.7 percent, that has gone to one percent with the new batch of rabbit monoclonals. So what that says is that that is strictly antibody dependent, that that particular clone of PR, the 1E2, is different and is obviously seeing a different epitope PR, and as a result, the percent of ER negative PR positive cases is now one percent versus it used to be 5.7 percent.

COFFEY, Q.C.:

Q. Using the different mono -

DR. DABBS:

A. Using the different clone, correct. So it is clone dependent and whenever I looked at those

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metrics, I also compared it to the PR 636 clone and our original clone that we were using. So I have three PR antibodies there and the results, while varying, are--you know, they're still robust results, but the expectations now in using this as a metric are different than what they were before. So that's the importance of metrics. It tells you where you are so that if something drastically goes wrong with your system that the medical director, who is a busy person doing lots of things, or the lab administrator, again a busy person doing lots of things, if there all of a sudden turns out to be a wild fluctuation, you can catch it quick. Years aren't going to go by, but a quarter will go by. But at least you'll say, it's time to put on the brakes. We got to figure out why this number has changed so drastically. That's what I mean by metrics.

COFFEY, Q.C.:

Q. Doctor, how--in terms of, for example, ER/PR and HER2/neu, how complicated, in fact, is it to actually keep the metric?

DR. DABBS:

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A. It's not complicated at all. We have a person, as I mentioned, who's dedicated to quality assurance and quality assurance projects at our institution, and the number of breast cases that we handle are a fair number, but it's fairly simple to go into the lab information system, abstract that information and just tally it up on an Excel sheet. So it's all electronic. There's really no pushing of paper.

THE COMMISSIONER:

Q. And the comparison that you're doing are internal comparisons?

DR. DABBS:

A. That's correct.

THE COMMISSIONER:

Q. You're comparing your results to results that you would have gotten in prior period of time, so presumably factors such as population base and all that kind of stuff don't enter into it. It's strictly what you are achieving internally.

DR. DABBS:

A. It's what I'm achieving internally, but also it gives me the ability to look at the

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literature and see, okay, what are the report of ER negative PR positive rates? And if you look at them, you know, they vary between two and eight percent. So, for example, if you're getting 10 percent or 12 percent, there's something wrong. That suggests to me that there may be an ER fixation issue or I would want to know what PR clone are you using.

THE COMMISSIONER:

Q. So let me make sure I understand this. What you're saying is that in doing what you call your metrics, which once again is a sort of look at things from somewhat of a distance, you are comparing internally. You're looking at what was being used at the time as an explanation for any differences, but in addition, you're looking to how you stack up against the available literature and a variation either from what the available literature would say to you is appropriate or from past experience using the same clone would cause you to say "do we have a problem? Let's look at it."

DR. DABBS:

A. Exactly. It gives you--it allows you to put

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your finger on the pulse of the results. You know, an example I might construct would be if you had a laboratory that was a two-day drive from here, or a hospital a two-day drive from here, and it contributed say 30 percent of your breast cancer specimens, if fixation was not optimal at that particular institution, it's going to affect your metrics. So if you change anything, if you change the fixation, the front, if you change the primary antibody, if you change the detection system, if you change the paraffin, you need to reoptimize and make sure that the results that you're getting are the same as before and the metrics is just another global way of looking at that. It's an internal comparison and it also gives you a connection to the outside world, what has been published. Should we be getting between 70 and 80 percent ER positive cases overall? And our metrics show 52 percent, there's something wrong inside. We're not doing well.

COFFEY, Q.C.:

Q. Another topic I wanted to ask you about is the purposes for which, in your experience, ER and

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PR tests are ordered by pathologists. I appreciate that they're certainly ordered routinely for primary breast cancer.

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. Are they utilized for any other purpose, in your experience?

DR. DABBS:

A. There are two other instances where one may order ER and/or PR. One would be specific requests by oncologists, and the group that I can think of at our institution would be the gynecologic oncologists, occasionally they will ask us for hormone receptors for endometrial cancers, rarely for certain kinds of ovarian cancers. That gives them documented evidence if they, for example, want to add an anti-estrogen therapy to patients who are already getting other therapies for disease. So that's one instance.

The other instance would be if it were in the process of working up tumours of unknown origin. Now let me explain that just a bit further. The presence of estrogen receptor

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can be useful in the work up of tumours of unknown primary site obviously in women. We're always looking for treatable diseases. So in our work up of tumours of unknown primaries, which generally are fairly extensive and have multiple antibody panels, the presence of estrogen receptor can point to either a GYN or a breast primary tumour. Now by itself, an estrogen receptor positive tumour does not necessarily mean a breast origin or a GYN. You have to take into account the entire panel before you arrive at that conclusion. But an ER positive can be a powerful piece of that puzzle, doing that detective work and trying to figure out what the source of the primary tumour is. So that would be the second instance in using that.

COFFEY, Q.C.:

Q. In that instance, the second instance, if one had reason to believe that for an extended period of time the ER results were producing at least a number of false negatives utilizing, in the second scenario, and that came to your attention, what, if anything, would that cause you to do?

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DR. DABBS:

A. Well, in the situation of the work up of tumours of unknown primary, it might cause some concern about the impact that a positive ER would have had in that particular case, and I think you would have to look at it on a case-by-case basis, because as I mentioned, there are a lot of other antibodies that are used in that work up and the case may be solved, even without an ER, okay. So -

COFFEY, Q.C.:

Q. An accurate ER?

DR. DABBS:

A. An accurate ER, correct. So could it have had an impact, yes, but I think you'd probably have to look at that on a case-by-case basis, because as I say, the ER result is just one part of that work up in that detective work.

COFFEY, Q.C.:

Q. And for example, if you were consulted and asked--you know, or told, look, we have--we've looked at and reexamined all of the primary ER negative tests, primary breast, I'm sorry, primary breast ER tests and negative tests originally, all primary breast ER negatives,

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we've gone through all them and we've done our examination, reexamination, that's done. Then you were told that we haven't looked at all the ER negatives for non-primary, and this covers seven or eight years, and you were asked, well, do you have any thoughts on what, if anything, we should do, we the institution should do? What would your view be?

DR. DABBS:

A. In that scenario, I would recommend that the tests be repeated with a properly functioning assay, because the goal there, as I mentioned, specifically with unknown primary, is to be able to identify those tumours that are treatable and one of them that is highly treatable would be a tumour that's ER positive, because there's a therapy for that. There's a medical therapy for that.

COFFEY, Q.C.:

Q. Doctor, the endometrial cancers that you referred to.

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. And same scenario and if it was used for

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endometrial cancers, would your response be the same, that it should be repeated?

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. So from your perspective, if there is cause to believe that the ER test was, to use, I think, Dr. Ejeckam's words, unreliable, erratic and unhelpful, your view would be that all the ER negatives should be redone?

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. Doctor, and I say all, not limited to primary breast, but include all?

DR. DABBS:

A. Correct.

COFFEY, Q.C.:

Q. Doctor, the subject of false positives has come up here at times. Could you tell us, please, about what you know about false positives in ER/PR testing?

DR. DABBS:

A. In false positives?

COFFEY, Q.C.:

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Q. Is there such a thing, first of all, as false positives, and if so, how common are they and how are they handled?

DR. DABBS:

A. I personally have not seen a false positive hormone receptor result, other than something that was fixed primarily in alcohol. So that brings to mind that if a tissue is improperly fixed in formalin, as I mentioned before, the next three solutions on the tissue processor are alcohol. So if something is getting just a very minimal exposure to formalin, it's theoretically possible that one could obtain a false positive result, based on alcohol fixation. The only other incident that I can think of would be with over antigen retrieval giving a simulated nuclear expression of something which happens to be biotin. If you're using a certain--the ABC method, as the method for immunohistochemistry in that situation, but overall, that should be exceedingly rare.

COFFEY, Q.C.:

Q. And Doctor, the mechanism in relation to the alcohol fixation, how does that actually--your

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understanding of how that works, if indeed that was to happen as the tissue which was not properly fixed to start with in formalin goes through the tissue processor -

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. - you know, how would that actually work then, the mechanism?

DR. DABBS:

A. Well, we do know that for certain antibodies, alcohol is not a bad fixative and the reason for that is because it doesn't generate all the chemical reactions that formalin does. So in some respects, some people use alcohol fixation routinely for a wide variety of antibodies, because the sensitivity is greater, and they get to use less antibody and don't even require antigen retrieval. However, as I mentioned before, the database that is built on hormone receptors, the whole data base and the outcomes associated with that have been on formalin fixed tissue, not alcohol fixed. So if you begin using alcohol fixative, and you say, well, I have, you know-

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-I'm getting positive results at a lower sensitivity, people don't know what that means with regards to what the outcome is. So there are--in immunohistochemistry, there are other items that can enhance your sensitivity for detection. Does that mean that we jump to use them all the time? No, not necessarily. For hormone receptor testing and HER2, we have a prescription for using this based on outcomes and to use something outside of that, then basically, your results are not within the parameters that have been previously performed and associated with outcomes. So that's the best way I can describe it.

COFFEY, Q.C.:

Q. Doctor, in your--from your perspective, if--well, I'll just ask, phrase the question in this way. What sort of circumstances, in your view, would warrant a laboratory, clinical laboratory, looking beyond the necessity of repeating a single test and requiring a wider review? What sort of circumstances, just kind of in general?

DR. DABBS:

A. Well, I think -

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COFFEY, Q.C.:

Q. And I take it, repeating a single test is not unknown at all. It's not common and you pointed to a percentage, I think it was less than two percent, yesterday.

DR. DABBS:

A. Right.

COFFEY, Q.C.:

Q. But, and I take it if it gets beyond two percent, your metrics are showing you that, you make inquiries but what else?

DR. DABBS:

A. Sure. Well, I think if for some reason, the clinician oncologists request a case to be repeated because it's negative, because the patient doesn't have many other options in terms of therapy, and if it turns out to be strikingly positive, that is a red flag that something definitely was not correct with that initial test result, and that should initiate, I think, a full scale look at when that case was done, under what conditions and you could probably track it down to who actually performed the test that day on a given instrument.

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So, you know, an unexpected marked significant change in a result is always a red flag, be it immunohistochemistry or a serum sodium or serum potassium or whatever. That's an issue that needs to be looked at by a team in the laboratory.

COFFEY, Q.C.:

Q. A quality assurance program in relation to an IHC laboratory, what would you expect to find or to be included in such a program, quality assurance, the approach to it?

DR. DABBS:

A. Quality assurance. Well, I think that first and foremost, one needs to have metrics in place so that you know where you are and you know how things are operating. You need to have all the items that I mentioned before and basically went through the consensus recommendation. Everything from proper grossing and fixation of tissue, proper thin slicing, and all the items associated with that, positive and negative, internal and external controls on the slide, the external controls on the slides, all those items that I showed from the, you know, recent consensus,

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those, to me, are best practices for immunohistochemistry and, you know, the metrics part of it and the use of FDA approved kits, all of that is, in my opinion, the optimal and the ultimate in terms of quality assurance for these complex tests that affect patient care.

COFFEY, Q.C.:

Q. Doctor, you have referred to FDA approved kits. Are there such things for ER and PR?

DR. DABBS:

A. Yes, there are.

COFFEY, Q.C.:

Q. Okay, and in the context of, for example, the Ventana automated machine -

DR. DABBS:

A. Yes.

COFFEY, Q.C.:

Q. - how does a kit figure into it? Perhaps you could just comment.

DR. DABBS:

A. Sure. Well, as with any FDA approved kit, it comes with instructions and reagents and it's a prescription. It's a cookbook, if you will. It says this is the way you do this test. If

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the test says that you incubate the primary antibody for 32 minutes, then you have to incubate it for 32 minutes. If it gives you a window, it says you can incubate it between, you know, 28 and 34 minutes, that's fine. But if you go lower or beyond that, it's not an FDA approved kit. So that's what the FDA kit means. You have to use, under these parameters that the company has tried and tested and brought it to us and have shown us comparable results with other outcomes, that's the reason for the FDA approved kit. So it has to be used to prescription. You can't just take the antibody out and use your own, you know, home brew, so to speak. So that's what -

THE COMMISSIONER:

Q. When you say FDA approved kits, I think in terms of things like, you know, approval of drugs, for example.

DR. DABBS:

A. Yes.

THE COMMISSIONER:

Q. Which means that somebody is looking at a particular drug and after X number of months

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or years, in some cases, examining within a laboratory, it says "okay, you can now use that." Would the same thing be happening to the Ventanas of the world who wanted to do this, they would have to present to some approval authority, their machine, the guidelines that they have arrived at and the authority would then, in turn, presumably, independently, examine those claims?

DR. DABBS:

A. That is correct, and an example would be, you know, for HER2 testing, when that first came out, DAKO had the Hercept test and that was the only approved test for that. Over time, another--Ventana came out with another antibody or actually took the CB11 antibody to FDA approval, and more recently, they have another HER2 clone, the 4B5, and in like fashion, the ER and PR for the SP1 and 1E2, I think have cleared, and DAKO has its set, and so each company, there are several companies out there that have approved kits that are available.

THE COMMISSIONER:

Q. Okay.

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COFFEY, Q.C.:

Q. Doctor, is there, within the pathology community, is there any disagreement about the need for FDA approval of the kits that are utilized?

DR. DABBS:

A. Well, I think that you will get differing opinions upon the necessity. There are good laboratories that will say that they do a fine job of using analyte specific reagents. These are not FDA approved kits. The burden is on that medical laboratory director to prove that their results are, you know, comparable. So that's a burden that is upon the medical director. There are differences of opinion, I think, in this consensus committee that was held in Santa Barbara. There were people who were balking at that. The cost is certainly a consideration and these kits are more expensive than building your own assay in house. But again, my point that I brought to the group was we're here for standardization and we're talking about all these issues related to pre-analytic variables. Why would you not want to standardize the test platform?

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COFFEY, Q.C.:

Q. The analytic part of it?

DR. DABBS:

A. The analytic part of it, and so subsequently, most of the people there agree that that should have been included. Are there some people who have different opinions? Yes, there always will be.

COFFEY, Q.C.:

Q. Ask you, Registrar, please, Exhibit P-2728? Doctor, this is a letter dated--memo or letter dated July 22nd, 2008. It's addressed to Dr. Nash Denic, clinical chief at Eastern Health. It's from Dr. Nik Makretsov. See him there. Have you had a chance to have a look at this document, Doctor?

DR. DABBS:

A. Yes, I have.

COFFEY, Q.C.:

Q. And Doctor, can you give us your thoughts on this, please? It's styled or introduced as, "following the discussion with you, I'd like to propose the draft describing the plan of action regarding the breast pathology practice at Eastern Health."

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DR. DABBS:

A. Yes. You know, as an overall statement, I felt that the content of this letter was really well put together and on target and I think really reflects a lot of best practices that are currently--that we currently have at our institution. He suggests using--to endorse the Royal College of Pathologists and UK Guidelines for reporting of breast disease, and these are sort of along the guidelines of the CAP synoptic reporting guidelines, which is what we use, and to operate and update, enrich current standard operating procedures regarding breast specimens based on those documents. Because what the synoptics do, basically, synoptics, baring anything else, if you look at that, it's sort of a starting point, because it tells you what you need to do upfront in order for the person who's doing the grossing and the person who's doing the microscopy and the person who's doing any additional complex testing. So synoptic reportings are standard operating procedure and a necessity for accreditation by the CAP and hospital laboratories in the States.

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And to implement weekly mandatory interdepartmental breast slides review by a panel of at least two pathologists, this is an excellent practice. I can tell you that, at our institution, we have several things. Every day at 1:30, we gather around a multi-headed microscope, and there's also a wall-mounted television screen, where we discuss cases that are of interest or difficult, difficulty, or just have educational aspects to it, because residents, fellows, and attending pathologists are there. But the other aspect that we do is for all new cancer cases, first diagnosis, a second pathologist reviews that and that's documented, and then the other thing that we do for all negative breast core biopsies is a second pathologist also reviews that. So that the goal there is to minimize any false negative reports on breast biopsies. So this is--number two is an excellent method of assuring quality. Number 3, "To reinstate breast pathology, radiology weekly grand rounds." Again, that's an excellent collegial item that, by the way, all these items that have been mentioned here are

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also seen in white paper by the Susan Komen Foundation that was published in the Breast Journal about a year and a half ago indicating that all these items here are sort of desirable aspects of an interdisciplinary breast team.

No. 4, "Organization steps towards the creation of a multidisciplinary breast unit engaging surgery, pathology, radiology." Yes, weekly management meetings. And we currently have that at our institution, as well. Again, this fosters interdisciplinary collegiality, exchange of information and whatnot. And you know, one of the nice things about this is that you get challenged by your colleagues. For example, if you're presenting a lobular cancer and you're telling the group in that room that it's ER negative, someone is going to let you know right then and there that that's not right, what else could this be, have you looked at it and so forth. So is a very open style meeting in our institution that enriches everyone.

No. 5, "Dedicate two pathologist assistants to breast pathology as a primary

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duty." That sounds like an excellent sort of centre of excellence approach, if you will, two people who will handle these specimens the best possible way. I would just caution and encourage that if those two pathologist assistants are away on vacation, that there are other people as competent to step up to the plate and do the same thing.

So, "to implement specimen audit in breast pathology in order to monitor any deficiencies in the specimen accession, gross examination." Yes, that's excellent. We have that, as well. Since we have pathologist assistants and residents rotating through our institution, our pathologist assistants are really the stable element there. And I treat them and actually established, I think, four years ago now, a method of examining them in terms of the quality of the work that they do. And so basically what we did was generate lists of all the things that they do and we look at the--at these lists quarterly and determine how people are doing in their position. Are there people who are, for example, cutting sections too thick, are there

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people who are--whose tissues they're submitting need to be reprocessed and just issues like that, so that we get feedback to people and are able to improve the system from within and how this is going on a quarterly basis.

And then finally, he's suggesting tissue microarrays for ER/PR and HER2 testing, which is an excellent valid way of monitoring quality assurance by putting these TMAs on individual patient's slides. It doesn't get any better than that. So it sounds like a very ambitious and a plan that's devoted to high quality.

COFFEY, Q.C.:

Q. They're the questions I have, Doctor. Thank you, Commissioner.

THE COMMISSIONER:

Q. That's it. Do you have questions of this witness?

MR. PRITCHARD:

Q. I don't have any questions, Commissioner. Thank you for your evidence, Dr. Dabbs.

THE COMMISSIONER:

Q. Mr. Simmons, would you like us to take the

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morning break before you begin? I'm assuming you want to ask questions.

MR. SIMMONS:

Q. I will have a few questions.

THE COMMISSIONER:

Q. Was that an unsafe assumption?

MR. SIMMONS:

Q. That's a safe assumption. And a break would be helpful, thank you.

THE COMMISSIONER:

Q. All right, then, why don't we take the morning break and then we'll proceed with your questions.

(RECESS)

THE COMMISSIONER:

Q. Please be seated. Mr. Simmons.

DR. DAVID DABBS, EXAMINATION BY MR. DANIEL SIMMONS

MR. SIMMONS:

Q. Thank you, Commissioner. Dr. Dabbs, I'm Dan Simmons, I'm the lawyer here for Eastern Health, which is the regional health authority that's responsible for the immunohistochemistry laboratory.

DR. DABBS:

A. Um-hm.

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MR. SIMMONS:

Q. I was very interested in your presentation, as I'm sure many people back at the lab and others were. And I want to start just by asking you some questions about the ad hoc working group that you referred to when you began your presentation because I understand it was from this ad hoc working group that met that these recommendations, consensus recommendations have been generated. Can you tell me a little more about how the working group was composed and how it came to be that this group of people have been addressing this question of developing standardized procedures?

DR. DABBS:

A. Sure. I think based on e-mail list serve type of communications that it began probably about three years ago that we decided that it would be a good idea to get together to formulate ideas based on evidence and to exchange this information and to meet at one place where we could do this in a more efficient manner and be able to have cross talk. And basically the people who subsequently got together were

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supported at, let's see, I think the first place that we met was in Santa Barbara and then the second place we meet was in Marathon, Florida. The first meeting, I think, was in 2006. This was sponsored by DAKO, and we had our first committee meeting there. The composition of the group was, as I mentioned, they were people in academia, reference laboratories, scientists. I probably wouldn't do justice to all the names of the people there, but basically all the people who have a high profile in immunohistochemistry in terms of publishing were invited.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. Some of those people did not make it, some of those people who did not make it sent representatives from their laboratory who were there, so it was a pretty good cross section of people in academia, reference laboratories and people associated with government who were there. The first meeting that actually generated a paper, the paper that was published last year on immunohistochemistry

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was actually, that took place in Marathon, Florida just prior to a course that is offered down there. It was offered at the end of January that year and it was offered by Dr. Yazidgee; he was the host for that conference. That conference was then repeated in Santa Barbara January of this year and we met right before that conference again. So that seems to--we've done that twice now. That seems to be a pattern. I don't know if we're scheduled to meet again. The next meeting is supposed to be in January for Dr. Yazidgee's course, actually, which I will be speaking at. So whether this group meets again, I'm uncertain at this point.

MR. SIMMONS:

Q. Okay. Would it be fair to say that the ad hoc committee, then, represented a fair cross section of the leaders in the field in immunohistochemistry?

DR. DABBS:

A. Very much so, yes.

MR. SIMMONS:

Q. In the United States?

DR. DABBS:

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A. Yes.

MR. SIMMONS:

Q. Any representation from outside of the United States?

DR. DABBS:

A. I hope I don't get this wrong. I don't know if there was anyone there from Canada or not. Like I say, I don't remember the names of all the people who were there, but I'm not certain. There were--well, at the meeting in Santa Barbara there were some people from Europe. There was Moensvyberg, who is the person who is the basically the director of Nordic QC out of Copenhagen. And I believe there was at least one person, perhaps two from UK NEQAS. I think Dr. Miller might have been one of the people, but I don't want to guess on their names. It was at least one person, perhaps two from UK NEQAS and other people from the States.

MR. SIMMONS:

Q. Now you mentioned it was three years ago that this initiative began through, I gather you referred to list serve?

DR. DABBS:

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A. Yes.

MR. SIMMONS:

Q. So I presume there is e-mail or other conversations among people?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. That lead to the formation of this ad hoc working group?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Why was it initiated, what were the background reasons for wanting to bring this group together to do this work?

DR. DABBS:

A. Well, I think that there was some inherent frustration on the part of these pathologists that given the way that things went with HER2 testing that now pathologists were trying to get a better handle on hormone receptor testing, which is also as important a prognostic and predictive test as HER2. And so the pathologists wanted to take the initiative, seeing what had happened with HER2

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testing and trying to optimize it and standardize it for pathologists across the country.

MR. SIMMONS:

Q. What was it that had happened with HER 2 testing?

DR. DABBS:

A. Well, the history of the HER2 testing was such that there was a fair amount of interlaboratory variation regarding results. This lead to dissatisfaction on the part of clinicians, our clinician colleagues, oncologists who treat breast cancer patients. And as a result of that there was a joint meeting, a gathering of pathologists from the College of American Pathologists and ASCO, the American Society of Clinical Oncologists to get together to try to come up with some scheme, proper scheme that would reflect more accuracy in HER2 testing. And as a result of that meeting guidelines came out for HER 2 testing and one of those guidelines was for the very first time that there was a statement regarding the mandatory minimum fixation time in formalin for HER2 and so on and all those

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guidelines came from this joint organization. So that's basically a synopsis of the HER2 story.

MR. SIMMONS:

Q. Those guidelines, I believe they came out, was it as late as 2007 that those were actually released?

DR. DABBS:

A. That sounds about right, yes, about two years ago.

MR. SIMMONS:

Q. Yes, okay. So because of this experience with HER2, I gather then that there was a recognition on the part of these leading pathologists who you were in communication with that the issue of ER/PR testing needed to be looked at similarly?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Is that a fair statement?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. Okay. And what were the types of concerns

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that people had about ER/PR testing that made these leaders want to take on this effort?

DR. DABBS:

A. Well this wasn't necessarily a completely new issue. But if you look at the literature and what had been done worldwide, there were issues with fixation, there were papers written about different methodologies, different reporting schemes and there was generally an unevenness in all of these parameters in the States.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. And so this attempt was to get together, to come to some consensus based on the evidence that was out there to try to make it more uniform so that laboratories would be able to adopt a more uniform method of reporting.

MR. SIMMONS:

Q. Okay. And you mentioned that the first meeting was sponsored by DAKO. Was the work of the ad hoc committee carried out under the authority or in connection with any kind of professional organization or governing body or

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regulating body?

DR. DABBS:

A. No, there was not. Although there were people from such bodies there, there was a person who represented the Association of Directors of Anatomic and Surgical Pathology, also known as ADASP, A-D-A-S-P, there was a person there who represented CLIS, Clinical Laboratories Standards Institute, CLSI, I'm sorry and other--but no other formal, it wasn't done under the aegis of any particular organizing membership or body.

MR. SIMMONS:

Q. So I'm curious then about what the effect and impact is of releasing a consensus statement like this with recommendations for standardization of parts of the process of ER and PR testing. Without an organization standing behind it, some licensing or professional organization, how do these recommendations then find their way into use in clinical practice in different laboratories?

DR. DABBS:

A. Yes, the, one of the people on this committee,

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the person associated with CLSI, indicated that this was information from the proceedings of this would be given to the CLSI. And also there were people there who were associated with committee memberships on the CAP. So at least in part while it wasn't, not formally set up, this information does get back to these governing bodies. And I can tell you that since the first paper that came out in the AIM Journal that some of those items have already showed up on CAP checklists regarding fixation and documentation and things of that nature. So while it's not done under the ageis of a formal body, the informal nature of it is an attestation that there's a need and the information does disseminate sort of upstream, if you will, to governing bodies who take notice of the importance of this. So it's, that's generally the way that process worked.

MR. SIMMONS:

Q. Right. Now, your first meeting was in 2006?

DR. DABBS:

A. Yes.

MR. SIMMONS:

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Q. By that time, at least here in Newfoundland and Labrador and likely in other parts of Canada the fact that there was a large scale ER/PR testing retesting being done here was known, it was public information. Was that known to you or other participants at the time that you embarked on this work in 2006?

DR. DABBS:

A. In 2006 it was unknown to me. I am uncertain if it was known to anyone else. It was not brought up during the proceedings of that committee. I would have remembered that.

MR. SIMMONS:

Q. Okay. And there are consensus recommendations, there's been two papers, one after the 2006 meeting and one now to be published out of the 2007 meeting. You say you're uncertain whether the consensus group will come back together again. Can you give me your view as to how far along this ad hoc working group has moved the issue of addressing the things on which consensus needs to be found and which standardization needs to be looked at in immunohistochemical testing for ER/PR?

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DR. DABBS:

A. Well, I think that the publication will certainly have impact and I think, as well, the governing bodies of which some of the members are associated with, CAP, CLSI, that information has gone back to those governing bodies. So I think we're still in the early phase of seeing what the potential fallout of that will be. But I feel fairly confident in that when these recommendations do come out and are actually published, that these will be taken up by the accrediting agencies for laboratories in the US, specifically the CAP. I have little doubt that that will occur.

MR. SIMMONS:

Q. Were there areas where there was--well, obviously consensus was reached for all the recommendations. But I gather from what you've said before that there may have been some degree of debate on some of these issues as to what the consensus would be. What were the more significant areas in which that debate had to take place in which there were differing views or opinions about what should be recommended?

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DR. DABBS:

A. Um-hm. Well, I think that every item that came up in the recommendations, that ultimately came up, were discussed very thoroughly.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. Everything from fixation to the antibodies that were discussed to the reporting method. Perhaps one of the more contentious was the issue of FDA approved kits. But again, I think that once the discussions were over, people had no problem including that in their recommendation. There was a varying degree of experience on the part of everyone there, everyone had different experiences. I'm sure that people from UK NEQAS and Nordic QC had different experiences from many of the Americans sitting around the table, and we all shared evidence, the best that we knew it. And so there was no single item that stood out and people pretty much came to an agreement that this is what needed to be done and basically everyone is on board with those

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consensus recommendations.

MR. SIMMONS:

Q. Okay. I gather from your evidence as a whole that since you've reviewed a number of papers that have come through at different times that have seemed to advance the knowledge and understanding of ER/PR by immunohistochemistry that the basic science of it has been better understood as time has gone on, is that a fair statement to make?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. And that there's been development and change in the testing methods and the available antibodies, reagents, detection kits and hardware over time, as well?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Yes, okay. Would it have been possible before the last couple of years to generate the kind of consensus on recommendations like this that you were able to do, if you had tackled that five years earlier, would there have been more

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uncertainty about what the recommendations should be at that time?

DR. DABBS:

A. I think that based on the literature that was in existence five years ago that probably very similar information would have come out of this.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. The only difference would have been that the SP1 antibody wasn't around at that time.

MR. SIMMONS:

Q. So can you offer any observation as to why it wasn't until '06, '07 that this effort was undertaken rather than, say, five years earlier, in 2001 or 2002?

DR. DABBS:

A. Yeah. No, I really can't speculate on that.

MR. SIMMONS:

Q. Okay. Thank you. The recommendations that the committee has made, this may be obvious, but I'll ask you anyway, do they represent the direction that IHC for ER/PR testing should be going in or, in your view, do they represent

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the existing state of testing as carried out in labs through the United States? In other words, once labs look at these recommendations are many labs going to have things to do to bring themselves into compliance with them?

DR. DABBS:

A. I think that this document was put together to show direction. I think that there are laboratories that have probably always practised a good practice similar to these recommendations.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. I think that it's meant to be a direction and that, yes, there will be laboratories that will need to pay attention to certain of these recommendations, perhaps some more than others.

MR. SIMMONS:

Q. Um-hm, okay. In your experience, when new information comes out in the literature about practices that are appropriate to be followed or that should be considered in something like IHC testing, how long does it take for those

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things to find their way into actual clinical practice in the laboratories, is there a lag time between the doing of the science and the research and then the implementation on a large scale?

DR. DABBS:

A. I think that generally there is a lag time. It's difficult because there are so many publications that are available to sort of wade through these and try to discern what impact they have. I think that papers such as the consensus recommendation with the list of people who were involved in putting that together, probably have more of an immediate impact just because of the nature of the group that gets together and puts together recommendations as opposed to a scientific paper, for example, with new information. So --

MR. SIMMONS:

Q. So would an advantage of the work of the consensus group be that the leaders in the field will put their heads together, consider the accumulated body of research that's been carried out, and distil that down into a set

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of recommendations that are more easily adapted by either clinicians into their regular practises?

DR. DABBS:

A. Yes, that's fair to say.

MR. SIMMONS:

Q. So the consensus statement makes it easier for someone else to come to these conclusions and to know what are the best practises to follow?

DR. DABBS:

A. It would.

MR. SIMMONS:

Q. Yeah. You were asked some questions by Mr. Coffey about laboratory accreditation in the United States, which is of interest to us because you may be aware there is no accreditation in this province for laboratories, and has not been aside from the general accreditation available for institutions. The Clinical Laboratory Improvement Act of 1988 --

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Did that have anything to do with encouraging

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or mandating laboratory accreditation in the United States?

DR. DABBS:

A. Well, it was--that was just one part of an ongoing act that came up with various improvements over time.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. One of the key items of CLIA 88 actually had to do with cytopathology and PAP testing, but each--whenever revisions or new information would come out regarding that Act, they were usually related to the laboratory. The inspection process has been in the States basically a function of the federal government.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. And they use agencies such as CMS, JCHO, and the CAP as bona fide accrediting agencies. So they operate at the pleasure of the federal government.

MR. SIMMONS:

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Q. So all laboratories have to be subject to accreditation by one of those agencies?

DR. DABBS:

A. Yes, they do.

MR. SIMMONS:

Q. And how long has that been the case, do you know?

DR. DABBS:

A. I don't remember exactly how long that's been, but it has been for quite a long time. I don't have the answer to that.

MR. SIMMONS:

Q. Would you say at least for the last ten years, if not longer?

DR. DABBS:

A. Oh, certainly, yes, yes.

MR. SIMMONS:

Q. I presume you're familiar with some of the work done in the United Kingdom done by Dr. Rhodes in which he looked at inter-laboratory variability of ER and PR testing results?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Has any similar work been done in the United

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States, any similar research?

DR. DABBS:

A. There have been similar studies performed on immunohistochemistry, in general, regarding, for example, epitope retrieval or antigen retrieval, and I think that was sort of a star point of Dr. Rhodes paper regarding hormone receptor, but ever since the introduction of that, there have been ongoing studies trying to compare methods in heating methods and different solutions for antigen retrieval. That all originated out of actually from Dr. Shon R. Chi who spent a great deal of time with Dr. Clive Taylor at the University of Southern California, and there's a lot of papers on antigen retrieval. It really opened up the field of immunohistochemistry because prior to that there were many antibodies that were desirable to use on formalin fixed paraffin embedded tissue that just did not work until antigen retrieval. So it opened up a whole new world and it also, as I mentioned before, it levelled the playing field for formalin, for fixation issues that you can have tissues fixed for any length of time, you

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could use antigen retrieval to bring it to a proper reaction product that can be used in the clinical sense, but in terms of other antigen retrieval methods in estrogen receptor, hormone receptor testing, there's not much.

MR. SIMMONS:

Q. And I--and I may have this wrong, but I understand that some of the work done by Rhodes and those with him in the UK, actually involved looking at the end result of hormone receptor testing and comparing it across laboratories where each laboratory was given the same tissue and asked to take it, prepare a slide, assess it, and report the result. Have I got that?

DR. DABBS:

A. That's correct.

MR. SIMMONS:

Q. Yes, and one of the outcomes of that was there was a significant variation found among laboratories for the results that they reported back on these testing at the time they did their study?

DR. DABBS:

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A. Yes, it was variation that was in the end thought to be due largely to antigen retrieval.

MR. SIMMONS:

Q. Uh-hm, okay, and--but I gather from what you've said, that there has not been a similar study done in the United States to assess whether at any point different laboratories in the United States were similarly reporting different results?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. Okay. Just in relation to the work done in the UK, as a result of the studies which showed variability among laboratories, do you know if there were any clinical consequences from that, and by that I don't mean changes in practises going forward in the future, but do you know if that initiated any concern about the validity of test results that had been already performed at any of those laboratories?

DR. DABBS:

A. Well, as far as antigen retrieval goes?

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MR. SIMMONS:

Q. As far as patient care, whether it initiated a concern that any patients had not had the correct results they needed for their clinical care as a result of this finding that there was considerable variation in some cases between laboratories and the results?

DR. DABBS:

A. Well, I think one of the directions that paper would have had an impact would have been on attempting to standardize the test kits and the testing method, and that's where I think companies ultimately saw that utilizing analytes specific reagents in home brew tests was a variation that was undesirable, and hence there was a push, at least in the States, to FDA approved testing kits where antigen retrieval was prescribed and the antibody detection methods were all prescribed.

MR. SIMMONS:

Q. So the research produced information that was useful to improve the quality of testing from that point forward?

DR. DABBS:

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A. Yes.

MR. SIMMONS:

Q. And that was the use which was made, to your knowledge, of that research, was it?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Okay. You've referred to your text which we've heard of before in this Commission. I think it's a reference valued by the technologists here now, and you mentioned it's in the second edition. The first edition came out in 2002, I believe, did it?

DR. DABBS:

A. I believe October of 2002, in the Fall, yeah.

MR. SIMMONS:

Q. You mentioned as well that there are some other texts and prior to your book in 2002, though, were there any other texts that addressed the technical aspects of immunohistochemical testing as comprehensively as the one which you've edited?

DR. DABBS:

A. There were texts that--I don't know that you would consider them textbooks per se, but they

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were more like manuals that were available through certain publishers, but they were more laboratory sort of basic science oriented and not oriented towards the clinical laboratory. So that's where my textbook differed, it was more applicable to the clinical laboratory.

MR. SIMMONS:

Q. And I gather that part of the reason for you preparing your textbook and initiating it was the recognition of the need for just such a text for immunohistochemical laboratories?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Which was not available before yours?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. You've told us about--and I may jump around a little bit here form topic to topic. You've told us about H scores and Allred scores and so on, and different means of reporting the interpretation of an ER/PR test, and if I understand correctly, there's at least four different variations that I've heard mentioned

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by you. One would be to simply report the result as positive or negative. Another would be to repot the percentage of nuclei that have stained positive that shown any staining. Third would be the Allred score, which you've explained how that works, and then the fourth would be the H score which you use in your institution. Are those primarily the four ways in which these tests have been scored and reported?

DR. DABBS:

A. Those are four common ways in which tests have been reported, yes.

MR. SIMMONS:

Q. Do you know if simply reporting the tests as positive or negative is still in use, or whether that's now been discounted and no longer accepted?

DR. DABBS:

A. I think if you survey probably in the States, it would probably be a minority.

MR. SIMMONS:

Q. Uh-hm, but you would still find that some institutions --

DR. DABBS:

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A. You may.

MR. SIMMONS:

Q. Choose to report that way.

DR. DABBS:

A. You may.

MR. SIMMONS:

Q. Was there a time when reporting as simply negative or positive was not in the minority, but maybe the predominant way of reporting this test?

DR. DABBS:

A. I think that the majority--the most prevalent method of reporting always had to do with some sort of number.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. And I think the most common number at least for the first ten years was probably the cutoff at 10 percent that I mentioned.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. So that was not just a positive or negative result. They would indicate that more than 10

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percent, and some laboratories went further and broke it down, the percentage.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. That's why the consensus group felt that it was more important to do a semi-quantisation because semi-quantisation is important for individual patients.

MR. SIMMONS:

Q. So do I understand then that if the percent is to be reported, there may then be a couple of variations on that. It could be reported as a number; 8 percent, 25 percent, 60 percent, 80 percent, or do I understand you to say that some practises may have been to say greater than 10 percent or less than 10 percent without defining it beyond that?

DR. DABBS:

A. There have been laboratories reporting as such, yes.

MR. SIMMONS:

Q. Yes, okay. Your laboratory reports the H score method?

DR. DABBS:

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A. Yes.
MR. SIMMONS:
Q. And for how long has that been done at Magee?
DR. DABBS:
A. The H score method basically is derived from a formula that shows the intensity and proportion of cells.
MR. SIMMONS:
Q. Uh-hm.
DR. DABBS:
A. And we began reporting the intensity and proportion of cells in 2002. About six months ago, basically what we decided to add to that was to do the math, if you will. If you do the math from that proportion and intensity, you derive the H score. So we decided to revise our reporting method in sort of a synoptic format. Basically, what we do is--and it wasn't just about the H score. We use proliferation indices, we use HER 2 score, and we use the ER along with lympathic space invasion as a sort of synopsis on the immunohistochemistry reporting form, and decided to add the H score to give our clinicians a quantitative number that would be

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an easy reference. In doing so, what we did was we went back and looked back and looked at 30 months of our repots, converted them all to H scores, and then looked at the median and mode percent of cells staining for each category. So, for example, if I see an H score of 250, that means automatically to me that he median number of cells staining in a situation like that is greater than 75 percent, and we have those sort of little mnemonics present on our reporting forms so that when a clinician sees that, they look at that and they say it's easily translatable, they can use whatever they want. So that they get used to it. So that an H score to them, 250, somewhere down the road as they get used to it, they'll think more than 75 percent of cell staining. So it's helpful in that regard.
MR. SIMMONS:
Q. So you don't now actually report the percentage of cells stained and the H score, it's only the H score, that's the only number that's given, is it?
DR. DABBS:

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A. No, we continue to report the percent of cells staining as well as their intensity.
MR. SIMMONS:
Q. Yes.
DR. DABBS:
A. And the H score.
MR. SIMMONS:
Q. And the H score.
DR. DABBS:
A. Right, and we have these little mnemonics in there that will show in bold brackets a mean score, H score of 250, equals greater than 75 percent of cell staining.
MR. SIMMONS:
Q. Shorthand, okay. Now in 2002, can you give me a quick example of how you would have actually reported an ER/PR test in 2002?
DR. DABBS:
A. Yes, we - since 2002 and to date, we have a statement on our ER/PR report that basically is a cut and paste from the NIH Consensus Conference that says that a negative result is zero staining and a positive result is any nuclear expression, and we say "and is semi-quantitated as indicated below", and basically

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that shows the brackets with the percent of cell staining, 1 plus, and percent, 2 plus, and there's a percent, and 3 plus.
MR. SIMMONS:
Q. Yes.
DR. DABBS:
A. The only thing that we added five or six years later was we did the math and applied that as well.
MR. SIMMONS:
Q. Now prior to 2002, how were they reported?
DR. DABBS:
A. Prior to 2002, to some degree they were reported by a H score method that was a little bit different than what we used to use. There are variations of an H score method. The one that was in use was based on a scale of zero to 500 and it was a little more tedious in terms--the scoring method, instead of zero to 3 plus for intensity, it went zero to 4 plus, and then there was a mathematical factor added in of 100, so that's why the spread was greater.
MR. SIMMONS:
Q. Uh-hm.

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DR. DABBS:

A. But the H score method as used, we did a internal validation with what that meant in terms of cell intensity and percent of cell staining over that 30 month period, and the H score, in general, you can use for any kind of immunohistochemisty staining. Basically, what it is, it's a combination of percent of cell staining and the degree of intensity. So the committee has been--one of the items we discussed for some time was trying to add some uniformity to how to report any immunohistochemistry stain, and basically we came down to a description that says we're supposed to say what is staining, where it's staining, and how is it staining.

MR. SIMMONS:

Q. Uh-hm, okay. So for ER/PR then, do I understand correctly that the consensus recommendation for how to report it is, in fact, the method that you used at Magee from 2002 until a couple of months ago?

DR. DABBS:

A. Correct.

MR. SIMMONS:

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Q. Rather than the H score?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. In your presentation, if we can bring up page 7, please, of P-2621. Dr. Dabbs, there's a reference here on your slide to the Perchuck et al ER ID5 study done in--published, anyway, in 1996?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Now when you mentioned this yesterday, with my note I may have this wrong, I understood you to say that based on this study, it concluded that a 10 percent report of ER staining was as clinically effective as reporting the exact percentage and the intensity of the staining. Have I got that right?

DR. DABBS:

A. That's correct, that's what the paper by Perchuck said.

MR. SIMMONS:

Q. So this would be one of the papers that would support the proposition that there's little to

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be added to the clinical usefulness by reporting the intensity versus just reporting the percentage. Would that be correct?

DR. DABBS:

A. Strictly speaking in terms of the result of the test, yes but there are other issues associated with reporting staining intensity which are of quality issues too.

MR. SIMMONS:

Q. Okay. So from the clinician's point of view then, this study, and there may be others that say the opposite, but this study would say that the clinician using the result gets as much value out of getting a percentage alone as out of a percentage combined with an intensity?

DR. DABBS:

A. Yes, that's correct, and if you--and there have been several studies performed, including whenever we looked at the 30 month period where we converted our reporting method into H score, that, yes, the answer is the percent of cell staining does correlate with scoring method of percent plus intensity.

MR. SIMMONS:

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Q. Uh-hm.

DR. DABBS:

A. And some people argue that there's some subjectivity--more subjectivity in the interpretation of intensity than there is percent of cell staining.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. But the utility--the real utility of reporting the intensity of staining is that your assay shows a range of intensity of staining and isn't all or none.

MR. SIMMONS:

Q. So it's--so the real usefulness of assessing the intensity then is as a quality assurance measure?

DR. DABBS:

A. At least--it is at least in part, but what it also permits you to do is to generate an actual quantitative number --

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. That is reasonably reproducible in terms of

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the H score because clinicians are clinicians, and clinicians everywhere, they like numbers, and there are other testing modes available for estrogen and progesterone receptor not by immunohistochemistry that will give an actual quantitative number. So what we do in our reporting format in our institution is we report raw scores of staining, percent plus intensity, we report the actual numerical number associated with that as well, and we also cite as references points what that means in terms of the median number of cell staining for any particular case.

MR. SIMMONS:

Q. Okay. On page 8, there is a reference in the slide in the bottom left there to a study published in 2005 by Fisher, and I understood you to describe this study as being one that compared ER/PR results from the older biochemical assay method to results using an immunohistochemical method?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Is that correct? I was curious, this being

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2005, I had gathered from the early part of your presentation that the biochemical assay method had been pretty well displaced by the IHC method by this time?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. And I was wondering what the purpose was in 2005 of doing that comparison here in this study?

DR. DABBS:

A. Oh, sure. Well, Dr. Fisher was the pathologist for the NSABP and this clinical trial was actually performed back in the 70s. So basically what it was, it was a follow-up cohort of those patients, about 400 patients in that B-09 protocol. So he had the DCC data. It wasn't like it had been generated anew.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. Okay, that was archived data, and so he had all the tissue blocks from those patients. So he basically, said, okay, this is how we did

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our ER then, let's see how we can--the scoring methods, and what that was basically was scoring methods, it was any or none, it was semi-quantitative with your eyeball, and there was a group that did a more detailed analysis with image analysis, and the conclusions of that were that any of those modes were equal in determining how patients outcome was with regard--in five and ten years, which is a really nice follow-up for that group of patients, but what it did not say or attempt to say was the importance of quantisation for the individual patient, okay.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. Because as you know, you can have patients who have 11 percent of cells or those who have 85 percent of cells, and I can tell you from my experience in looking at all the data and doing the cross-analysis, that someone with 80 percent of positive cells is virtually certain to be ER positive and PR positive, and it's that group of patients that respond best to therapy. So if the clinician has a patient

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who is young and healthy, and has no contra-indications to this medicine which can give you--put you at increased risk of endometrial cancer, it can give you strokes, it can give you thromboembolism, not to mention some other less than satisfactory side effects like hot flashes and what not. For a patient who is healthy like that, it should be no problem, but if this patient has relative contra-indications, medical contra-indications or is elderly and frail, and their ER is 11 percent or 5 percent compared to 80 percent, you look at that and the clinician has to weigh, you know, weighing the risk/benefit.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. Am I going to harm this patient more by giving this medicine or am I going to be doing her better by giving her this medicine, and that's where quantisation for the individual patient becomes important. It's not important for populations.

MR. SIMMONS:

Q. Now you said that those that are ER positive

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and PR positive are known to respond better to hormone treatment?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. And that's based on clinical studies, is it?

DR. DABBS:

A. Yes, it is, multiple clinical studies.

MR. SIMMONS:

Q. Now the next piece of that, you said that a high ER score is usually also a high--a PR positive?

DR. DABBS:

A. That's correct.

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. Basically, it goes the best responders are ER positive and PR positive, and those ER scores are almost always more than 80 percent cells.

MR. SIMMONS:

Q. Has there been any clinical study looking at jus the ER score and the intensity of the ER score, ignoring whether the PR is positive or negative and correlating that with clinical

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outcome?

DR. DABBS:

A. Yes, there have been, and basically the hierarchy, if you will, would be--of course, the patients who respond best are ER positive, PR positive. The next group is ER positive, PR negative.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. The next group is ER negative, PR positive.

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. And the group that tends not to respond are the ones that are double negative.

MR. SIMMONS:

Q. I understand that, but has there been any study to take the ER score and compare scores of 1 percent, 10 percent, 20 percent, 50 percent, 80 percent, and assess clinical outcome compared to the percentage on that basis that you know of?

DR. DABBS:

A. Yes, well, most of the papers that have

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outcomes associated with it, that includes either biochemical assay or IHC, have comments about the method, the response, if you will, the patients who have 1 percent of cells don't respond as well as patients who have 50 percent. That's virtually in every paper that has an outcome associated with it. It was the paper by Harvey in 1999 that was sort of a seminal paper that took the barrier, if you will, down to greater than 1 percent of cells.

MR. SIMMONS:

Q. Right.

DR. DABBS:

A. But in the paper that actually was in the mid 90s by Mascarelli, 1995, that's where they did the ID5 with the 10 percent and 5 percent cutoff and found the difference.

MR. SIMMONS:

Q. Yeah.

DR. DABBS:

A. That was sort of the telltale then that maybe we could go lower than 5 percent.

MR. SIMMONS:

Q. Uh-hm, okay. On the next page, page 9, you have a slide and I think this is in--there's a

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slide on the lower left here also headed "Different procedures intra and inter laboratory compromise standardization".

DR. DABBS:

A. Uh-hm.

MR. SIMMONS:

Q. Was that to be "intra" and "inter" laboratory?

DR. DABBS:

A. Yes, "inter" and "intra".

MR. SIMMONS:

Q. Inter and intra laboratory, and you've identified the preparation phase, the staining phase, and the interpretation phase there with arrows with a series of different steps in the procedure identified in each of those phases, a total of, if you add them up, I think there's 14 different steps there that you've categorized, and on the very bottom there you've got 3 to the power of 14 equals 4.8, and is that million?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Million procedures. So I may be interpreting this wrong, but do I take you to be saying

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here that if in each of those 14 steps there are three possible variations of the way to perform it, that step, that means that for the total process there's 4.8 million different variations in the whole process?

DR. DABBS:

A. Yes, potentially to sort of--it's a high impact slide that show that of these three particular phases, there are a total of 14 different kinds of variations. So you could change one in there, you know, and change the next one, and change the next one. The point being that there are no two laboratories that may have the same exact fixation method or the exact same paraffin, or the same temperatures in their tissue processor and so forth. So the issue here was that--was an attempt at standardization.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. It's ideal to be able to get a control on all of these phases and that's what we attempted to do at the consensus conference was address the pre-analytic, analytic, and post-analytic

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factors.

MR. SIMMONS:

Q. So aside from the standardization through the recommendations that were made, would it be fair to say that of these 14 step procedure, laboratories in the United States do employ variations in each of those steps from laboratory to laboratory?

DR. DABBS:

A. There are variations inherent in every laboratory. There are many devices, tissue processors, that vary between laboratories.

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. There are tissue processors in--multiple tissue processors in a hospital, and, you know, there may be three different brands of them all operating differently. So what we try to do, though, what we've recognized over time is that fixation is absolutely key. Extreme temperatures are absolutely key. You don't want to overheat specimens during processing, and all of those features basically flowed from the evidence that we, as

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a group, put together and acknowledged that were probably most important in minimizing the impact of the--the high impact of the slide.

MR. SIMMONS:

Q. One of the things we've heard is that ER/PR testing has to be optimized within each lab that's doing it, and would that be because there has not been the kind of standardization which you're now promoting, that it had been necessary for each lab to separately optimize and validate its variation on these different steps?

DR. DABBS:

A. Yes, exactly.

MR. SIMMONS:

Q. And have there been any--it's one thing to say there's no standardization of the steps. Has there been any consensus or standardization of the way you go about validating your own testing even?

DR. DABBS:

A. Well, I think that the first paper that came out in the AIM Journal had a very nice description, and I think I alluded to some of these, how to do immunohistochemistry in

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general, especially for those cases that are not categorical like ER and PR testing, that you're supposed to take a certain number of cases --

MR. SIMMONS:

Q. Uh-hm.

DR. DABBS:

A. A certain number that are high expressors, certain ones that are low expressors, and certain ones that are intermediate, or negative, and use those as your optimization procedure. That information has been gleaned, if you will, from immunohistochemistry literature over the ages, but I think that this committee for the first time, you know, congealed it and put it in its first round of recommendations in the paper that came out last year.

MR. SIMMONS:

Q. In 2007.

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Okay. There's been some discussion regarding training and qualification of laboratory

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technicians who perform immunohistochemistry, and since you're here from another jurisdiction, from the United States, it's an opportunity to find out the way things are done where you are. I presume there is some formal type of licensing for laboratory technicians in Pennsylvania, is there?

DR. DABBS:

A. Yes, there is.

MR. SIMMONS:

Q. Is that a state responsibility or US federal government, or would you know?

DR. DABBS:

A. It's a state responsibility, so they operate under licensing in the local state, but they also have to have qualifying exams and pass those from their schools that they attend, be it in histotechnology, you know, or whatever area.

MR. SIMMONS:

Q. Right. Is there any special licensing or some set of licensing specifically for technicians performing immunohistochemistry?

DR. DABBS:

A. There isn't a specific licensing per se, but

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there is an examination that one can sit for that shows sort of a special qualification, if you will, in immunohistochemistry.

MR. SIMMONS:

Q. And who sponsors that examination or who makes it available?

DR. DABBS:

A. That examination, as I recall, is sponsored by the ASCP.

MR. SIMMONS:

Q. Okay.

DR. DABBS:

A. I believe it's the ASCP. I'm not 100 percent certain on that.

MR. SIMMONS:

Q. Okay. To your knowledge, is there, are there any special courses of training available for technicians in immunohistochemistry? We know that there's some schools that technologists can go to to learn histochemistry, but are there--is there specialized training available for immunohistochemistry?

DR. DABBS:

A. There are courses available, sponsored by various organizations and probably the largest

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organization is holding their meeting right now in Pittsburgh, the National Society of Histotechnologists.

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. They have lots of workshops, people who are prominent in the field giving lectures.

MR. SIMMONS:

Q. Okay. So it wouldn't be--the school where a technologist would go as a student to learn the basics of their profession, that wouldn't be where you would go to do the immunohistochemistry course? It would be something offered by an organization like the National Society of Histochemistry?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Yes, okay. More in the line of continuing education?

DR. DABBS:

A. That's true. Now I can tell you that we--in as far as histotechnology schools go, we have a school at our institution and those students

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are exposed to immunohistochemistry, just like they are everything else in the laboratory, as part of their training program.

MR. SIMMONS:

Q. Their basic program?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Okay. You'd mentioned that there's--I think you have a research lab at your institution as well?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. As well as a clinical lab. Do you, in your position, play any role in the management of the technologists and technicians, staffing issues, filling positions, that sort of thing?

DR. DABBS:

A. Well, I work closely with our laboratory administrator and the person who works closely with her is our manager for surgical pathology. So when there are staffing issues, I hear about them, whether people are leaving or have been hired. We have a rather

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extensive checklist of competencies that people are made to go through and sign off, whether they be histotechs or people doing immunohistochemistry or path assistants or whatever. There's a competency for everything that they need to sign off.

MR. SIMMONS:

Q. Are you able to offer us any comment or observations regarding the availability of appropriately trained people, technologists for immunohistochemistry?

DR. DABBS:

A. Yes. Generally speaking, if people are going to be--if histotechnologists are going to be doing immunohistochemistry, it comes from a desire from them from within to want to do this, and we train them on it. Again, I say we, you know, we document all of their competencies. We don't force anyone to do that. We have a select group of people who do that and they rotate whenever. It's their responsibility through that particular, you know, service arm of the laboratory. Is it difficult to get qualified people? I would say in general it's difficult to get

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histotechnologists where we are, and that's why we created our own school.

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. So that sort of helps us out in the long term. Yes, it is difficult to get qualified people who are interested in that, and you know, it sort of goes back to what I was saying earlier when I was giving the presentation about the Dextran-coated Charcoal method were done by technicians who are very heavily versed with laboratory science, you know, chemical columns, all sorts of very complex aspects of a scientific laboratory, not a hospital laboratory, and one of the reasons why that never really took on in hospitals, because those people just generally didn't work in hospitals, nor could hospitals afford that, you know, complex equipment.

MR. SIMMONS:

Q. In your presentation, page 17, please? There's a mention here, on the right-hand side, in recommendation 11, of the three antibody clones that are recommended. One of

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those being SP1, and at this point in your presentation, I have a note that you mentioned a study performed in 2006 concerning SP1, and my note was that it compared ER results to testing performed using the 1D5 antibody.

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. Does that sound familiar? And I'd noted that you'd said that using the SP1 clone, there were eight to ten more positive cases than there were using the 1D5?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. All right. So out of 100 samples run in that study, there would be eight to ten samples that would have been reported negative using 1D5 and positive using SP1?

DR. DABBS:

A. I believe that was the conclusions of the author in that particular study, where I think they used the one--greater than one percent of cells cut off.

MR. SIMMONS:

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Q. Yes.

DR. DABBS:

A. And I think the cases that became positive were all weakly positive.

MR. SIMMONS:

Q. Okay. So there were--out of 100 tests, there would have been eight or ten that went from zero with 1D5 to weakly positive with SP1?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Which, by your definition, would be moving from negative to positive?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Have any--are you aware of any similar studies comparing the SP1 clone to the 6F11 clone?

DR. DABBS:

A. To the SP1 versus the 6F11 clone?

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. Just an in-house study that I looked at because we were using the 6F11, and the 6F11,

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according to the literature, is slightly more sensitive than the 1D5.

MR. SIMMONS:

Q. Okay.

DR. DABBS:

A. Okay, so when we were--when I was looking at converting to the SP1 clone, I took 20 or 25, I can't remember which, of our negative cases with 6F11 and came up with three that were weakly positive. They were actually--they were less than one percent of positive cells, but if you're including any cases that are--rather a positive result is any nuclear expression, then they would be considered very weakly positive. So in essence, by looking at our select group of negatives with the SP1, according to a very comparable protocol from what was published in JCAHO 2006, I was able to reproduce the exact number of cases that became weakly positive with that.

MR. SIMMONS:

Q. Okay. So if I understand correctly, of the 20 to 25 cases you tested using 6F11 that were negative, meaning zero, on retesting with SP1, there were three that were now weakly

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positive, although very weakly positive?

DR. DABBS:

A. Um-hm.

MR. SIMMONS:

Q. So had those cases first been tested after the introduction of SP1, they would have been reported as positive cases in your institution?

DR. DABBS:

A. They would have been reported as weakly positive, less than one percent of cells.

MR. SIMMONS:

Q. Okay, and would that have been any cause at all for any concern for you to look back at any other negative cases that had been done using 6F11, out of any concern for the clinical treatment of the patients?

DR. DABBS:

A. I don't think so. Basically, the investigation there was to look and see if the study that was published could be reproduced in my laboratory, and it was, and I think that just as these antibody clones become available and evolve, that the 1D5 is a little bit less sensitive than the 6F11, which apparently is a

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little less sensitive than the SP1, and but the key thing is that they're all very robust antibodies and that they give solid, reproducible and accurate results. You have to keep in mind that every--since they are monoclonal antibodies, they have a very limited range of specificity. So that where you may see one being positive weakly, another one may well be negative, because when these antibodies are generated, the antibodies that are generated are generated against specific areas of the estrogen receptor molecule and they're that specific. So while the 1D5 may see epitope A, 6F11 may see a part of A and most of B, epitope B, and SP1 might see A, B and part of epitope C. Okay. So you really don't know until you begin testing these on tissue. But they all show very comparable results, in terms of immunostaining.

MR. SIMMONS:

Q. So there are base scientific reasons why you would see some differences among the three antibodies, in recognition of positivity?

DR. DABBS:

A. Based on the clone, yes.

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MR. SIMMONS:

Q. So then, as a clinician or as a pathologist who's selecting an antibody here, how do you determine which one is best? How do you determine in any particular case which one is producing the right result, when you have one saying a positive and one saying a negative?

DR. DABBS:

A. Well, I think what you have to look at is with the outcome studies that have been performed with each one of these clones, and they all show very good correlation with endocrine response in outcomes of large numbers of patients, thousands of patients, and that's really the proof that the antibody and that testing measure works. We all know that whenever we have some of these conversions from negative to weakly positive, like in example from 6F11 to SP1, that there are many clinicians for a select group of patients where a weak, you know, changing to one percent or less than five percent, whatever cut offs that they would use clinically may have no impact. A patient who is very weakly positive, they think might not get much of a

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bang out of the therapy and think, you know what, I don't think that this individual patient is going to benefit by this. But if you look at the overall outcome studies and response, yes, patients who are high expressors are going to respond best. The ones who are low expressors, no matter whether they're SP1 weak or 6F11 weak or 1D5 weak, and in fact, if you look back at the consensus statement from the NIH that I showed, if you read into further areas which I did not show, it will say--it says that if tissue is not available or the result is uncertain that the patient should be treated as though they're ER positive.

MR. SIMMONS:

Q. That was the 2000 NIH consensus statement?

DR. DABBS:

A. Yes. So you know, while there apparently is some subjectivity in terms of testing method, there also is subjectivity from the clinician, in terms of who are they going to treat with a given result. It's not all cut and dry and black and white.

MR. SIMMONS:

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Q. Okay. Just to go back for a second then to that 2006 study, comparing SP1 to 1D5 with the eight to ten percent difference. Just presuming now that you had a laboratory that was switching from 1D5 to SP1 and their own concordant study matched the results of this 2006 study that you referred to.

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. They would have a situation where the clone they're using tomorrow, the SP1, was going to find eight to ten percent more positives than the one they used yesterday, the 1D5. In your experience, would that be any cause for consideration of reexamining your recent negatives under the 1D5? Because presumably, you'd find eight to ten percent of those that were now positive and patients who presumably could benefit from that information.

DR. DABBS:

A. I think really, the answer there revolves around what clinicians do with these extremely low expressors and I think, in general, that doesn't really do very much for clinicians.

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Whenever they see a very low expressor like that one percent or less or something where there's just, you know, one positive cell, that doesn't do too much for their clinical decision making.

MR. SIMMONS:

Q. Okay. You gave some evidence regarding dilutions of antibodies and in conjunction with the optimization of an antibody, such as the ER antibody, and I believe I either saw reference or heard you say that the process you'd use for introducing a new antibody would be to start with the manufacturers specifications sheet and see the dilution that was recommended on it, and then try probably a dilution one above and one below, and you'd run some test slides and see which, and I'm not sure if you said this or if I read this in your book now.

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. But does that sound right?

DR. DABBS:

A. Yes. That was part of the actual first paper

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that came out, the recommendations, yes.

MR. SIMMONS:

Q. Okay, yes. Now when you say one above and one below, just to take a concrete example, if the manufacturer's recommendation is a dilution of one in 50, one part of antibody to 50 parts of, is it dilatant?

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. Yes, okay, what would the one above be and what would the one below be?

DR. DABBS:

A. Okay. So if you have one in 50, then the one below would be one in 100 and the one above would be one in 25.

MR. SIMMONS:

Q. Okay. So they would be -

DR. DABBS:

A. A stronger and a weaker dilution.

MR. SIMMONS:

Q. So the one above would be half the recommended dilution?

DR. DABBS:

A. Right.

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MR. SIMMONS:
Q. And the one--and the next one would be double the recommended dilution, and you would compare these, results of each of those, and you would select among one in 25, one in 50 or one in 100, as the dilution that you would use?
DR. DABBS:
A. Correct.
MR. SIMMONS:
Q. Okay. Now if you are comparing--well, you also spoke about a potential source of error in the testing being variations in the dilution that's actually used, maybe as a result of pipette calibration, for example, or technologist error in the preparation of the dilutions. If you were working with a one in 50 dilution, would it be fair to say that the type of error that would result from pipettes or technologist error would probably be much less of a difference from one in 50 than the alternatives that you've chosen when you've done your validation? I didn't put that very well. If you want to achieve a one in 50, what sort of error would you expect to find if

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there's not appropriate attention being paid to issues like calibration and technical control of the dilution?
DR. DABBS:
A. I find that impossible to answer, because if the technician really doesn't--isn't well versed in using the pipette and/or calibrating it, then they could be off on both parts. They could be off on the antibody concentration, as well as the dilatant. So you could end up with--I have no idea what that titre ends up being.
MR. SIMMONS:
Q. Okay. Mr. Coffey asked you about a possibility of there being false positives in ER and PR testing and one of the--you mentioned that there's two ways in which that might occur, and one of them you said was that if there was too much antigen retrieval when using the avidin biotin method, the ABC method, that there could be an effect on the slide which I understood you to say could be mistaken for positivity?
DR. DABBS:
A. Correct.

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MR. SIMMONS:
Q. Right. Would that same concern apply to the peroxidase, anti-peroxidase method?
DR. DABBS:
A. Probably not.
MR. SIMMONS:
Q. Okay. You've spoken about internal controls. Is it correct to say that you can interpret an ER or PR result without an internal control, that the presence of an internal control is not a mandatory element to be able to interpret the result?
DR. DABBS:
A. And to that I was speaking, if you have a core biopsy which is 100 percent tumour and doesn't have any normal tissue and you have a proper external control that's placed on the same slide -
MR. SIMMONS:
Q. Yes.
DR. DABBS:
A. - and you have a positive result, that would be an acceptable result. That would be no cause to reject the specimen. On the other hand, if the result, in the same situation, if

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the external control was negative on the slide and the test tissue was negative, that's a cause for concern. That's saying that most likely the antibody wasn't dispensed or something else went drastically wrong to give you a negative result times two. And again, a safe measure for a situation where you have tumour with a positive external control on the same slide and a negative tumour result still means that it should be repeated on the resected specimen to assure that that negative result wasn't due to sampling alone.
MR. SIMMONS:
Q. Okay. You were shown a memo prepared by Dr. Khalifa here back in 1998 at the time when what was then the Health Care Corporation here was switching, the laboratory was switching to ER/PR testing from the biochemical assay method to the immunohistochemistry method. And in the course of some questions that you were asked then, including by the Commissioner, I think you were asked to describe what would be the appropriate way to validate the introduction of the IHC method in those circumstances. And I'm not sure I

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gathered from your answer, I'm not sure I understood if you actually explained what would have been the ideal way to do that. And I'm wondering if maybe you could try that again for me?

DR. DABBS:

A. Okay. You mean moving from the -

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. - biochemical assay to immunohistochemistry?

MR. SIMMONS:

Q. Yes. What would a lab do, what would be the way for a lab to tackle that in '97, 1998 based on what was known at the time?

DR. DABBS:

A. Based on what was known at the time?

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. Basically in '97 and so forth the papers by Mascarelli and Perchuck were out there regarding 1D5. So I think by using that methodology for the 1D5 that was published, and I think at that time the 1D5 was probably

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the only ER antibody that was available and the 6F11 came, I think, a little bit later.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. And the SP1 until recently. So it would have been acceptable to recapitulate the methodology that Perchuck et al used and Mascarelli and in the process of working that up, verifying the optimization and the conditions for that. Then doing comparative studies with your data that you have with the dextran-coated charcoal method like the paper by Fisher and comparing them, cross comparing them, they came up with a ten percent cutoff, ideally, if it was available locally to have outcome studies associated with those patients who had the biochemical assay. Then you would have a clinical validation, as well. But my point is since Perchuck did a clinical validation with that test, then it would be acceptable for the setting up the assay to set up the assay exactly as they did using the same cutoffs and expecting the same sort of outcome result. But it would have to be

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followed to the letter.

MR. SIMMONS:

Q. Um-hm. Pretty well all labs in North America at some point made the switch from biochemical assay to IHC for ER/PR testing.

DR. DABBS:

A. Yes.

MR. SIMMONS:

Q. From your experience and your knowledge do you know if that was a commonly followed approach exactly as you set out here or do you know what other labs have done when they've made that switch -

DR. DABBS:

A. I do not know what other laboratories have done.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. I do know that the best practice and one of the items that we tried to get across through the consensus recommendations is that, you know, we looked at what was out there validated, not only technically, but also clinically.

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MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. And that's why we cite the paper by Harvey et al from 1999, that was the paper that Allred was also on, where they discovered that it was the one percent, patients who had one percent or more did have an outcome that was associated with endocrine manipulation. So whether people utilized that information, per se, is beyond me, I don't know for sure. But what we wanted to do was at least point in the direction that if this is clinical validation that you're looking for, these are the conditions that you have to have to use and you have to use this scoring method, this antibody, under these conditions. You can't just--you cannot just obtain an antibody, work it up your own way and say this guy used ten percent, I'm going to use ten percent. That's not a clinical validation.

MR. SIMMONS:

Q. So aside from going to the literature and doing that kind of review and finding those studies, back in '97, '98, do I take it then

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that there was nothing equivalent to a consensus recommendation about what the process should be to introduce ER/PR by IHC?

DR. DABBS:

A. Well, I think that the papers, there may not have been a consensus statement, per se, but the papers by Perchuck, by Mascarelli and then a few years later by Harvey, clearly demonstrated that this is the process that they followed. And I think that, you know, a reasonable pathologist knowing the vagaries of individual testing should be aware that they can't pick an antibody out of the sky and work it up and expect to have the same outcome as something that was published and validated clinically.

MR. SIMMONS:

Q. A few other specific things coming out of your examination this morning. You were asked some questions about, by Mr. Coffey, about refrigeration of specimens once placed in formalin. And if I understood you correctly to say, what I gathered from what you'd said was that the important thing is to get the specimen sliced within an hour of when it was

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removed from the--of surgical removal, and that whether it goes in formalin before or after that would not--I'm sorry, I'm confused now. The important thing was the slicing and if it had to wait before being sliced, refrigeration maybe might be of some advantage. But once it makes it into the formalin, refrigerating it in formalin isn't going to add anything to the fixation of the specimen?

DR. DABBS:

A. Refrigeration in formalin will not add anything to the specimen, no.

MR. SIMMONS:

Q. Is it possible that refrigeration in formalin would actually slow the effect of the penetration of the formalin?

DR. DABBS:

A. That's certainly conceivable since we know that heating formalin will accelerate fixation and penetration, in fact, yes.

MR. SIMMONS:

Q. Okay. You discussed reprocessing of tissue this morning. Do I gather from your evidence that reprocessing is something that does

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happen on occasion in your laboratory at Mcgee?

DR. DABBS:

A. It happens in our laboratory; I'm sure it happens in every laboratory to some degree.

MR. SIMMONS:

Q. Sure, right. And you've told us that reprocessing, if a specimen is adequately fixed, reprocessing should have no effect on it?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. I gather that. If it's inadequately fixed, reprocessing won't improve the specimen?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. Now, if the reason for reprocessing is that the specimen had not been adequately dehydrated during the tissue processing phase, would reprocessing have some positive effect then?

DR. DABBS:

A. Well, it would have a positive effect on

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allowing the technician to cut an adequate section.

MR. SIMMONS:

Q. Yes.

DR. DABBS:

A. But it wouldn't have an effect on immunohistochemistry.

MR. SIMMONS:

Q. And would have no effect on IHC. So in essence then fixation will have an effect on the IHC, but whether the tissue is reprocessed, well fixed or not, is not going to have any particular effect on the performance of the IHC test?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. Now you've told us about the metrics that you gather in your lab. Can you give some indication of how long your lab has been gathering this sort of information?

DR. DABBS:

A. Sure. Think for a second. This information has been gathered since 2000--in the form that I'm familiar with.

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MR. SIMMONS:
Q. Yes.
DR. DABBS:
A. Since I became chief and that would have been in 2003.
MR. SIMMONS:
Q. Okay. And do you have any idea how common a practice that is among immunohistochemistry laboratories you're familiar with, to track these sorts of metrics that you're tracking in your lab?
DR. DABBS:
A. I do not know how frequent that is. I think that one of the items, you know, the sort of new paradigm for complex testing, this includes ER/PR and HER2, HER2 has been a lot more visible in many respects and people, you know, would say, well, what's your positive rate for HER2.
MR. SIMMONS:
Q. Um-hm.
DR. DABBS:
A. Because in the literature there are many papers that say, you know, 20 to 30 or 25 to 35 percent, and that's not what--those numbers

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have been tossed around without qualification. If you look at the original clinical trials where they considered patients who were two plus and three plus -
MR. SIMMONS:
Q. And this is the HER2 now, you -
DR. DABBS:
A. Yeah, the HER2, right.
MR. SIMMONS:
Q. Yes, okay.
DR. DABBS:
A. That number may hold up, but if you look at patients who are actually three plus, the number is closer to 15 percent and probably doesn't rise beyond 18 percent.
MR. SIMMONS:
Q. Okay.
DR. DABBS:
A. In a laboratory that's performing the test correctly.
MR. SIMMONS:
Q. Okay. This morning also that in discussing that same topic you mentioned that your laboratory had moved to what you called controlled fixation?

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DR. DABBS:
A. Yes.
MR. SIMMONS:
Q. And I think I understand what you mean by that, but can you explain to me a little more just what exactly you mean when you refer to controlled fixation?
DR. DABBS:
A. Sure. The controlled fixation basically is documenting how long the specimens are sitting in formalin.
MR. SIMMONS:
Q. That's the documentation?
DR. DABBS:
A. That's the documentation.
MR. SIMMONS:
Q. Um-hm. And when was that introduced in your laboratory?
DR. DABBS:
A. That was introduced in our laboratory right in January of 2007. That was right after our, one of our meetings.
MR. SIMMONS:
Q. Okay. Do you know how common a practice that is in other immunohistochemistry laboratories?

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DR. DABBS:
A. I know that it's becoming more common just in chatting with various people and getting phone calls and whatnot. I have, you know, given talks at various national organization meetings since then and people are on board with that and it's becoming a part of the CAP checklist that they use to accredit laboratories.
MR. SIMMONS:
Q. In talking about the change to the SP 1 antibody this morning you also said, or I noted that you said that your rate of cases that were ER negative, PR positive prior to the SP1 was 5.7 percent?
DR. DABBS:
A. Well, the SP1 antibody, that's the ER antibody.
MR. SIMMONS:
Q. Oh, the ER antibody, that's right, yes.
DR. DABBS:
A. Yeah, that's -
MR. SIMMONS:
Q. Yes, SP1 is the ER antibody, right. So using the SP1 for the ER antibody you had 5. 7

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percent of your cases that were ER negative and PR positive?

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. And after introduction of the SP1 that went to one percent?

DR. DABBS:

A. Well, it wasn't the SP1, the introduction of the SP1. It was the PR clone 1E2.

MR. SIMMONS:

Q. Oh, okay. So the PR clone changed, also?

DR. DABBS:

A. The PR clone changed also, right, also to a rabbit monoclonal, correct.

MR. SIMMONS:

Q. So you had fewer cases that were ER negative, PR positive. Was that because you now had more ER negative, PR negative or more ER positive, PR positive?

DR. DABBS:

A. There's more ER positive, PR negative.

MR. SIMMONS:

Q. Okay. Is there any clinical significance to that change in proportion?

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DR. DABBS:

A. Most likely not, and the reason for that is the literature, if you look at that, clinicians are uncertain what to do in many respects with the ER negative, PR positive group.

MR. SIMMONS:

Q. Um-hm.

DR. DABBS:

A. They tend to respond at least in the small amount of information that is out there, it's a pretty small group of patients. The most recent paper, I believe, was in JCAHO, and I think Dr. Ellis', Ian Ellis' name was on it. They had a small number, they actually came out with an uncertain result but they tended, they looked like they were maybe slightly responders like a very weak ER. Other clinicians believe that they act like a double negative, an ER negative, PR negative. But, so when you take into amount the small amount of information that's out there, it looks like it's sort of equivocal in terms of response.

MR. SIMMONS:

Q. So no clinically significant enough to merit,

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for example, going back and looking back at any of the patients who had been in a category that you now know to be reported differently?

DR. DABBS:

A. Correct. The only issue there would be if, you know, if your ER positive rate was somehow not within the realm of what's been published, that would be the concern. But other than that, no.

MR. SIMMONS:

Q. Okay. By the way, are you aware of any circumstance where any laboratory in the United States or elsewhere has used their metrics and found that their positivity rate was out of line and then have then gone back to look at previous cases to determine if there should be any treatment changes or clinical consequences?

DR. DABBS:

A. I am not aware of any literature to that effect.

MR. SIMMONS:

Q. Um-hm. Or anecdotally of any circumstances where that's happened?

DR. DABBS:

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A. No, no.

MR. SIMMONS:

Q. Okay. Mr. Coffey asked you about false positives this morning. And you told us personally you haven't seen a false positive result. And you said it was possible or theoretically possible to get a false positive if something had been primarily fixed in alcohol after very minimal exposure to formalin. Now, I think I've got that right.

DR. DABBS:

A. Correct.

MR. SIMMONS:

Q. I think I got that right. When you say very minimal exposure to formalin, what would that be, how minimal would that be, can you give us some indication of what we're talking about there when we say minimal exposure to formalin?

DR. DABBS:

A. Probably less than an hour or two.

MR. SIMMONS:

Q. So it would have to be less than an hour exposure to formalin for the later exposure to alcohol to theoretically have the effect of

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producing a false positive?
DR. DABBS:
A. Correct.
MR. SIMMONS:
Q. Right. And you say theoretically. Is there any kind of clinical evidence of false positives being produced in that way?
DR. DABBS:
A. Only in the regard whenever I had the--was looking at primary alcohol fixation that was this molecular friendly fixative.
MR. SIMMONS:
Q. Yes.
DR. DABBS:
A. What I would do is I would take the biopsies and divide them and part would go to our standard processing and start to--and others to alcohol. And that's where I noticed some weak positivity show up, weak to moderate positivity and it was really erratic, you couldn't predict when it would happen.
MR. SIMMONS:
Q. And in that case the biopsies going to the alcohol, had they ever been in formalin?
DR. DABBS:

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A. No.
MR. SIMMONS:
Q. No?
DR. DABBS:
A. They never saw formalin.
MR. SIMMONS:
Q. Okay. You spoke about FTA approved testing kits as being a recommendation that if possible that it's a good idea to use those. And this may be a technical question, you may not know this, may have to get this from someone else. Do you know if the Ventana benchmark automated tester is an FTA approved piece of equipment?
DR. DABBS:
A. Yes. I think the brand name that they give to that is Pathway or something like that.
MR. SIMMONS:
Q. Well, the one we're familiar with the Ventana Benchmark XT.
DR. DABBS:
A. The XT, yes, that's the machine. And the product that they use for that is, I believe, the marketed name is Pathway.
MR. SIMMONS:

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Q. Um-hm.
DR. DABBS:
A. It's a trademark for that line of FDA approved products.
MR. SIMMONS:
Q. Okay, so that line of approved products, would that include the pre-dilute antibodies meant for use in that machine and the detection kits, the other reagents used in the testing process in that machine?
DR. DABBS:
A. Yes.
MR. SIMMONS:
Q. Yeah. So when you refer to an FDA approved kit, would the Ventana Benchmark XT with those antibodies and reagents meet what you're suggesting in your recommendation there?
DR. DABBS:
A. That's correct, that would be one particular marketed line by a specific vendor. There are other vendors.
THE COMMISSIONER:
Q. Dr. Dabbs, how long has this process of FDA approved kits been going on?
DR. DABBS:

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A. Well, I think that there's been a move to that ever since the Hercept test for HER2 testing came about. There was a move to that to have more uniformity and a move away from analyte specific reagents in hospital laboratories because of potential internal, you know, variations. When was that, I would say it became more prominent for the hormone receptor at the turn of the century, earlier this decade.
THE COMMISSIONER:
Q. Thank you.
MR. SIMMONS:
Q. Thank you, very much, Dr. Dabbs. That's all my questions.
THE COMMISSIONER:
Q. Thank you, Mr. Simmons. Mr. Browne, it's getting near to the lunch hour, so I suggest we have the break for lunch and then we'll continue. But could you give me your estimate?
MR. BROWNE:
Q. I'll be 15 or 20 minutes. Mr. Simmons has covered a lot of the areas, so I'm just going to go back over (inaudible).

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THE COMMISSIONER:
Q. All right. Mr. Pritchett?
MR. PRITCHETT:
Q. We don't anticipate any questions, Commissioner.
THE COMMISSIONER:
Q. Ms. Newbury?
MS. NEWBURY:
Q. I'll be about 15 minutes or so.
THE COMMISSIONER:
Q. Mr. Crosbie?
CROSBIE, Q.C.:
Q. Not more than 30 minutes.
THE COMMISSIONER:
Q. Mr. Pike?
MR. PIKE:
Q. No questions. Thank you.
THE COMMISSIONER:
Q. All right. I guess we can govern ourselves accordingly for the next witness who is in the lineup. Thank you, we'll break for lunch and reconvene at five after two.
(LUNCH BREAK)
THE COMMISSIONER:
Q. Please be seated. Mr. Browne.

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DR. DAVID DABBS, EXAMINATION BY MR. PETER BROWNE
MR. BROWNE:
Q. Good afternoon, Dr. Dabbs. My name is Peter Browne, we met yesterday. I represent individual physicians, mainly pathologists and oncologists who have been called before the Inquiry. I just want to cover some of the areas, actually, just go back, Mr. Simmons covered with you in his cross-examination. But before I do that I just want to have a point of clarification. If we could, Registrar, have Exhibit P-2622. This is Dr. Dabb's curriculum vitae. And, Doctor, it may be my misunderstanding of--and if we could just scroll down here? Here we go. Doctor, your training here, it says July, 1976 to July, 1981, Medical College of Ohio. I take it that's your MD training?
DR. DABBS:
A. Correct.
MR. BROWNE:
Q. And then May, 1978 to May, 1979, pathology fellow. Did you do your fellowship during your undergraduate training or -
DR. DABBS:

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A. That's a good question. Actually, that's a good pick-up. In the States there was initiated, I think, a few years before this, probably, I'm going to say around 1975, a program called a Post-Sophmore Fellowship year. And what it was was it was created by pathology societies to attempt to increase the influx of people from medical school and garner an interest in them so that perhaps they might go into pathology. It was a recruiting method. So what I did in medical school, at the end of my sophmore year, which I think would have been 1978, I technically dropped out of medical school for a year and stayed at the Medical College of Ohio Hospital and did a fellowship in pathology and basically I did everything that a first-year pathologist in training would do during that year. And then at the end of that I reentered medical school, finished my clinical clerkships and graduated. And that year actually counted towards my residency requirements from the American Board of Pathology.
MR. BROWNE:

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Q. You admit that that's not the normal path that most pathologists follow?
DR. DABBS:
A. That's not the normal path, correct. It was something that the American Board and pathology organizations wanted to use to increase the interest of medical students in the realm of pathology.
MR. BROWNE:
Q. Okay. And you also mentioned, as well, that during your residency training you received a lot of attention and training in IHC, is that correct?
DR. DABBS:
A. Correct.
MR. BROWNE:
Q. Was that unique to your particular residency? Because we've heard, the Commissioner has heard a lot of evidence from several pathologists who have testified before her that depending on where you trained, your residency, the focus may be different. We've heard about training in anatomical pathology, general pathology and the different focuses there. So again, was that sort of a unique

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experience that you had as opposed to just general pathologists?

DR. DABBS:

A. I think it was probably more heavily weighted to immunohistochemistry in the residency where I was, yes.

MR. BROWNE:

Q. Okay. And I think you also mentioned in response to one of the questions of Mr. Coffey that between 1980 and 1984 where you did your residency, that was sort of the epicentre for immunohistochemistry?

DR. DABBS:

A. Yes, pretty much.

MR. BROWNE:

Q. And also again, just sticking with some sort of unique characteristics, if I may, and maybe I'm misinterpreting this, but you also had a fellowship in cytology, is that correct?

DR. DABBS:

A. There was--no, I did not have a fellowship in cytopathology.

MR. BROWNE:

Q. Sorry -

DR. DABBS:

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A. The last, towards the end of my residency I did a fellowship actually in diagnostic electron microscopy and surgical pathology.

MR. BROWNE:

Q. Okay.

DR. DABBS:

A. Now, you'll see under the -

MR. BROWNE:

Q. The certification, that, sorry, that's where I was -

DR. DABBS:

A. That was the certification, correct. And you know what, that examination was the very first time that examination was given and I think up until the year of, I want to say sometime in the 1990s a fellowship to sit for that examination was not necessary, but then it became necessary, I think, in the mid '90s, somewhere around that that you had to take a fellowship in cytology in order to sit for that examination.

MR. BROWNE:

Q. Okay. And just focusing on the cytopathology certification. I got the impression from your answer yesterday that that gave you another

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sort of additional advantage with the fact that this training helped you look at cellular formation as opposed to again the broader pathology residency. Is that a fair encapsulation of what I understood you to say?

DR. DABBS:

A. It is a fair, I think, analogy. It's just another tool, a different tool to look at cells. And you know, another aspect of that was electron microscopy, which is not in use nowadays very much, it's been supplanted by immunohistochemistry. So, you know, the tools in anatomic pathology, they vary with regards to how you examine tissues and cells and they all compliment each other.

MR. BROWNE:

Q. Would the cytopathology, though, help you, I guess, more in the--dovetail more with the immunohistochemistry interpretation?

DR. DABBS:

A. Not necessarily. I think cytology, the applications of immunohistochemistry and cytology, it helped in that particular area, yes.

MR. BROWNE:

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Q. Okay. Now, I understood you to say that by 1997, I think I got the quote correctly, that you got frustrated by lack of references there were and there were very few textbooks around the subject matter of immunohistochemistry. Is that--did I capture that statement correctly?

DR. DABBS:

A. Yes.

MR. BROWNE:

Q. Okay. And then as a result of that you approached publishers and then in 2002 the first version of your textbook came out?

DR. DABBS:

A. Correct.

MR. BROWNE:

Q. And, Registrar, if we could have P-1767? Doctor, this, Mr. Simmons, I think you spoke to this quite extensively this morning. This, in fact, is the document that we were talking about in terms that it came out of the Florida conference in 2006--or, sorry, it started in Santa Barbara and then Florida in 2007, is that right?

DR. DABBS:

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A. Correct.
MR. BROWNE:
Q. And this is the document that the authors Goldstein--so this was the ad hoc committee of which you're a member, I see down -
DR. DABBS:
A. Yes.
MR. BROWNE:
Q. Several people listed down in the lower right-hand corner.
DR. DABBS:
A. Yes, and there are--right, exactly.
MR. BROWNE:
Q. And I just wanted to sort of just focus on his, if I could, for a second and just have you sort of comment further, if it's necessary. But in the paragraph on the screen, just above "Preanalytical Factors" it begins, "Despite the improvements of reagents, automation, authors over the years have consistently noted the inconsistent quality of IHC assays. Unlike previous IHC epochs, most of the causative responsibility rests with the individual laboratory performing IHC." And then--and it goes on "and specifically the

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lack of standardization, attention to quality assurance programs." So by this time, it was evident to those gathered around the table about these meetings that there was a, can I say, human cry to move people in this direction?
DR. DABBS:
A. There was more of a concerted effort to acknowledge that there were variations that people saw in the published literature that needed to be addressed in a more focused manner that would have more of a global impact on the community.
MR. BROWNE:
Q. Okay. And then further on down it says, "Unfortunately, laboratories often do not appreciate the negative impact on their specimens and the validity of IHC performed on them by diverging away from these recommendations." So while all this information, I think if we look at the back--there's close to 100 references that are cited as the basis for these recommendations. But the observation was made, look, we need to bring all this literature together and develop

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these consensus statements, is that what I understand to be -
DR. DABBS:
A. Yes, that was the call.
MR. BROWNE:
Q. Okay. In the period that's under sort of review by the Commission, 1997, 2005, did your lab change its practice in respect of, say, the antibodies that it used?
DR. DABBS:
A. The laboratory changed, let's see. Well, I arrived on the scene in 2001 and I know that one of the things that we changed was we changed our HER2 antibody kit. We were, I believe, with the 1D5 antibody. We migrated to 6F11 and I'm trying to think of the date when that might have been. That might have been somewhere between 2003 and 2005. And then more recently to the SP1.
MR. BROWNE:
Q. Okay, so you have changed antibodies. What about the nature of your antigen retrieval, we've heard various evidence about the various approaches to antigen retrieval. The time that you at Mcgee, I guess is what you can

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speak of now. Have you changed the approach, your approach to antigen retrieval?
DR. DABBS:
A. The approach to antigen retrieval has been changed according to the protocols that have been established for these FDA approved kits that we use, yes.
MR. BROWNE:
Q. And you spoke yesterday about fixation times and I sort of want to draw this into, make a comment that you made, that there have been changes in fixation times based on ASCO and CAP recommendations. I didn't quite capture when those recommendations came out. Is this referring to this document or prior to that?
DR. DABBS:
A. No, it doesn't refer to this document. The CAP, ASCO guidelines which came out approximately two years ago, that was regarding HER2 testing and the recommendation there was that tissues had to be fixed for at least six hours for tissues that were going to have HER2 testing.
MR. BROWNE:
Q. Okay. Prior to, I guess this document, were

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there any recommendations or guidelines by ASCO and CAP with regard to ER/PR?

DR. DABBS:

A. No, not at all.

MR. BROWNE:

Q. Okay. So there was no standard guidelines in terms of fixation?

DR. DABBS:

A. Correct.

MR. BROWNE:

Q. Okay. So we can take it that up to this point in time most--we could not be certain as to what fixation times any lab was following throughout the United States?

DR. DABBS:

A. Well, there are multiple papers that have been published ever since the ER by IHC became prevalent. Some of the authors in those papers were Hector Battifora, for example. He clearly--well, he did some studies that clearly demonstrated that fixation--that results were dependent upon fixation time and so they had recommended sort of time windows. I don't know that there was necessarily a minimum time recommended as strongly as were

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maximum times for that. But there are papers that do tangentially address fixation and the importance of fixation for ER testing.

MR. BROWNE:

Q. And do these papers address like various, like we see with Rhodes paper and so on, sort of the cause and effect of various lengths of fixation time?

DR. DABBS:

A. Yes.

MR. BROWNE:

Q. You spent a bit of time yesterday and again today talking about, I think, the importance of reporting intensity. And I understand your views and you've explained to the Commissioner how you view it as an important tool for clinicians. We spoke about this, actually, yesterday, as well. And what prompted that discussion was your reference to Dr. Nadji, Professor Nadji in Florida. And is Dr. Nadji a member of this consensus group?

DR. DABBS:

A. He never attended any of the meetings, so the answer to that would be no.

MR. BROWNE:

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Q. Okay. Nevertheless, Dr. Nadji, and we have, Registrar, if we could put up on the screen Exhibit 2630? Has that been entered? Okay. Dr. Nadji is recognized in the area, he's published extensively in the area of immunohistochemistry, has he not?

DR. DABBS:

A. Yes.

MR. BROWNE:

Q. Okay. And this article is entitled, "Quantitative Immunohistochemistry, Estrogen Receptor in Breast Cancer, Much Do About Nothing." And if we look--I'm sure if that's my highlighted--it is my highlighted copy. But it says in the bottom paragraph of the, I guess, the abstract of this paper, he says, "In this review I attempt to prevent"--excuse me, "present an argument that is based on our current information, quantatation of ER IHC is neither technically reliable nor clinically relevant." Now, I know that you've, in fact, you indicated to me yesterday that you've written response to this. Is that correct?

DR. DABBS:

A. We wrote a paper that was aimed at addressing

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issues associated with this, yes.

MR. BROWNE:

Q. Okay. But I guess the point I'm drawing upon here is that there are people--there are two schools of thought on this, are there not, and that Professor Nadji represents the argument, at least in this paper, presents the argument against quantification, whereas you put forth the argument for quantification. Is that a fair synopsis?

DR. DABBS:

A. Yes. And I think, you know, basically if you put it in perspective, I don't know that there are two camps, necessarily. I think that the recommendations from the consensus group are clear and clearly represent the majority. I think that Dr. Nadji in his experience and perhaps with one other person who has published on this topic are in the distinct minority. If you look at the literature on Ligand Binding method throughout its entire history, you will find out that they quantitate that and the clinicians used those quantitative results to determine if they were going to give patients endocrine therapy.

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Whenever you take a test that is a continuous variable like that and you want to change the testing format, the onus is upon the laboratory director to see to it that that, the change or the translation of that test into a different format is properly optimized and validated. In other words, if we were talking about serum potassium and the range by this machine over here is 3.5 to 5.6, okay, and I decided to try a new test and I'm going to report is as positive or negative, okay, people are going to die because potassium is a very crucial analyte. Well, I don't consider that estrogen receptor and progesterone receptor are any less crucial because patient management and patient outcomes are based on therapy, and so, therefore, in my mind, and in the minds of the consensus group, we all fully acknowledge that if you even look at the immunohistochemistry literature--in fact, one of the very first paper that attempted translation that I cited where they looked at immunofluorescence of cells with antibodies to estradiol and determined that there was a heterogeneity of cellular staining. If you

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look at the immunohistochemistry literature throughout the decades, you will find that every paper discusses at least that. So I reject outright any assay that tells me that it's all or none immunostaining. That's not a properly validated assay, in my opinion, or the opinion of the people of this group, of the opinion of UK NEQAS people. So that's how I view that. I think this paper is a minority. I felt that it needed to be responded to, and that's why we put together our experience in our argument based on information that a properly validated immunochemistry assay is in a select group of percentage of cases going to show strong positive cells, negative cells, weakly positive cells, and intermediate positive cells, just like that slide--that single slide that I showed you, that picture, at the beginning.

MR. BROWNE:

Q. But, I guess, after getting these sort of divergent views, I guess you recognize--you would put Dr. Nadji in the minority, doesn't that heighten the necessity to have, as we now

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have with the 2007 and now the 2008, the need for consensus because of these sort of differing views?

DR. DABBS:

A. That's correct, and I'm certain that Dr. Nadji knew of these meetings. In fact, one of them was in his own back yard and he didn't attend. No one on this committee had any influence over him, it was his choice to attend or not, but I can tell you that an all or none assay for immunohistochemistry ER, all or none, does not exist in my mind, and it's not a properly validated translated assay.

MR. BROWNE:

Q. We--in your presentation yesterday, you dealt with the issue of--we can--I think it's P-2629. Oh, no, your PowerPoint, my apologies. Yes, sorry, actually let's just deal with that. I think, if I made a note to myself correctly yesterday, Doctor, you mentioned I think it's recommendations 11 and 12, that some labs are still using 10 percent. Is that --

DR. DABBS:

A. Yes.

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MR. BROWNE:

Q. Did I--okay, and this is why I wanted to sort of cover this off with you. In the paragraph --this is the article you put into evidence yesterday, comparison of evaluations for hormone receptor in breast carcinoma. The notion here, and I'm looking at the paragraph, "In particular, endocrine response uncertain was to find some expression of steroid hormone receptors quantitatively low, usually considered less than 10 percent of cells positive are qualitatively insufficient to indicate a substantial change in response". This notion, has that been talked about for a number of years, and, in particular, I would just--you dealt with this to some extent with Mr. Simmons this morning. In England, and we have--I think I put it in as an exhibit, P-2619, Doctor. Registrar, can we enter P-2619.

DR. DABBS:

A. While that paper goes up there, the paper that was up here, if I can just sort of scroll down to a particular place where I wanted to illustrate something--okay, under the

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discussion that I have up here, "As for ER, the bimodal distribution of the ER score by DAKO manual staining using antibody 1D5 was pointed out. That is in more than 94 or 90 percent of cases the tumours were completely ER negative or unequivocally ER positive. These results suggested that DAKO immunohistochemistry assay is too sensitive and perhaps not sufficiently specific". So they're citing basically results that are similar to Nadji as published in the past, which another group out of Boston has published in the past regarding the conditions of that test. So they're acknowledging here that they too experienced bimodal distribution, but noticed it's only with that one --

MR. BROWNE:

Q. Particular --

DR. DABBS:

A. Yes, which is the one that Nadji and the group in Boston had published on, correct.

MR. BROWNE:

Q. Sorry, Doctor, if we could enter P-2619, and I just want to--there's a comment here, Doctor,

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I'll get you to comment on or respond to, and I think you spoke to this to some extent in response to a question from Mr. Simmons this morning and that's the importance of these values for clinicians and the subjectivity surrounding that for oncologist, in particular, and this was a 1998 article and it talks about the cutoffs at 1 percent, I think, out of the literature out of the United States and so on, but this paragraph right here says, "Perhaps different cutoffs should be used, depending on the clinical situation, i.e., in the adjuvant or metastatic setting. It is the aim to identify patients who will respond to a particular regime or those who will not", and it goes on and talks about, for example, in a woman who's node negative and has a small low grade tumour, should have little impact, and again using--again responding to the 1 percent. If you look up above here, just right here, "A recent editorial in the British Medical Journal advocates a very low cutoff for selection of patients for adjuvant endocrine treatment, the San Antonio group having found significant benefit in women with

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tumours containing only 1 percent positive cells". So is this sort of paragraph speaking to what you talk about, you know, that in that 1 to 10 percent category, it's important for clinicians to weigh all the various factors and I think they talk about here, and some of those examples: tumours size, lymph node involvement, distant metastatic spread and so on. So there are other considerations especially are significant in that 1 to 10 percent. Is that what I understand these authors in the literature to be saying?

DR. DABBS:

A. I agree, and I think that this paper actually demonstrates that pretty nicely. If I could just scroll up here and show you this particular graph right here, which is a graph of ER predictive score versus the percent of patients responding, you know, their scoring method--basically, UK NEQAS uses a combination of proportion of cells plus intensity.

MR. BROWNE:

Q. Uh-hm.

DR. DABBS:

A. And they came up with the scoring method here

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which is not too dissimilar to any other scoring method, whether it be Allred or H score or whatever, but if you look at the highest score here which is 9, you have close to 80, you know, 75 percent of patients responding, but I will point out here that at a score of zero, 10 percent of patients are responding, and, you know, that's a--that number is a significant number in the States, I can tell you. If you tell a patient that they have a 10 percent chance of having metastatic tumour in their axilla from their breast tumour, I would bet you that the vast majority of them are going to want to have surgery to have that axilla--an axillary dissection. I think if you tell certain patients that they have--even though their test result was negative, they have a 1 in 10 chance of responding to a therapy, you know, it's easy for us to all sit in this room and talk about what if's, but if a patient who has cancer is looking for some straw to grasp, that 10 percent becomes 100 percent, and that's why, just as you pointed out, and I indicated earlier, when you get down to these

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real small, you know, between 1 and 10 percent, it really matters on an individual basis and that's why quantisation is important and this shows it right here.

MR. BROWNE:

Q. And I guess quantisation, plus the other factors that are involved --

DR. DABBS:

A. Exactly.

MR. BROWNE:

Q. And that leads to that discussion between the oncologist and the patient to come to that decision as to whether or not this treatment is appropriate?

DR. DABBS:

A. Correct.

MR. BROWNE:

Q. Risk/benefit analysis.

DR. DABBS:

A. Right.

MR. BROWNE:

Q. Doctor, I'm not sure if it's Professor or Dr. Lester Layfield, are you familiar with any of his --

DR. DABBS:

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A. Yes, I know Lester, yeah.

MR. BROWNE:

Q. He did some studies in 2000, a survey of labs across the United States.

DR. DABBS:

A. Uh-hm.

MR. BROWNE:

Q. Are you familiar with that particular --

DR. DABBS:

A. Yes, I am.

MR. BROWNE:

Q. And in that, if I'm correct, there were some labs using a 30 percent cutoff at that time?

DR. DABBS:

A. Well, there was a lab, and I wasn't sure which one it was, and I don't know if it was the one in St. John's or wherever that was, I wasn't familiar with it, it wasn't actually elucidated in that paper.

MR. BROWNE:

Q. I think they were US labs that were involved in that. Were there Canadian labs involved in that as well?

DR. DABBS:

A. I thought it was done in North America. It

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was a survey.

MR. BROWNE:

Q. Okay. You spoke to tumour --

THE COMMISSIONER:

Q. Can you find that paper that you --

DR. DABBS:

A. I do, and I can find it. I'll now provide it to you, Commissioner. Tumour Hetrogenicity. Doctor, you spoke to this as well, and I understand--and I want to make sure I understand correctly. Given a tumour which is five to six centimetres in size, and I think the recommended sectioning is five microns in terms of when you create the slides, do I understand that you should--the variability of that tumour should only be around 1 percent in terms of if you were to take various sections, a change of between--the risk of change between ER positive and ER negative? Probably I haven't said that correctly, but you spoke to that yesterday and I wasn't quite sure, you wouldn't expect differences of more than 1 percent.

DR. DABBS:

A. Right, and by that, I meant, you know, using

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the criteria that a negative result is 100 percent negative. I think by doing further sections on that, the likelihood of finding focal staining would probably be not more than 1 percent.

MR. BROWNE:

Q. Okay. I made a note yesterday--I'm not sure if Mr. Coffey framed the question in this fashion or not or I wrote it down that way, but you spoke to the expected rate of 2 percent in your lab, which if you get above 2 percent, you get concerned?

DR. DABBS:

A. And that referred to repeats of immunohistochemistry tests in general.

MR. BROWNE:

Q. In general. I'm not sure if it was in terms of error rate or anything like that described in that manner, but is there a discussion about error rates in general in immunohistochemistry in the literature?

DR. DABBS:

A. When you say error rates, do you mean --

MR. BROWNE:

Q. Changes in results. We talk about the NEQAS

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variability between labs and so on.

DR. DABBS:

A. I am not aware of any. I think the most exhaustive studies that have been done were probably UK NEQAS showing variability, but conversions, I'm not aware of.

MR. BROWNE:

Q. Okay. The Royal College of Pathologists of Australia did a quality assurance review. Did they touch on that in any way in 2006, or did they compare variability?

DR. DABBS:

A. I think that was more of a variability comparison as well.

MR. BROWNE:

Q. Were the results similar to what NEQAS found in terms of the lab?

DR. DABBS:

A. They weren't too dissimilar.

MR. BROWNE:

Q. Registrar, if we could see Exhibit P-0113, please. Doctor, this is the exhibit you were shown, Dr. Ejeckam's memo, and if you recall in the second memo, you were asked about core biopsies. I'll just get it up here, "ER false

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negative results increase in core biopsies. Therefore, where possible, restrict requests to excisional biopsies", and you spoke to that yesterday. Is it possible--you said, in fact, it's the exact opposite?

DR. DABBS:

A. Correct.

MR. BROWNE:

Q. Is it possible that this may be speaking to the problem of getting enough representative tissue and tumour on the slide? I mean, that is a known problem with core biopsy.

DR. DABBS:

A. Well, it's a known problem in that there can be a variation. For example, you know, a negative core biopsy result, but then you should repeat that on the resected specimen. However, that's a real distinct minority compared to what should be positive. So, you know, your positive for ER should be, you know, 75 to 80 percent. That's an unusual statement there.

MR. BROWNE:

Q. There was some discussion about slides. In your lab, do you use particular slides for

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immunohistochemistry?

DR. DABBS:

A. We do use slides that are basically constructed to maximize adherence of tissue sections to them.

MR. BROWNE:

Q. And what type of--we've heard about positive charged slides and there was another--histo grip was another example.

DR. DABBS:

A. Yeah, there's a variety of brands out there, and we use something that basically has something akin to a positive charge on it. I don't remember the precise brand name of it, but, yes, that's an important aspect of it, along with--the really critical aspect is baking the sections and making sure that they're water free before they go for IHC.

MR. BROWNE:

Q. So the two go hand in hand.

DR. DABBS:

A. Very much so.

MR. BROWNE:

Q. But it--I guess, you don't use normal slides that you would, say, use for other routine

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pathology?

DR. DABBS:

A. Correct, exactly.

MR. BROWNE:

Q. Doctor, the Commission has heard a lot of evidence about resources and funding for immunohistochemistry programs. I'm sure--I'm not sure how much you about the Canadian system and how it is funded through government and so on. It's much different than the United States. It is akin to the National Health Care Program in the United Kingdom, so there are some similarities there. I recognize that your experience may be limited in that regard, but just generally, do you have an particular views on the importance of having appropriate funding irrespective of the source for carrying out an immunohistochemistry program?

DR. DABBS:

A. Uh-hm. Well, I think that education in immunohistochemistry is part of anatomic pathology, and I think that that's where the training really should take place so there's an equal exposure of all trainees who are

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being trained to be pathologists, and so, therefore, it would follow, in my way of thinking, that if a program is going to have-- be training pathologists to be board certified in anatomic pathology, that they should have all the wherewithal and the resources to train anatomic pathologists in the discipline of immunohistochemistry, the importance of the nuances, and the technical aspects and how to interpret and so forth, just like any other aspect of surgical pathology.

MR. BROWNE:

Q. And in terms of the clinical application there as well in terms of sufficient funding, are you talking continuing medical education as you go through or are you talking about the sort of lead up into being certified as?

DR. DABBS:

A. Sure. I think that the training program is a starting place, starting point. From then on, pathologists go have a wide variety of choices at national meetings. There's lots of national meetings that occur where there are lots of speakers who speak to different aspects of immunohistochemistry with different

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levels of orientation. For example, let's see, this will be the third annual course on immunohistochemistry. The course is conducted by Yazidgee. He is one of the people on this paper. Last year, it was held in Santa Barbara. The year before that, it was held in Marathon, Florida. It's coming back to Marathon, Florida for this January. So it's a week-long course. It's everything you could possibly know about the technical aspects of IHC. I think he markets it fairly well. Everyone that I know in my department got an e-mail and they said "well, what's this?" So the word is out there. I think that there's been a need for this.

Some years back, in the mid 80s to early 90s, the Society for Applied Immunohistochemistry, which is actually sponsoring this course that I just described, was more active on a local level. They would have quarterly meetings in New York City and people would travel there and look at interesting cases and whatnot. There were a fair number of pathologists interested in that. That sort of atrophied, to some degree,

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and now things are starting to pick up, at least specifically oriented to IHC.

Again, there are plenty of organizations. There's plenty of speakers at the U.S. and Canadian Acadamy of Pathology meeting, which is either held in the U.S. or in Canada. The American Society of Clinical Pathologists has lots of courses, didactic, presentation, on the subject, and there are other local and national speakings at State levels and whatnot. So there's ample opportunity for CME, continuing medical education, in immunohistochemistry.

MR. BROWNE:

Q. But in order to do that, you need to have proper funding to allow people to go to that, would you agree?

DR. DABBS:

A. Yes, indeed.

MR. BROWNE:

Q. Doctor, the notion of--and one of the problems that was mentioned here, and I think you saw, to some extent in Dr. Banerjee's report, turnover of staff, pathologists, technologists and oncologists. Is that difficult--putting

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aside the notion of, you spoke to having metrics and that assumes, I guess, to some extent you have a sufficient computer base in which--and technology to do that. Would that lead to problems--would turnovers of these types of individuals lead to problems in seeing trends, do you think?

DR. DABBS:

A. I think definitely, particularly if their stays here, or wherever, were very short lived. Yes, that certainly could be a contributing factor.

MR. BROWNE:

Q. One last area, Doctor. You spoke, I think towards the end of the session this morning, about the importance of, or the relevance, I should say, of use of ER/PR for unknown primaries. Do you know whether it's standard practice to treat on a basis of ER/PR result in relation to an unknown primary?

DR. DABBS:

A. I think if a pathologist is confident in their work up that they're dealing with a carcinoma that is ER positive and/or PR positive and it's likely everything points to a GYN

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primary, for example, gynecologic primary, then yes, I think that a clinician would take that information into account and use that as information based therapy.

MR. BROWNE:

Q. Thank you. Thank you, Doctor. Thank you, Commissioner.

THE COMMISSIONER:

Q. Thank you, Mr. Browne. Ms. Newbury?

DR. DAVID DABBS, EXAMINATION BY MS. JENNIFER NEWBURY

MS. NEWBURY:

Q. Good afternoon, Dr. Dabbs. My name is Jennifer Newbury and I represent the Canadian Cancer Society, Newfoundland and Labrador Division. I just wanted to ask you a couple of questions this morning, starting with the issue of fixation of a specimen in alcohol, whether inadvertent or intensional, and the possible effect or impact of any tissue reprocessing, and perhaps I'll refer first to the article that you've seen at least once today, P-1767. This is the article of Goldstein and Clive Taylor, and I'm going to show you--you're well familiar with this by the sounds of it. On page, starting on page

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11, there are some questions and answers that appear to be related to the article. I'm not sure if you're familiar with this part of the document of that.

DR. DABBS:

A. Yes.

MS. NEWBURY:

Q. And on page 13, in the middle column, at the top, there's a reference there, an answer given by Dr. Badve?

DR. DABBS:

A. Badve, yeah.

MS. NEWBURY:

Q. And he indicates that "standard processing protocols entail the use of alcohols after the tissue is fixed in formalin. Alcohol is also a fixative with relatively rapid penetration. So if unfixed tissues are loaded onto a processor, they're more likely to undergo significant alcoholic fixation which can lead to altered IHC and false positive results." So this is a concept, I believe, that you were speaking about this morning.

DR. DABBS:

A. That's correct.

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MS. NEWBURY:

Q. Was this discussed at any of the meetings with your consensus group?

DR. DABBS:

A. Yes, it was.

MS. NEWBURY:

Q. Okay, and I think you'd mentioned earlier that there are no studies per se on this, no actual groups of specimens taken, or are these more just observations?

DR. DABBS:

A. I think these are observations by people who have done internal--a look at their internal quality and comparison studies. For example, when I looked at a certain tissue processor I had on loan for two months, I didn't publish that. I didn't think that that was something--that was not my goal to publish. I think that people had recognized, in general, that alcohol was a very different--had a very different mode of fixation. It's a coagulation type of fixative and doesn't do what formalin does, and therefore immunohistochemistry, we know, becomes highly sensitive with that, used as a primary

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fixative, and so the caution upfront that we tried to stress was that if a tissue isn't properly fixed in formalin when it goes into the alcoholic dehydrations, that could be a problem because then the tissue sees alcohol as its primary fixative, if it hasn't had enough formalin exposure.

MS. NEWBURY:

Q. Okay, and that could then lead to the problem of false positives, due to the over sensitivity?

DR. DABBS:

A. It could be.

MS. NEWBURY:

Q. And you'd indicated to Mr. Simmons this morning that inadequate fixation that could possibly cause this would be fixation of less than an hour or two?

DR. DABBS:

A. I would say an hour or two, yes.

MS. NEWBURY:

Q. And you indicated that the false positives that might arise from that weren't even consistent, so it's not like you would expect with each and every specimen in that situation

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would lead to a false positive?

DR. DABBS:

A. Correct.

MS. NEWBURY:

Q. Okay. What if there were other issues with fixation, not just the time of fixation, but if the pH level, for example, of the formalin wasn't properly maintained or adjusted at the beginning?

DR. DABBS:

A. Yes, that in itself could be a problem, and you know, when I was in residency, I'm aware that there were laboratories that made their own formalin and buffering mechanism. Of course, if one is going to do that, it's prudent upon the laboratory to regularly check the pH of formalin to make sure that the composition hasn't changed and that everything is working as it should. Nowadays, many laboratories, including ours, buy pre-made with a predetermined pH buffered, neutral buffered formalin. So it becomes less of a problem, especially if, you know, whenever you buy formalin in packages, bottles, you tend to use it fairly rapidly. So it's not like it's

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going to sit around for the laboratory for a year or two, and be changed composition. So that's one of the benefits of at least obtaining formalin that's already prepackaged.

MS. NEWBURY:

Q. Okay, and if for some reason or another the formalin was sitting around the lab, it would be necessary to check the pH from time to time?

DR. DABBS:

A. Yes.

MS. NEWBURY:

Q. And what about a situation where fixation might be affected by the size of the specimen being too large, if it's not adequately cut when prior to being put in formalin or shortly after being put in formalin, would that be an issue as well that could cause some false positives, if exposed to alcohol?

DR. DABBS:

A. It could. It could also cause false negatives because, for example, if you have a reasonably large portion of tissue in a bucket and the person who's taking a section from it, say, cuts into the middle of that and takes a

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section somewhere in the middle of that specimen, in other words, one that has not been--where the surface hasn't been exposed to formalin. You're getting something which is an unknown, in terms of fixation. So you could get a poorly fixed specimen out of a centre section from thick tissue that's been sitting in a bucket and, of course, that will give you--that will be poorly fixed, and chances are, you won't get a good result with that.

MS. NEWBURY:

Q. Okay, and it could go either way?

DR. DABBS:

A. Sure.

MS. NEWBURY:

Q. And I'd like to refer to your presentation, Exhibit P-2621, please, and on page 14 of the exhibit. Recommendation number five there, there's a reference, and I believe you commented yesterday, during your evidence, that it would be okay to use alcohol as a fixative, but you would have to validate with appropriate alcohol fixed cytology specimens, and this isn't easy to do. So I assume that

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you're saying that you can't rule out the possibility that alcohol could be used as a fixative?

DR. DABBS:

A. Well, our cytopathology colleagues use alcohol as a primary fixative for many of the fluids. Now if one is going to use alcohol as a primary fixative, then one should use alcohol as a primary fixative for their control tissues, okay, and ideally, they should be cytology specimens as well, so that they're fixed in the same way and processed in the same way, and that's possible to do. But again, there's a great deal of labour and expense involved in doing that, and validating that with, you know, probably 100 specimens and with a lot of different kinds of antibodies, if you're going to be using a lot of different kinds of antibodies. That is why cytology, immunohistochemistry and cytology is best performed on a formalin fixed paraffin embedded blocks, or in the instance where I mentioned, if we're going to a clinic to do a needle aspirate on a patient who is thought to have recurrent or metastatic breast cancer

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that we want to make sure that we have formalin on our cart whenever we go to the clinic, so that whenever we do the aspirate, we basically put that material into formalin to make a cell block from it, so that ER/PR and HER2 can be done and used with our controls that exist in the laboratory.

MS. NEWBURY:

Q. So then this doesn't mean then that ER/PR using primary fixative of alcohol is something that would be recommended?

DR. DABBS:

A. It's not desirable at all.

MS. NEWBURY:

Q. Okay, and certainly, if you're not cognizant that fixation of a specimen is occurring inadvertently by alcohol due to the inadequate fixation, that would be a problem in your view?

DR. DABBS:

A. Correct.

MS. NEWBURY:

Q. Okay, and you commented to Mr. Simmons, and perhaps yesterday as well, that reprocessing wouldn't have any effect on the performance of

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IHC, and this is the tissue reprocessing that have been mentioned to you and you were aware of that taking place?

DR. DABBS:

A. Yes.

MS. NEWBURY:

Q. In various laboratories. I just want to make sure I understand why reprocessing of tissue wouldn't have an effect on the performance of IHC, and perhaps--this is my understanding from what you indicated yesterday. Is this due to the fact that an improperly fixed specimen would already have been exposed to alcohol several times through the initial tissue processing, so the tissue reprocessing doesn't really expose that specimen to any more alcohol than the initial tissue processing to begin with?

DR. DABBS:

A. That certainly is one of the arguments that I would make, in that whenever you go back, basically what you have is the original tissue and the exposures that it had experienced. If it had experienced little formalin time and done an alcohol time, nothing that you do from

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then on is going to change that. If you have a specimen that was well fixed upfront and needed to be reprocessed because it didn't dehydrate well or something like that, when you take it back, that specimen is still well fixed primarily. So when you take it back and dehydrate it again and embed it in paraffin, nothing that you're doing there is anything different than what you did the first time. So there's nothing there that you're doing to harm the tissue.

If for some reason it got exposed to extreme temperatures during that, that could potentially impact it. But in general, tissue reprocessing is a harmless phenomenon. It's a harmless task that is meant to make the tissue more readily cuttable and most of those are due either to section thickness being too thick in the cassette or poor dehydration.

MS. NEWBURY:

Q. That being said though, would tissue reprocessing not be desirable generally speaking, for any other reasons?

DR. DABBS:

A. Well, there's one specific reason where it

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would be undesirable and that would be, for example, if on the specific block that contains the tumour that the tumour is a small portion of tumour and you're reprocessing that and you take it back and then you have to reface the block and cut it. You may be--you may end up having barely enough or not enough to do your testing, depending on how--you know, let's say you have a three millimetre tumour and you've already cut off several sections and they didn't work, then you take it back, you reprocess it, you put the block on a microtome, you reface it and now you're cutting through the last millimetre or 0.5 millimetres. It's possible that you may end up not having enough tissue to do the testing on. So reprocessing is undesirable. No pathologist likes to see that in the laboratory. At the very least, it will delay the case probably one whole day because it takes another full day to be reprocessed and a new slide made.

MS. NEWBURY:

Q. Dr. Dabbs, I wanted to ask you a couple of questions now about what have been called

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retroconverters, and those are converters from positive results to negative results, and Dr. Denic has given some evidence about this, and we have some numbers. Perhaps I'll just bring up the exhibit, just for clarity, P-2662 please, okay, and just for the benefit of those in the room, these are some numbers that were brought up earlier, after the ER/PR problem arose here, and there's a note there, confirmed positive results, and that's referring to ER positive results, I understand, of 12 and there were retroconverters of four, and those have been explained to be ER results that converted to zero. So there would be a total of 16 positive results that have been tested, ER positive results tested and four of those had converted to negative results, and perhaps to further elaborate on that, for your benefit, before I ask you any additional questions, I could show you what I understand to be those, the numbers associated with those retroconverters, and that would be Exhibit P-0720, please.

And this is just some data had been

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provided, and line 35 is what I understand to be one of the retroconverters, and I'll just show you a column up the top. There are the original ER results and the original PR results and next to that are the subsequent results for ER and PR respectively, and line 35, the original ER was 30 and the original PR was 40 and the subsequent ER/PR results were zero and zero, and that was considered a retroconverter.

DR. DABBS:

A. Now are these percent of cells, the 30 and the 40?

MS. NEWBURY:

Q. Yes, that was the percent of cells, that's my understanding. I don't think intensity was taken into account. Page 14, line 520, there's actually a couple of lines for 520, but the first one, there's a result of 40 for ER, zero for PR, and then subsequent results of five for ER and zero for PR.

MR. SIMMONS:

Q. That one's not on retroconverter, Ms. Newbury.

MS. NEWBURY:

Q. It's not considered a retroconverter?

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MR. SIMMONS:

Q. The list is at 1373.

MS. NEWBURY:

Q. Okay.

MR. SIMMONS:

Q. There's seven, narrowed down to four.

MS. NEWBURY:

Q. Perhaps we can look at that exhibit then. There have been several lists here, so I've had a hard time trying to figure out. I don't believe this is the full list though, is it?

MR. SIMMONS:

Q. That's a list of seven, and the four that are later considered retroconverters are among the seven on this list. That's my understanding of it.

MS. NEWBURY:

Q. Okay. Well, I'm just going to present this as a hypothetical.

DR. DABBS:

A. Okay.

MS. NEWBURY:

Q. Okay, and I'll refer to the first two numbers of 30, 40, 30 ER and 40 PR, and converting to zero, zero. I'm going to go to--perhaps I can

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go back to Exhibit 720, please?

THE COMMISSIONER:

Q. Is the point that these illustrate the -

MS. NEWBURY:

Q. I just want to show the numbers.

THE COMMISSIONER:

Q. - do we have to go any further?

MS. NEWBURY:

Q. I just want to show the numbers and ask for comments based on that, because the list--this list that I have here is more comprehensive than the subsequent list. So I'm not sure what the -

THE COMMISSIONER:

Q. You mean you're saying more than four or are you saying four?

MS. NEWBURY:

Q. I'm saying four.

THE COMMISSIONER:

Q. All right.

MS. NEWBURY:

Q. Based on the--I have that list that has four of what I understood to be the retroconverters. I don't know which is the best list, because this one has fewer, the one

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that Mr. Simmons referred to, has fewer than four, I believe.

MR. SIMMONS:

Q. No, there were seven--that list has four that remain as retroconverters. On the seven on that list, I can't--the redaction is there.

MS. NEWBURY:

Q. Okay.

MR. SIMMONS:

Q. (Inaudible) four.

MS. NEWBURY:

Q. I've tried to cross reference it and the numbers don't add up to me. Anyway, perhaps what I'll just do is give you a couple of examples, and referring again to page 20, this is Exhibit 0720, line 20, or sorry, line 776. We have an ER result initially of 25 to 30 and a PR result of 50 and next to that, we have zero and zero are the ER/PR results respectively, and below that, on line 778, there is an ER result of 10 to 20 and a PR result of 40 to 50, and then the subsequent testing showed zero and zero. Just given those numbers, so we'll just look at three out of the four numbers, instead of all four, what

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could explain, in your view, those change in results? What are the possibilities?

DR. DABBS:

A. So basically, we're talking about cases that are clearly positive and become negative by another test.

MS. NEWBURY:

Q. Yes.

DR. DABBS:

A. Well, I guess the first and foremost thing that I would say is I would want to look at both sets of slides and see, make sure that what is being called positive and what is being called negative are in fact true positives and true negatives.

MS. NEWBURY:

Q. Okay, so interpretation issues?

DR. DABBS:

A. Interpretation would be a key item. And then if these results hold up, then I would want to know, the next thing I would want to know would be what methods and what clone antibodies are being used in each assay. I'm assuming the second assay is being done elsewhere, and I say that though with a word

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of caution because, you know, if we're going from 30 and 40 to zero, zero, that's a big jump, which I would not expect with any clone, either the 1D5, 6F11 or SP1. So if something else was used, I would need to know that. So if one of the standard clones are used, then I would want to know, for the second test, in my mind becomes suspect. If in fact the first test is a bona fide true positive, the second test, in my mind becomes suspect. I want to know everything about how that assay was carried out.

MS. NEWBURY:

Q. Okay, and there has been some evidence here, and I'm not sure now with the confusion about what are the retroconverters, but there has been some evidence that four retroconverters have been reviewed by one of the physicians and they were thought to be interpretation issues in the sense that the staining was background staining, rather than true staining of the nuclei. Does that cause any less of a concern in terms of validity of ER positive test results to you?

DR. DABBS:

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A. In that regard -

MS. NEWBURY:

Q. And let's just say, if we have the numbers of 16 positive test results and four of those being misinterpreted as positive, does that cause any concerns?

DR. DABBS:

A. I can tell you the way I would approach that.

MS. NEWBURY:

Q. Yes.

DR. DABBS:

A. I would look at those cases specifically and if I determined that they were not interpreted correctly, I would want to know who the pathologist was, and if they were four different pathologists for four different cases, that would be one issue. But if they were four cases and one pathologist, that would be a totally different realm. So then what I would want to do probably is pull maybe a dozen other cases that that person had signed out and check them, and then it becomes a personal quality assurance issue, a professional issue with a specific pathologist. So that's how I would go about

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that.

MS. NEWBURY:

Q. And what if there were four separate pathologists coming up with those results?

DR. DABBS:

A. If they were four separate pathologists, then what I would want to do is pull probably at least a dozen cases that they had signed out previous to this, these index cases, look at them and see how widespread the problem was, but nevertheless, at a minimum, if it turned out that they had interpreted everything else appropriately, they would need to be told that the interpretation on these cases was incorrect and they would need to generate an amended report.

MS. NEWBURY:

Q. And how about if there were other known concerns generally, in terms of lack of optimization of any of the procedures for the testing which might cause background staining or cytoplasmic staining, would that cause you any additional concerns, in light of possible misinterpretations?

DR. DABBS:

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A. It would be. It certainly would depend highly on what the sections looked like. On occasion, with select antibodies, you might find a cytoplasmic staining with estrogen receptor. That's rare. It's a phenomenon that does happen and probably is related to the tumour type. There are select tumour types that might do that, but other background staining, that's a general term which, you know, would need to be looked at critically and see exactly what that was.

MS. NEWBURY:

Q. Okay. So basically, there would have to be some further analysis of those particular slides.

DR. DABBS:

A. Certainly.

MS. NEWBURY:

Q. Just to see what exactly is going on, what else might have contributed to those positive interpretations?

DR. DABBS:

A. Yes.

MS. NEWBURY:

Q. Okay. Dr. Dabbs, on this exhibit here, and I would have had this page open, there have been some other results that I wonder if you can comment upon. Let's start with line 767, and again, the same, it's the original ER, original PR, then the retesting of the ER, then retesting of the PR results. Line 767 shows a negative ER result and a PR result of 40 to 50, and then upon retesting, the results were zero and zero. Now these weren't included in what had been called retroconverters because the ER result initially was negative and remained negative. It was the PR result here that changed from a figure of 40 to 50, and there are several others, and I can just perhaps quickly refer to a couple of other examples, just to give you some flavour.

The next line is 827. There's a negative result for ER, 60-70 for PR, and then zero and zero, and there have been some others, and I'll show you a smaller change, not as significant a change, because there is a variety of different types of results here. So line 348, there's a negative ER result, then a PR result of 20 to 30, and then on

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retesting, that changes to less than one for ER and five for PR. Can you explain these types of results?

DR. DABBS:

A. Again, part of it may be interpretation, and again, part of it may be technique. If one is interpreting background staining as a positive staining, that becomes a significant issue, and you know, looking at the results here that you're showing me, they seem to be significantly different between the original and the retest, and so that's why I say that it's either an interpretation problem or technique.

MS. NEWBURY:

Q. And could the same type of factors that caused these differing results from the original PR test to the subsequent PR test, could those types of factors be the same type of factors that might influence ER results?

DR. DABBS:

A. They could be.

MS. NEWBURY:

Q. Okay. We've heard that PR tends to vary more than ER.

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DR. DABBS:
A. It tends to be more heterogeneous, yes, but the same factors are in play.
MS. NEWBURY:
Q. Okay, and would you say that with PR results, there would be a--because of the heterogeneity of the PR, that there might be a greater swing, if you take different slices from different parts of the specimen?
DR. DABBS:
A. Certainly, yes.
MS. NEWBURY:
Q. Okay. But in light of results of this nature, what would you do if you saw this? What types of steps would you take if you saw this in your own institution?
DR. DABBS:
A. Well, I would want to study the slides first and make sure that the interpretations are correct. If they're incorrect, I would need to go to the pathologists who made the primary observations and point that out. I think that the issue of false positives with the background here, you know, that was pointed out, is probably the most critical aspect of

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this. The other aspects are, you know, I think about the technique and I want to know what clone antibody is used and under what conditions and if the test between the first and the second are really way off and I agree with the first result, then I would be concerned about the second assay, how it was performed. So it really is a great deal of detective work.
MS. NEWBURY:
Q. Sure. Dr. Dabbs, you had indicated that one possible source of a false positive is over antigen retrieval with the avidin biotin or ABC method, and we've heard references here to the LSAB or labelled strept avidin biotin method. Is that in that category?
DR. DABBS:
A. Yes, it is. It has biotin as well, yes.
MS. NEWBURY:
Q. And how exactly does that antigen retrieval occur using that particular method?
DR. DABBS:
A. Well, there's biotin normally present to some degree in the nucleus as well, which isn't really unmasked unless you get into the realm

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of really extreme antigen retrieval. So I have seen this on a particular case and the first time I saw it, it was pretty dramatic. It was actually on some research tissues, and it's the type of thing that when you see it, you know, you look at it and you go, well, this--it turned out that the antigen that I was looking for had no business being in the nucleus, so it was sort of an obvious tip off that there was something awry there. But for something where you're looking in the nucleus, it can become problematic, to say the least.
MS. NEWBURY:
Q. Okay, and how would a pathologist generally recognize this or perhaps even a technologist in the work up stage of a specimen? How would one know that over antigen retrieval is taking place or has taken place?
DR. DABBS:
A. Well, I think that a distinct clue would be if you're running a proper negative control in which the primary antibody is replaced with anti serum from the animal of the primary antibody you're using, because then you also are using the detection kit in there as well.

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So if you're exposing that in the same manner with extreme antigen retrieval, you should get the same result in a negative control.
MS. NEWBURY:
Q. And in the event that a negative control has not been used, is there anything about the appearance of the slide that could tip you off that this has taken place?
DR. DABBS:
A. It would be extremely difficult to unravel that and discover that.
MS.NEWBURY:
Q. So then the--I take it the primary quality control method of avoiding this or ensuring that it hasn't taken place, would be the use of negative controls?
DR. DABBS:
A. Yes.
MS.NEWBURY:
Q. And, presumably, having your proper standard operating procedures to make sure that the antigen retrieval was done properly to begin with that it was established up--set up as a proper test, is that correct?
DR. DABBS:

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A. That's correct.
MS.NEWBURY:
Q. Okay, and are there any quality control programs, random sampling, that you would recommend to avoid these--any of these types of problems of false positives, whether it's through interpretation issues or through over antigen retrieval?
DR. DABBS:
A. Well, I think in terms of the protocols, once standardized protocols are adopted, it's going to be very difficult to get into extreme situations like that with antigen retrieval false positives. Some detection systems are now moving away from biotin altogether and are going into polymers which are more sensitive and cannot possibly give that sort of artifact. On the other hand, interpretation-wise, it's important for colleagues to show each other cases. For example, if there needs to be some remediation of a particular pathologist, say, in interpreting ER or PR, I would want to have them see the cases, fill out their worksheet as to what their result it, and then, you know, I would be the

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secondary reviewer as chief of the service to show that, yes, you know, you got the next 50 correct and you're on your own again, you know. That's basically how it would work in-house.
MS.NEWBURY:
Q. Thank you, Dr. Dabbs, those are all the questions I have.
THE COMMISSIONER:
Q. Mr. Crosbie.
DR. DAVID DABBS, EXAMINATION BY CHESLEY CROSBIE, Q.C.
CROSBIE, Q.C.:
Q. Good day, Dr. Dabbs, I introduced myself on one of the breaks, Ches Crosbie. I represent the members of the Breast Cancer Testing Class Action. Can I bring you back to the issue of the therapeutic uses of ER/PR testing, I understand in certain gynecological cases, and in cases of cancers of unknown primary origin, unknown primary, could you say a few words as to how--you seem to be of the opinion that there should be some review done of those cases, given that the haven't been retested for ER/PR, is that correct?
DR. DABBS:

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A. Regarding the issue of using ER and PR in gynecologic cancers, I know institutions vary, and these requests come specifically as prescriptions written by gynecologic oncologists to perform hormonal receptor testing on a subset of tumours. Most of the time, in my experience, these have been endometrial cancers or certain kinds of ovarian cancers, and these requests are relatively rare also in my experience. So it really is on a case by case basis. In other words, what I'm saying is if there are clinicians at the hospital who in a fairly routinely fashion say that I want to have ER done on my patient with endometrial cancer, then you would have to see how many of those kinds of cases there are. I think you could probably find that out by canvassing the oncologists to see if they, in fact, request those tests.
CROSBIE, Q.C.:
Q. These would be the gyne oncologists?
DR. DABBS:
A. Yes, correct. Regarding tumours or unknown primary, as I mentioned before, it may be

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useful to have a look, but the only way that one would be able to tell for certain is to look at the individual cases and see what the workup subsequently showed because it's not about just one antibody, the ER, but there are other antibodies that are part of that entire puzzle of trying to discern what--the tumours origin, and only in that context can one determine specifically by looking at the entire case and say, you know what, on this one we--you know, the ER was negative, maybe we should repeat it. That's--it's a contextural issue for tumours of unknown origin.
CROSBIE, Q.C.:
Q. So would you expect ordinarily to undertake the inquiry to the extent that inquiry is needed, for example, vis a vis the gyne oncologist, somebody would have to canvass them, would they?
DR. DABBS:
A. I think so, and perhaps the chief of the service, either the gyne service, or the chief of pathology, might have some number to think of in terms of how frequent this is an issue,

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going forward and looking at the cases.

CROSBIE, Q.C.:

Q. I'm not getting the sense the numbers would be high then in your --

DR. DABBS:

A. Probably not, probably not, at least --

CROSBIE, Q.C.:

Q. Guesstimate, yeah.

CROSBIE, Q.C.:

Q. Right. I think they would be low in general for both groups.

CROSBIE, Q.C.:

Q. Thank you. Can I just--this was touched on, and perhaps it wasn't left in any doubt, but I just want to come back to it, that's the question of the value of the negative control. If I understand this correctly, this is a piece of patient tissue which is set with your array on the same slide, but you don't add antibody to this piece of tissue, is that the idea?

DR. DABBS:

A. Well, typically the negative control is a separate slide that has the patient tissue on it, and applied to it is everything except the

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primary antibody. The substitute for the primary antibody typically would be serum from the animal of the primary antibody type. For example, if the primary antibody type is an anti-rabbit, then you would want to use a rabbit anti-serum, just plain rabbit anti-serum in place of the primary antibody on that tissue, and then you apply all of the other steps and develop it as though you were developing the test. Everything on that slide should be clean negative.

CROSBIE, Q.C.:

Q. No staining?

DR. DABBS:

A. No staining whatsoever, correct.

CROSBIE, Q.C.:

Q. Would you say that it's mandatory to use a negative control?

DR. DABBS:

A. Yes.

CROSBIE, Q.C.:

Q. Would it have been so in 1997?

DR. DABBS:

A. Yes, it should have been.

CROSBIE, Q.C.:

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Q. Could you--not that I want to tarry on this, but could you say a brief word about how clinical outcome validation is done? I'm guessing that this relies on feedback from the oncologists about the patient's history as time goes on.

DR. DABBS:

A. The clinical validation?

CROSBIE, Q.C.:

Q. Yes.

DR. DABBS:

A. Yes, well, that would be a significant undertaking, and I think that it would involve an actual institutional review board process whereby you're following a group of patients clinically. You obviously would have to have clinicians given their input onto standardized forms of what's considered to be response parameters for the drug in question, and follow them over a select period of time, and then using that information with your scores and our cutoffs, and giving that to an appropriate person who is extremely well versed in clinical statistics, to be able to make meaning out of it and using regression

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analysis, finding where the best cut points are for positive/negative for that using that assay with that particular clinical group. So it is not an easy undertaking.

CROSBIE, Q.C.:

Q. Sounds like a considerable organizational effort?

DR. DABBS:

A. It does and it costs money.

CROSBIE, Q.C.:

Q. Briefly, is your dedicated quality assurance person also tasked with liaising with any insurer?

DR. DABBS:

A. The person who does quality assurance for our laboratory does not have any external contacts with insurers. That person monitors designated parameters that we sit down at our monthly meeting and go over as an entire group. We have myself--I'm there, our laboratory administrator, and all the managers of the subsections of the laboratories, and our co-directors of surgical pathology are there. We go over all of these parameters and discuss them. The other duty of this person

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is to do tasks basically as I assign them. So if I want to look at a particular quality issue, then I say I want to do a probe looking at, you know, these parameters for this particular group of patients, and I want it to run for the next month. Then she'll collect that data and sort it and present it to me as I request. There are ongoing issues that she does. For example, the metrics that I mentioned, she'll send those to me on a quarterly basis as Excel sheets, so that I have those to review. So this is all documented. It's part and parcel of quality control quality assurance throughout the laboratory.

CROSBIE, Q.C.:

Q. Thank you. Do you have any familiarity with the Mount Sinai lab?

DR. DABBS:

A. I personally do not.

CROSBIE, Q.C.:

Q. So you know it by reputation, for example?

DR. DABBS:

A. I know it to some degree, yes.

CROSBIE, Q.C.:

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Q. Does it have a good reputation?

DR. DABBS:

A. Yes, it does.

CROSBIE, Q.C.:

Q. This, of course, as you may be aware, has been called the reference lab for the lab here in St. John's. I've been over this with a previous witness who was the former CEO of Eastern Health, and just to be sure we're on common ground in understanding some of the features of the institution in which our lab is embedded, Mount Sinai, for example, is affiliated with the University of Toronto and our lab here is affiliated with Memorial University. It has--it's in a hospital complex with a 337 bed acute care hospital, it has a 78 bed children's hospital, there's a medical school, as I may have mentioned, with 52 placements each year, and there's also a residency program in pathology and other specialties, and in 2005, for example, there were 204 residents in the various specialties. There's a nursing school, a pharmacy school, and a cancer treatment centre which is attached to the main hospital. It's all part

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of what's characterized as the Health Sciences Complex. I wonder if I could ask the Registrar to bring up Document P-00278.

REGISTRAR:

Q. What was that number again, Mr. Crosbie?

CROSBIE, Q.C.:

Q. 278. This, as you can see, is authored by a pathologist, Dr. Maung, January of 2007, pathology workload review for this province. I'd ask the Registrar to take us to page 9, please. Perhaps a little further down the page. I guess I can adjust that myself. Yes, in the paragraph that starts "For St. John's laboratory, which is", you will see, "It also serves the province as the tertiary esoteric referral and academic centre with undergraduate and graduate training programs and time allocated to research activities". That's Dr. Maung's choice of description, I guess, for the pathology laboratory here in St. John's. Can we now go to Document 121, please, and this, sir, as you can see is "Review of Immunohistochemistry lab", and it was prepared for the Vice-President of the hospital, and if you could move down, the

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authors were Mr. Gulliver, Program Director, and Dr. Cook, Clinical Chief, Laboratory Medicine, October, 2005, and in essence, it's a proposal for establishing the immunohistochemical laboratory processes on a sound footing." And then if we could go to page 2 of that, please? Item 1.2 is entitled, "Objective" and says, "The objective of this proposal is to identify the requirements needed to implement a complete quality assurance program for immunohistochemistry lab, ensuring that we provide a standardized and reliable service equivalent to the Mount Sinai reference lab in Toronto." Thank you for bearing with me on all of that because what I'm coming around to is from what you know about our lab here in St. John's and given the background information that I've given you, as well, is this objective achievable for our lab?

THE COMMISSIONER:

Q. Mr. Crosbie, perhaps we first ask the witness whether or not he feels he's in a position to answer that question.

CROSBIE, Q.C.:

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Q. Of course.
DR. DABBS:
A. So they're saying here that the objective of the proposal was to identify the requirements needed to implement, yeah. I think that, you know, is I have to read this in the context of the entire document, and I think that it's a laudable goal, that is, you know, at the outset of this document, but I think that's about all I can say for it.
CROSBIE, Q.C.:
Q. You're not in a position to say whether you feel it's achievable?
DR. DABBS:
A. Well -
CROSBIE, Q.C.:
Q. You'd have to read the document, is what you're saying?
DR. DABBS:
A. Yeah. I think that whether it's achievable, I would have to know everything about--let me put it in context. If I was to make an objective for a similar process in my institution, I would have to have a read on the need in the institution, the willingness

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of administration to go through with it, the funds that are available, which I don't have for, you know, the laboratory here. But I think that it's clearly the proper thing to do.
CROSBIE, Q.C.:
Q. I'd like to go over with you now some of the points, it's about 13 that I drew from your evidence to the Commission, and you can tell me whether I've got this more or less right or not. The first one, I wrote these out last night, so the first one I have here is that in your view adoption of the 30 percent cutoff in 1997 was ill advised and not reasonable. Is that correct or incorrect?
DR. DABBS:
A. I think based on the information that I have that that antibody that was published in that paper was actually not in use here. If I'm correct in that, then the answer to your question would be correct, I would agree with it.
CROSBIE, Q.C.:
Q. And it seems that in 1997 the adoption of the IHC technique was probably not appropriately

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validated, is that correct?
DR. DABBS:
A. In 1997?
CROSBIE, Q.C.:
Q. Yes. Or, well, the document you specifically looked at, I think, was from 1998, but in that time period.
DR. DABBS:
A. As far as you're referring to the document by Dr. Khalifa?
CROSBIE, Q.C.:
Q. I am, yes.
DR. DABBS:
A. Yes, I agree with that.
CROSBIE, Q.C.:
Q. I believe you told us that IHC is now considered to be a component of general pathological or pathology practice, is that correct?
DR. DABBS:
A. Correct.
CROSBIE, Q.C.:
Q. It's part of your standard armormentarium?
DR. DABBS:
A. Yes.

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CROSBIE, Q.C.:
Q. And has been so since 1997 or even before that?
DR. DABBS:
A. Before that, yes.
CROSBIE, Q.C.:
Q. And then you characterized one of the practices of Eastern Health, in particular, the absence of an SOP as a recipe for disaster?
DR. DABBS:
A. Yes.
CROSBIE, Q.C.:
Q. You don't care to qualify that, you stand by that statement?
DR. DABBS:
A. Well, I think that every laboratory technique and test has to have a written operating procedure so that people who are at least, on the least going to be trained in that particular testing procedure have something to read and understand and go by and have as a reference should it be needed for purposes of optimizing testing procedure.
CROSBIE, Q.C.:

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Q. Mr. Coffey identified to you three cases which dated from a period prior to the, what the institution identified as the index case, which we know as the Deane case, which in your opinion should provoked the pathologists or at least pathology staff to conduct an investigation, is that correct?

DR. DABBS:

A. I believe that's correct.

CROSBIE, Q.C.:

Q. The reason I say pathologists is because in the index case that the institution identified here, it appeared to be driven by the oncologist inquiring into the change in results rather than by any pathologist. But you would expect the pathologists themselves to undertake an investigation if they realized there was a dramatic change in result?

DR. DABBS:

A. Yes.

CROSBIE, Q.C.:

Q. I also understood that you were of the view that Dr. Ejeckam's analysis, when we looked at those memoranda of Dr. Ejeckam from 2003, his analysis of the problem in the lab failed to

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recognize the extent of what you characterized as a global problem?

DR. DABBS:

A. Are you referring to the visit that Dr. Ejeckam or the--oh, I'm sorry. Yes, I agree, right, I agree.

CROSBIE, Q.C.:

Q. And that you felt that, in fact, what should have been done, Dr. Ejeckam, you may recall, actually closed the lab for some improvements for a period of five weeks or so. But you felt that they should have called for help from outside?

DR. DABBS:

A. Well, I don't know if they would have called or if it was mandatory to do that. I think that that was certainly a viable option that would have been available to them, yes.

CROSBIE, Q.C.:

Q. I also took it from your evidence that IHC testing for DCIS is an unsettled area with no consensus as to best practice?

DR. DABBS:

A. I think that there is some variation even in the States on this issue. You will find areas

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where they don't do that testing, you will find areas where areas where they do do the testing. And it's not that one group is wrong and one group is right. I think that this is the type of evolving area that only outcome studies will give us information. I'm not aware of anything published yet in terms of ER/PR testing for DCIS associated with outcomes in patients with, you know, the risk reducing endocrine therapy and whether that has any impact on development of new tumours or new invasive tumours, that literature does not yet exist.

CROSBIE, Q.C.:

Q. If this is beyond your scope of expertise, please say so.

DR. DABBS:

A. Sure.

CROSBIE, Q.C.:

Q. But my question was going to be is the option of testing for DCIS, hormone receptor testing, something which clinicians ought to discuss with the patient? And it may be that you don't have an opinion on that.

DR. DABBS:

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A. Yeah. I don't have an opinion on that particular interaction between the oncologist and patient. But there seems to be, at least in part, a scientific basis for wanting to do testing along those lines in order to determine if the patients are going to get endocrine therapy, because the endocrine therapy is not without risk itself.

CROSBIE, Q.C.:

Q. I took it that the lab here would have been closed down if inspected during the subject period, 1997 to 2005 to standards prevailing in the United States. Is that a correct understanding?

DR. DABBS:

A. I think that's a correct statement.

CROSBIE, Q.C.:

Q. And when asked about acceptable error rate, your reply was that the lab, your lab is dissatisfied with anything two percent greater of tests which have to be repeated and then you investigate the problem?

DR. DABBS:

A. Well, just to clarify that, the two percent cutoff is for just repeats in

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immunohistochemistry. This would be a result of tissues that need to be reprocessed or stains that come back and there's a part of the tissue that is not there. Usually these relate to tissue processing issues and not to false negatives or false positives. That goes into a whole new realm. That, whenever--you know, if I were to see that, that becomes an issue, a sentinel event where that needs to be thoroughly investigated between myself, laboratory administrator, technicians involved and so forth. So that two percent really relates to daily workings of the process, tissue processing, labelling issues, things of that nature, things that don't raise a red flag and are a cause for a sentinel event. This is just sort of standard operating procedures. There's a known recognized repeat rate, if you will, on immunostaining, there may be something wrong with the immunostainer, it may give an error rate, it may not dispense an antibody, it all depends on, you know, a bunch of those factors. But that two percent does not include any serious event, if you will. That's the kind of language we use in

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the States, there are serious events, sentinel events are sort of analogous, that's a totally separate issue.

CROSBIE, Q.C.:

Q. And that information about repeat rate would be given you in your metrics on a quarterly basis?

DR. DABBS:

A. The repeat rate is seen by us on a monthly basis.

CROSBIE, Q.C.:

Q. Did you characterize the test failures here in your view as being largely technique failures?

DR. DABBS:

A. To the best of my knowledge, yes.

CROSBIE, Q.C.:

Q. You stated, as well, that a negative invasive lobular would provoke deep concern in your institution?

DR. DABBS:

A. That's correct. And that's the type of event that I would consider to be a serious or sentinel event, something that needs to be thoroughly investigated because of the rarity of that result. It would be cause for concern

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to look at the testing, the fixation and how the specimen was handled and how the specimen, in fact, was interpreted.

CROSBIE, Q.C.:

Q. And I got an overall sense of validation as something that should be done in house, as it were?

DR. DABBS:

A. Correct.

CROSBIE, Q.C.:

Q. And I think you said that variability for this particular test should be no greater than for any other path lab procedure?

DR. DABBS:

A. The variability in ER testing?

CROSBIE, Q.C.:

Q. Um-hm.

DR. DABBS:

A. Correct.

CROSBIE, Q.C.:

Q. Is it mandatory for a lab to have QA when undertaking this kind of testing?

DR. DABBS:

A. Yes, it is.

CROSBIE, Q.C.:

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Q. Would that be true in 1997?

DR. DABBS:

A. Yes, it would.

CROSBIE, Q.C.:

Q. Is constant optimization mandatory?

DR. DABBS:

A. Yes, it is.

CROSBIE, Q.C.:

Q. That's all I have for you, Doctor. Thank you for coming such a long distance.

THE COMMISSIONER:

Q. Thank you, Mr. Crosbie.

CROSBIE, Q.C.:

Q. I appreciate it.

THE COMMISSIONER:

Q. Do you have anything arising, Mr. Coffey?

COFFEY, Q.C.:

Q. No, Commissioner, I do not.

THE COMMISSIONER:

Q. Mr. Coffey, I have been provided with a copy of a document which I assume, Mr. Browne, is the one that you referred to earlier?

MR. BROWNE:

Q. Correct, yes.

COFFEY, Q.C.:

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Q. That's Exhibit P-2617.
THE COMMISSIONER:
Q. And you want that entered so I will have the complete picture, do you? You say yes, Mr. Coffey?
COFFEY, Q.C.:
Q. Oh, yes, please. Oh, I apologize, Commissioner. I thought you were just going to go right ahead and do it. The Layfield, that's what you're talking about? Yes, please, Commissioner.
THE COMMISSIONER:
Q. All right, thank you. That is now entered.
EXHIBIT ENTERED AND MARKED P-2617.
THE COMMISSIONER:
Q. Okay, that just leaves me to thank you very much, Dr. Dabbs, for, as Mr. Crosbie would put it, coming all this way and for what has been for me a very interesting two days. I very much appreciate your contribution.
DR. DABBS:
A. My privilege.
THE COMMISSIONER:
Q. Thank you. Well, we'll break and then proceed with the next witness.

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(RECESS)
THE COMMISSIONER:
Q. Please be seated. Ms. Chaytor.
CHAYTOR, Q.C.:
Q. Thank you, Commissioner. We have a number of new exhibits this afternoon.
THE COMMISSIONER:
Q. Okay.
CHAYTOR, Q.C.:
Q. It's P-2618, 2631, 2632, 2633 and 2634, please?
THE COMMISSIONER:
Q. Entered.
EXHIBIT ENTERED AND MARKED P-2618.
EXHIBITS ENTERED AND MARKED P-2631 THROUGH 2634, INCLUSIVE.
CHAYTOR, Q.C.:
Q. Thank you.
DR. KARA LAING, EXAMINATION BY SANDRA CHAYTOR, Q.C. (CONTINUED)
CHAYTOR, Q.C.:
Q. Registrar, could we have, please, P-0557? And, Doctor, I realize last day when we met, we were up to the disclosure of October, 2001, but there's just--so don't be too concerned if

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I'm back in August here, but there are a couple of points that I just wanted to raise. This is a note of Dr. Williams dated August the 8th, 2005.
DR. LAING:
A. Um-hm.
CHAYTOR, Q.C.:
Q. And the meeting is Dr. Cook, Williams and Dr. Gulliver--or, sorry, Mr. Gulliver. And it says "Note 16," no date. So I take it it's sometime shortly after that because then the next one in the series is still in August.
DR. LAING:
A. Um-hm.
CHAYTOR, Q.C.:
Q. So sometime around August 8th, apparently. He says, "Dr. Cook and myself talked with Dr. Laing. Prior to 2000 ER/PR negative postmenopausal women got Tamoxifen anyway. This practice changed in 2002. Of women who test positive, most are ER positive and PR positive, less are ER positive and PR positive, five to ten percent are ER negative, plus PR positive. It was felt this number is now less than five to ten percent." So I just

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wanted to ask you your recollections around this period of time or any other time with Dr. Cook and Dr. Williams around the issue of cutoffs and issues, basically, of what was used at different periods of time for treatment of women with anti-hormonal treatment.
DR. LAING:
A. Sure. Well, first of all, the first bullet I'm not sure, I have no idea what that means. That would not have been something that I would have said. There was a time prior to my practice and certainly not ever when I was a resident or in my practice a European practice in some countries that they would just simply would not test ER/PR receptors at all and that post-menopausal women would have been treated with Tamoxifen and not even considered for chemotherapy. But this certainly wouldn't have been, it wouldn't have been prior to 2000, this would have been even long before that. And certainly, as I said, my only experience as both as a resident and fellow and in practice would be treating patients who did have testing done. So I'm not certain

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where that comment--I'm not sure why he's written that there like that.

CHAYTOR, Q.C.:

Q. So those dates would be incorrect?

DR. LAING:

A. That's right.

CHAYTOR, Q.C.:

Q. And in terms of it being long before even 2000, would it have been before 1997?

DR. LAING:

A. Oh, yes.

CHAYTOR, Q.C.:

Q. Okay.

DR. LAING:

A. Yes, yeah.

CHAYTOR, Q.C.:

Q. So not at all within--this would not have been the practice at any point during the time period that's under consideration?

DR. LAING:

A. No, no, no. I mean, I started as an oncology resident in 1996 and certainly at that time Canadian practice was standard to measure ER/PR on breast tissue. Of the women who test positive, most are ER positive, and I think

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you know, that's a correct statement. And we've talked about the number of 75 being a number overall. We've talked about of those people, you know, 75 percent of those would be positive for both and then a smaller number ER positive, PR negative and then a much smaller number would be ER negative, PR positive group. And as I said, you know, this being around ten percent, noted to be five to ten percent here we, again, discussed the fact that, you know, upon review and when we sat down and actually looked at this all together in the tumour panel, we noticed that there was certainly a number of patients who fit into that category of being ER negative and PR positive.

CHAYTOR, Q.C.:

Q. Okay, and in 2005 would you have thought it was as much as five to ten percent of tumours being ER negative and PR positive?

DR. LAING:

A. Around that, around that number, for sure. And -

CHAYTOR, Q.C.:

Q. And you indicate that it's now felt to be

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lower than that?

DR. LAING:

A. It's now felt to be lower than that. I didn't listen to all of Dr. Dabbs' testimony, but I did catch a little bit of it and he was even raising this issue of the fact that now that number is felt to be even smaller and smaller. He used two to eight percent. I mentioned that when we've looked back at some of the large adjuvant hormonal trials and looked at the number of patients who were ER negative, PR positive on those studies it had been in the order of, you know, three to five percent. And in things that I've read recently in the past year or so related to this issue some pathologists have argued that you don't--you shouldn't have expression of your progesterone receptor unless you have expression of your estrogen receptor. So I think we're seeing that group getting to be a smaller subset of the patients that we see.

CHAYTOR, Q.C.:

Q. Now, did you also--do you also recall that you discussed with Dr. Cook and/or Dr. Williams the issue of the cutoffs at different points

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in time and -

DR. LAING:

A. Yes.

CHAYTOR, Q.C.:

Q. Yes, okay. And did that all take place in the same discussion, sometime in August of 2005 or was that a separate discussion?

DR. LAING:

A. Oh, it would have been around that time. But I could only go by, since I don't have any notes myself from that time period, but certainly we did discuss what the cutoffs had been. And I had mentioned to you already about the San Antonio meeting in late 2000 and then a change into 2001 as to when ten percent was being used more and more as the cutoff for determining whether or not hormonal therapy would be offered to patients.

CHAYTOR, Q.C.:

Q. Doctor, in talking to Dr. Williams and Dr. Cook about using anti-hormonal treatment, did you tell them that decisions are made not only on the basis of a cutoff but also could be influenced by how close the patient is to the cutoff, for example, if you had a patient who

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was 15 percent, was that discussed?

DR. LAING:

A. No. I think we would have discussed that, you know, there would be many factors that would influence the decision as to whether or not a patient would be offered hormonal therapy, and certainly one of those, obviously, would be what their report was. And you know, we did have discussions about that people were looking at level of expression and, in fact, we had some early discussions, as you can see from Dr. Williams' notes that we've looked at already, about the importance of whether people were ER positive and PR negative could that potentially influence how they would respond to treatment, not that--but not something that we would use to make a definitive decision about how to treat them. And this came out of the idea that patients that were ER positive and PR negative may benefit better from Aromatase inhibitors. But that was only one subset analysis of a trial and that has not been substantiated in further retrospective reviews of these studies.

CHAYTOR, Q.C.:

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Q. So would they have understood, for example, if you had--and I believe the word that may have been used in the progress notes that we looked at last day, that's in reference to Ms. Coffin, was a borderline case. So in talking to Dr. Williams and Dr. Cook would they have understood that in borderline cases somebody who, you know, came in above the ten percent but above that cutoff, that they also at the time, based on them being only 15 percent, 16 percent, 20 percent, if it was considered a borderline case, that would have gone into your, influenced your decision as to whether or not this patient should be offered Tamoxifen, so that back in 2002, for example, if the person was coming across as a weak positive, you know, close to--above ten percent cutoff, but still not much above, a borderline case, that that person, that would have affected or influenced your thinking as to whether or not, along with the other factors in the case, whether the person should be offered anti-hormonal treatment. Did you have that kind of a discussion with Doctors Cook and Williams?

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DR. LAING:

A. Not that I remember to that degree of detail. However, I think it's important to stress that it's not necessarily--and, you know, you've brought me back to that case. It wasn't the level that ultimately plays the biggest decision in whether or not somebody is going to take a hormone. It's, you know, what the risk/benefit is going to be. And the thing with using what the level is, so to look and say, well, you know, is it different if it's 50 percent or different if it's 95 or 100 percent is that you have to be certain that, you know, that that level is as accurate as it can be. And so, you know, it's something that we think about but not something that, you know, is as much of a factor as whether they make the cutoff to be positive or negative.

CHAYTOR, Q.C.:

Q. Yes, and I just used that as a particular example.

DR. LAING:

A. Sure.

CHAYTOR, Q.C.:

Q. But -

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DR. LAING:

A. I mean, even today in the clinic, if I'm deciding to treat somebody who's, you know, might come back as 15 percent ER positive and ten percent PR, then, you know, I'm going to offer that person hormonal therapy. If they have an absolute contraindication, I'm not going to give it to them. If their relative benefit is very small, maybe only an absolute benefit in terms of one or two percent, I'm likely not going to give it to them. But my thinking of that person is not going to be hugely different than the person who's sitting in front of me with something that's 95 percent and 95 percent, because although we look at it in a prospective, we're looking at it on a go forward. In many of the clinical trials we still don't have enough data to support that these relative levels of expression of these predictive markers or even expression of other predictive markers or even expression of other predictive markers like HER2 are enough for us to say that that means that people should or should not have a certain hormonal therapy or not.

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CHAYTOR, Q.C.:
Q. Yes, was one of the factors -
DR. LAING:
A. I think eventually we will.
CHAYTOR, Q.C.:
Q. It's one of the factors that goes into your decision making, though, because you, in Ms. Coffin's situation, the fact that she turned out to be strongly positive, then she was, notwithstanding any risks involved, she was offered the treatment.
DR. LAING:
A. But it was a different treatment.
CHAYTOR, Q.C.:
Q. Yes. But what I'm thinking is, and that's why I said anti-hormonal treatment, whatever that might be.
DR. LAING:
A. Right.
CHAYTOR, Q.C.:
Q. So I'm just wondering whether or not Dr. Cook and Dr. Williams understood that it's not a draw a line in the sand if you're ten percent, that there are other factors and depending if someone were to turn out to be strongly ER

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positive, that may sway your decision in one direction as opposed to that person being just slightly above the ten percent cutoff?
DR. LAING:
A. I would have explained things to them similar to what I would have explained in my opening presentation. Whether they understood that or not, I think you probably would have to ask them.
CHAYTOR, Q.C.:
Q. Okay. And if we--I understand then in September that you would have attended the exit interview with Trish Wegrynowski?
DR. LAING:
A. Yes, that's correct.
CHAYTOR, Q.C.:
Q. And perhaps you could tell us what do you recall from that meeting?
DR. LAING:
A. Sure. So, I had received a phone call from Dr. Williams to ask if I would be able to attend her exist interview, and my first question was, you know, why would you like me to come along. She, as you know, had been there to look into the laboratory. And he

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mentioned that she felt that it might be valuable if somebody from the clinical side was present in case there were questions or, you know, issues that came up. So I agreed to attend the meeting.
CHAYTOR, Q.C.:
Q. So, I'm sorry, it was Ms. Wegrynowski's idea that you or somebody from the clinical side -
DR. LAING:
A. I think between her and Dr. Williams they felt that it would be valuable to have someone from the clinical side, that's correct.
CHAYTOR, Q.C.:
Q. Okay. Sorry.
DR. LAING:
A. Okay, so I was asked to attend the meeting; I went. And as you know, the various other people were there from the lab and pathologists and Dr. Williams. And she started the meeting by asking all of us to identify who we were and why we were in attendance. And so I explained to her that I was a medical oncologist involved with the care of patients with cancer and that I had been, you know, involved with this issue to

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date and that's why I was there. So then she basically went on then to outline to all of us present her findings. She went--you know, it was a rather thorough presentation of the various issues and things that she had found. She talked about training of personnel and ongoing importance of continuing medical education and understanding of the lab personnel as to why they were doing the test and how it was utilized. She talked about issues in terms of, you know, the reagents and the fixation and the buffering and all the sort of stuff that wasn't, you know, stuff that I would be overly familiar with. And she didn't have any, not that I can recall, any specific questions directed to me. And that's what I remember from the meeting.
CHAYTOR, Q.C.:
Q. Okay, and overall, sitting there, being the clinician in the group, looking after the patients who were affected, what did you take away from what Ms. Wegrynowski was saying and how did you feel about it?
DR. LAING:
A. What I took away was that she identified that

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there were a number of areas that needed improvement in the lab, but felt that these were areas that certainly could be addressed. There wasn't one sort of striking thing that she said, you know, this was because of one thing. And I thought that she made her comments, at least my perception at that time, was in a very constructive way. And I never really sort of thought about it very much again after that. I knew that, you know, the lab people were there and they were going to address her recommendations and, of course, knew that a similar thing was happening with the pathologists with Dr. Banerjee, although, as I said, I wasn't directly involved at all in any of the meetings with him.

CHAYTOR, Q.C.:

Q. So it's the kind of thing that you walked away from and, as you say, you didn't think much of afterwards? So it wasn't the kind of thing that raised any particular alarms or concerns, what you were hearing her say?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

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Q. Okay. Did she mention whether or not there was an issue with not having any standard operating procedures in place?

DR. LAING:

A. She may have, but I don't remember that specifically.

CHAYTOR, Q.C.:

Q. Okay. And would you have understood what that meant and the significance of that?

DR. LAING:

A. Yes, because we use standard operating procedures in my area, as well. And, you know, there are areas within medicine, for example, when I think about standard operating procedures, I think about clinical trials. I do audits for the clinical trials group and I know that we've been looking for the last couple of years as regular item now is do clinical trials groups have standard operating procedures and we--that's part of our auditing process.

CHAYTOR, Q.C.:

Q. And did she raise concerns about lack of quality control measures and overall quality assurance issues for the lab?

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DR. LAING:

A. Yes, she would have in that discussion.

CHAYTOR, Q.C.:

Q. And did that cause you any concern?

DR. LAING:

A. I think at that time, you know, I was thinking about it in the way that, you know, somebody had come and was making recommendations that to me sitting there in that room people were taking very seriously and I guess I was more thinking about it on a go forward basis.

CHAYTOR, Q.C.:

Q. And communications issues amongst the personnel within the laboratory medicine program, did she raise any issues in that respect?

DR. LAING:

A. She may have but that's not something that I recall.

CHAYTOR, Q.C.:

Q. And what you heard in terms of lack of standard operating procedures and issues involving quality control and lack of a quality assurance overall program, did it cause you any concern as to anything else that

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may be happening in the lab, any other tests that you have to rely on every day?

DR. LAING:

A. Certainly we rely on the lab, as you know, for many, many tests that are done. She didn't--she wasn't there to review those particular aspects of the lab and it wasn't something that I was thinking of at the time.

CHAYTOR, Q.C.:

Q. What did you think that--what did you understand she had reviewed?

DR. LAING:

A. That she had reviewed the immunohistochemistry lab.

CHAYTOR, Q.C.:

Q. So any test, not just ER/PR, but the -

DR. LAING:

A. Oh, yes, right, all the tests that were done -

CHAYTOR, Q.C.:

Q. The IHC lab overall?

DR. LAING:

A. That's correct, yes. But not the biochemical lab or the hematology lab or any of the other lab aspects.

CHAYTOR, Q.C.:

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Q. What were you told was the purpose of her review and Dr. Banerjee's review, for that matter?

DR. LAING:

A. My understanding was that because of this issue that this was taken upon as a peer review, that they would have someone from the outside come in and have a look at things and see if they could make recommendations of how things could be improved on a go forward basis.

CHAYTOR, Q.C.:

Q. Okay. And prior to hearing Ms. Wegrynowski raise the issue of quality assurance and quality control, had you assumed those things would have been in place in the IHC lab?

DR. LAING:

A. To be quite honest with you, I, you know, not working in the lab and not being directly responsible or, you know, I guess it would be--you the same as asking me did I think those things would happen in other areas of the hospital and my answer would be yes.

CHAYTOR, Q.C.:

Q. And you would assume, yeah.

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DR. LAING:

A. Yeah.

CHAYTOR, Q.C.:

Q. And so I take it you were somewhat surprised by that, to hear that there were issues of that nature?

DR. LAING:

A. Somewhat, but, you know, even when I look back on what she was saying and talking about all these various steps of the test and those sorts of things, they didn't--you know, they wouldn't have had the same meaning to me as if someone was perhaps talking about maybe how a patient would go through the process from, you know, ordering chemotherapy to that patient, you know, being delivered the drug. It wouldn't be something that I would be familiar with in my day-to-day work.

CHAYTOR, Q.C.:

Q. If we could have, please, P-0596? Those are notes -

DR. LAING:

A. Oh yes, Dr. Williams, right.

CHAYTOR, Q.C.:

Q. Dr. Williams, yes, and unfortunately, I don't

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think he had those transcribed for us, but these, we understand are notes of the meeting with Dr. Wegrynowski that happened on September 22nd, 2005. Doctor, if you had known beforehand that there were any issues of quality assurance or quality control measures not being in place in the IHC lab, would you have done anything about it?

DR. LAING:

A. I'm not certain how I would have known that information.

CHAYTOR, Q.C.:

Q. No, but if, if you had, if that had come to your attention?

DR. LAING:

A. I probably would have spoken to the person who would be in charge of that, so the clinical chief of laboratory services. I think it would be no different, again, if someone came to me today and said there was a problem with a CAT scanner or something like that, I would go and speak to whoever was responsible and see if I could clarify what the concern or issue may be.

CHAYTOR, Q.C.:

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Q. Okay, and this is--in attendance, we can see here, it's Dr. Cook, Dr. Laing, Ms. Predham, I think it's Mr. Gulliver, and Dr. Williams, and Trish Wegrynowski of Mount Sinai, and I think it just says Mount Sinai technical person, but we know her as Trish Wegrynowski, and "statement of affairs. Frustrated and overwhelmed," and we understand this from Ms. Wegrynowski and Dr. Williams, this would have been referring to the technical staff.

DR. LAING:

A. I thought that said staffing. Number one, I thought it said staffing.

CHAYTOR, Q.C.:

Q. I see, but I've had a chance to look at it a few more times.

DR. LAING:

A. Okay, statement of affairs, okay.

CHAYTOR, Q.C.:

Q. And hear other people interpret it.

DR. LAING:

A. All right.

CHAYTOR, Q.C.:

Q. So correct me if I'm wrong -

DR. LAING:

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A. Okay, no, that's fine.
CHAYTOR, Q.C.:
Q. - someone else in the room, but I understand-- is it state of affairs or staffing?
MR. BROWNE:
Q. Staffing.
CHAYTOR, Q.C.:
Q. Is it staffing? All right, you could be right, staffing. My memory is not as good. "Causes. communication issues, do not understand the theory. Need to work together as a group. Need to -
DR. LAING:
A. Identify who they should report to.
CHAYTOR, Q.C.:
Q. There you go. You can read his writing a lot better than us.
DR. LAING:
A. It's just being a physician, I think.
CHAYTOR, Q.C.:
Q. That's it. You all write the same, okay. "Suggest technical director for the immunoperoxidase laboratory," I think. Is that what it says?
DR. LAING:

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A. Um-hm.
CHAYTOR, Q.C.:
Q. "Need triangular line of communication." So you recall were all these issues discussed, do you recall that being discussed?
DR. LAING:
A. I recall the--I guess what I remembered from that was that she said that she felt it was important that the staff understand why they were doing the test, not simply that they were doing this test, but you know, how it was being utilized at the other end.
CHAYTOR, Q.C.:
Q. Okay. So she was concerned about the knowledge level, I take it, of the technologists, in terms of the purpose for which they were doing their work?
DR. LAING:
A. That's the thing that I remember.
CHAYTOR, Q.C.:
Q. And do you recall any other detail in terms of this issue of needing a triangular line of communication, head for the immunoperoxidase -
DR. LAING:
A. No.

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CHAYTOR, Q.C.:
Q. - to be an MD, any of that?
DR. LAING:
A. No.
CHAYTOR, Q.C.:
Q. Okay, and do you know what this word says?
MR. BROWNE:
Q. Fixation.
DR. LAING:
A. Oh, fixation.
CHAYTOR, Q.C.:
Q. "Fixation, two sites."
DR. LAING:
A. "Must have same protocols."
CHAYTOR, Q.C.:
Q. "Must have same protocols. Need pathology assistants."
DR. LAING:
A. Right.
CHAYTOR, Q.C.:
Q. "We have had problems with fixation." So you do recall her discussing problems with fixation?
DR. LAING:
A. Um-hm.

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CHAYTOR, Q.C.:
Q. And did you understand what that meant when she talked about fixation?
DR. LAING:
A. My understanding was it was, you know, from the time that the tissue was taken from the patient and put in the formalin and delivered to the lab.
CHAYTOR, Q.C.:
Q. Okay, and I think this is controls.
DR. LAING:
A. Controls.
CHAYTOR, Q.C.:
Q. Do you recall a discussion about controls and what may have been lacking or any recommendations she had regarding controls?
DR. LAING:
A. Not specific details, no.
CHAYTOR, Q.C.:
Q. "Must be running positive and negative controls. Validation must be done, and record keeping"
DR. LAING:
A. Yeah, she was -
CHAYTOR, Q.C.:

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Q. Talked about the buffers, the antibodies, which you've mentioned.
DR. LAING:
A. Yes, I remember her talking about that, yeah.
CHAYTOR, Q.C.:
Q. Okay, and "need to write their own manuals. Reagents must be validated," and then it goes on. I don't know if you've had a chance to look at this in any detail in preparation for coming here, but -
DR. LAING:
A. I didn't look at it in great detail, but I did see it prior to coming here, and of course.
CHAYTOR, Q.C.:
Q. Okay, and I take it then this is consistent with what you remember her talking about, and the issue of competency testing, give scenarios to the techs. So having something in the way of competency and testing for the techs. And at this point in time, it appears you're still doing HER2/neu testing, and do you recall what was said about that? "Move off the benches quickly as is possible."
DR. LAING:
A. No.

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CHAYTOR, Q.C.:
Q. Okay.
DR. LAING:
A. I don't know what that means.
CHAYTOR, Q.C.:
Q. Okay, and overall then, it ends with "ensure validation processes in place." How long do you recall--how long did this meeting last with Ms. Wegrynowski?
DR. LAING:
A. I'm not 100 percent certain, but I would say that it was probably in the order of about 45 minutes. It certainly wasn't, you know, kind of a 10-minute briefing. It was a fairly lengthy meeting, from what I recall.
CHAYTOR, Q.C.:
Q. And was there any discussion then of the group of you afterwards, after Ms. Wegrynowski left? Was there any discussion amongst the individuals from Eastern Health in attendance?
DR. LAING:
A. Not that I recall. I'm sure that the lab people probably discussed it further, but when she was finished, the meeting was over, I would have left.

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CHAYTOR, Q.C.:
Q. Were you provided a copy or did you see a copy of her report when it was presented?
DR. LAING:
A. No.
CHAYTOR, Q.C.:
Q. And did you also sit in on Dr. Banerjee's interview?
DR. LAING:
A. No.
CHAYTOR, Q.C.:
Q. And did you see, at any point in time, or were you provided any information regarding his report or the outcome of his review?
DR. LAING:
A. No, only in preparation for this testimony, and just the piece that we looked at last week about the 92 percent.
CHAYTOR, Q.C.:
Q. That's right, I asked you about that.
DR. LAING:
A. Yeah.
CHAYTOR, Q.C.:
Q. Doctor, we know Ms. Wegrynowski came back then in the spring of 2006. Did you meet with her

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at that time?
DR. LAING:
A. No.
CHAYTOR, Q.C.:
Q. So you weren't asked to sit in on the follow up interview?
DR. LAING:
A. No, I was not.
CHAYTOR, Q.C.:
Q. And do you know if any clinician did, anybody from oncology?
DR. LAING:
A. No, I don't--not that I know of at all, no.
CHAYTOR, Q.C.:
Q. Okay. Doctor, just one other point to go back to on the decision about disclosure and then perhaps we can carry on a little bit in chronology, in the order of the chronology here. When the issue of whether to tell the patients upfront or prior to the retesting or around the time the retesting was happening and you've told us in some detail about your input into that last time. At any point in time in the discussions, did you hear anyone refer to any issues regarding insurance

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company's opinion on it, HIROC's opinion, any issues with insurance coverage?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. So you've never--you never heard that discussed within your ear shot?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. Okay, and have you since learned anything along those lines about the issue?

DR. LAING:

A. Not in any great de--no, not that I can think back to, no.

CHAYTOR, Q.C.:

Q. Okay, in any detail whatsoever, has it ever been suggested to you, whether or not the insurer had any input or any view on the issue?

DR. LAING:

A. Not--there was some discussion later on, as to, I believe Dan Boone was at one of the meetings at some point, and I was asked did I recall him making any comment about it, and I

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didn't.

CHAYTOR, Q.C.:

Q. Okay. So you may have been in attendance at meetings in which it was discussed, but you wouldn't remember?

DR. LAING:

A. I don't remember discussing it, no.

CHAYTOR, Q.C.:

Q. All right, and no one ever brought to your attention any issue about any concern as to any effect disclosure might have on insurance coverage?

DR. LAING:

A. No, not that I--no.

CHAYTOR, Q.C.:

Q. Okay. If we could have, please, P-2589? And this is an e-mail from Heather Predham to yourself and others, including Dr. Williams and Ms. Pilgrim, and it appears that it's a draft of a letter and it's now October 4th, 2005. So a couple of days after The Independent story has run.

DR. LAING:

A. Right.

CHAYTOR, Q.C.:

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Q. And it's a draft letter to physicians. Do you recall having had any input into this draft letter or any letter potentially to go to physicians?

DR. LAING:

A. Dr. Gardiner had drafted a letter to go to physicians and I had been sent an e-mail asking if I could put in sort of what the recommendations was, which is this paragraph, "it is recommended that patients who are now known to be ER/PR positive should be offered Tamoxifen for five years, if it is contraindicated," dah, dah, dah, "then aromatase inhibitor could be considered if they were post-menopausal."

CHAYTOR, Q.C.:

Q. So you drafted that paragraph?

DR. LAING:

A. Yes, because that would be--I think, I'm not sure if this was the--what it had finally, but that was what our recommendation was going to be at that time, was that people that were hormone receptor positive would be offered Tamoxifen or if that was contraindicated or not tolerated, then an AI, and that was the

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decision that we had made as to how we would treat these patients.

CHAYTOR, Q.C.:

Q. Which physicians was this letter intended to go to?

DR. LAING:

A. It was intended to go to--my understanding was that it was going to go out to physicians within the province, so it would include family physicians, surgeons, people that would potentially be following up on breast cancer patients.

CHAYTOR, Q.C.:

Q. And what was the purpose in sending such a letter at the beginning of October, 2005?

DR. LAING:

A. That at this point, this would have been as we know that this was something that broke in the news just a couple of days before this. So there had been some discussion with Dr. Gardiner and Dr. Williams as to whether or not they would send some information to physicians that may be dealing with these patients. But subsequent to this, we made a decision that we would do the tumour panel, that we would do a

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tumour board specific to this issue, which we would then not only look at just sort of generally recommending this to all patients, but we would look at the patient's prognosis at this point in time to make a recommendation that was a little bit more specific to the information that we had at hand about individual patients.

CHAYTOR, Q.C.:

Q. So do you know whether or not this type of letter ever went out to the physicians?

DR. LAING:

A. I don't know, in fact. I'm not sure. It was going to come from Dr. Gardiner, but then we moved on and I don't recall having any further discussions about that letter and turned my attentions to the tumour panel.

CHAYTOR, Q.C.:

Q. Okay, and if we could have, please, 2590? And this is an e-mail again from Ms. Predham and it's sent to you and Ms. Pilgrim, Dr. Williams and Ms. Bonnell. It's October 18th, 2005, and the re: is a patient letter, and attached here is a draft to "Dear Patient."

DR. LAING:

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A. Um-hm.

CHAYTOR, Q.C.:

Q. October 17th, 2005. "We are contacting patients that have been diagnosed with breast cancer between 1997 and 2004. Our records show that the initial pathology results from your breast cancer indicated that your tumour was negative for estrogen receptors," and it goes on from there. Did you have--do you recall receiving this e-mail, and did you have any input into the drafting of the letter to the patients?

DR. LAING:

A. I recall receiving the e-mail, but I didn't, to this date, I didn't have any input into the drafting of that letter.

CHAYTOR, Q.C.:

Q. And do you know whether or not such a letter ever went out to the patients?

DR. LAING:

A. At that time, you know, we had clearly had lots and lots of discussion as we went through about a letter prior to when this became public knowledge, and really afterwards, I wasn't involved a lot with any further

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discussions about whether a letter would still be sent or not, and from then on, most of--as I said, most of what I was focused upon was the tumour panel.

CHAYTOR, Q.C.:

Q. So if this letter didn't go out at that time, do you recall taking part in any discussion as to whether or not a letter should be sent or the decision ultimately not to send such a letter?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. Okay, so while you were sent a draft of what the letter could potentially say and you're saying you didn't provide any input into the actual content of the letter, nor did you provide any input into as to whether or not you should be telling the patients anything at this point in time?

DR. LAING:

A. Well, at that point, we had--we were starting the tumour panel and, you know, patients would be then contacted by the physician and then if the results didn't change, initially they were

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being contacted by people from the Quality office.

CHAYTOR, Q.C.:

Q. And however, I understand it was still early, in terms of even getting results back from Mount Sinai?

DR. LAING:

A. It was, yeah.

CHAYTOR, Q.C.:

Q. And you would have only had your first tumour board panel four days before this, October 13th.

DR. LAING:

A. Okay.

CHAYTOR, Q.C.:

Q. So I'm just wondering whether you thought it would be a good idea to get something out to the patients and, you know, let them know that they are one of the people that are being reviewed because the matter is now a matter of public discussion. So let them know they are one of the people being reviewed and what they can expect in terms of any follow up?

DR. LAING:

A. Sure, but as I said, I just was not part of

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any of those subsequent discussions about the letter.

CHAYTOR, Q.C.:

Q. So if you had been included in the discussion, you would have thought the letter was a good idea to go to the patients?

DR. LAING:

A. You know, at this point, one could--I mean, looking back, if you're asking me to do that, you know, would a letter have been the best way? Would a phone call have been a better way? I can't help but think of subsequent letters that were sent to patients and often they raised more questions than they gave answers to, but so, you know, I guess looking back, perhaps some sort of contact, whether a letter or a phone call, may have been beneficial to patients, in retrospect, but as I said, really at this point, we were, from the point of view of the physicians in the Cancer Care Program, concentrating our efforts on the tumour panel.

CHAYTOR, Q.C.:

Q. Yes, and I'm just wondering though, in terms of because, of course, you were--you did have

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a significant role to play and -

DR. LAING:

A. Prior.

CHAYTOR, Q.C.:

Q. - in terms of the disclosure to patients, and your opinion on that was sought, and it appears, you know, given some weight, in terms of how to disclose and when to disclose to the patients. So just wondering how much involvement then you had at this stage then, after it has broken in the media.

DR. LAING:

A. Not a lot on this issue, no.

CHAYTOR, Q.C.:

Q. Not a lot at all?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. In terms of what should now be told to the patients and what manner in which they should be told?

DR. LAING:

A. Yeah.

CHAYTOR, Q.C.:

Q. You weren't contacted and your opinion wasn't

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sought?

DR. LAING:

A. No, and of course, you have to realize that at this point, we are having a lot of contact with the patients as clinicians. So by this time, we're getting phone calls to the Cancer Centre. Every day that I'm in the clinic, I'm talking with patients about this issue, and dealing with it, you know, at that level, getting calls from my own patients and -

CHAYTOR, Q.C.:

Q. Yes, for those coming through the door or for those who were already have--are still patients of the clinic?

DR. LAING:

A. Or even people calling.

CHAYTOR, Q.C.:

Q. Yes.

DR. LAING:

A. Yeah, and people calling. So -

CHAYTOR, Q.C.:

Q. So your idea as to, you know, perhaps making--sending the letter or not sending the letter, your opinion wasn't solicited at this point in time. Okay. And we know that telephone calls

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were made later on then in the month, and again, there was an attempt to try and reach patients by telephone. Were you involved in that decision?

DR. LAING:

A. No, no, I wasn't involved in calling those patients or, you know, we sort of went on and were still dealing with what was coming in the clinic and the queries that were coming that way, the patients that were coming to the clinic, and doing the tumour panel.

THE COMMISSIONER:

Q. Just to make sure I'm clear on this point, Dr. Laing. In this e-mail from Heather Predham to a number of people, including you, Ms. Predham raises certain points in the body of the letter and then says "let me know what changes you made." So do I take it you did not respond?

DR. LAING:

A. Not that I have any recollection of. No, not at all.

THE COMMISSIONER:

Q. Okay, thank you.

CHAYTOR, Q.C.:

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Q. And Ms. Predham writes in the final paragraph of her letter, "I'm going to send this on to Dan Boone as well. I'm not sure how HIROC will feel about notifying people at this point in time and whether the media attention will make any difference." Do you recall any discussion around that?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. And do you recall when you read that wondering what that could be referring to?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. So Doctor, at this point in time, by the middle of October, you're seeing patients. They're showing up in the clinic and they've heard about the issue.

DR. LAING:

A. Yes.

CHAYTOR, Q.C.:

Q. And they're asking you questions about it.

DR. LAING:

A. Yes.

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CHAYTOR, Q.C.:

Q. And the Cancer Clinic is also receiving phone calls, and you're receiving some phone calls directly yourself on this issue. But the administration or the people handling the issue didn't ask your opinion as to what should--whether or not this letter should in fact go, whether or not phone calls should take place?

DR. LAING:

A. No, that wasn't something that I can recall being asked to come and sit in a meeting and formally discuss, no.

CHAYTOR, Q.C.:

Q. They're sending along the letter to you, so they're obviously looking for your input, in terms of what would be said to the patients in the letter, should it go. But whether the letter goes or whether phone calls are made, you're not asked your advice on that?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. And in terms of the staff at the Cancer Clinic being able to answer the questions that may be posed to them, the frontline staff, the people who are greeting the patients as they first come in, were they given any information as to what could be told to the patients?

DR. LAING:

A. Well, most of the times when we would get phone calls or queries, they were actually directed to us. You know, if patients called looking for test results or they have questions, most of the time that information would be forwarded directly to us as a memo, or it would be sent through to one of the nurses working with us, but most often those queries even to date come directly to the physician.

CHAYTOR, Q.C.:

Q. I'm just wondering back then, though, what the staff were told. You know, undoubtedly they're going to get questions and what were they told, and were they told in any--were they given a memo, were they told anything directly to be consistent as to here's what patients need to know, here's who to put them in contact with?

DR. LAING:

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A. Well, at some point, and I'm not exactly sure which process, but Nancy Parsons was given as the contact person for people to inquire as to whether or not they had to be retested because that was where the master list, if you will, of patients who had been sent for retesting was. So certainly if patients wanted to call and ask us questions, you know, what's going on, is this about me, then we could look and say, well, you know, no, I know that your hormone receptor positive, I know how I've treated you, and if it was my patient, I could let them know. If it was someone who was asking if they had been retested, then eventually we would direct that they would call Nancy Parsons phone number to see if they were being retested or not.

CHAYTOR, Q.C.:

Q. And how was that--how was that information given to the staff at the Cancer Clinic?

DR. LAING:

A. I'm not certain if it would have been a memo or if we would have told them.

CHAYTOR, Q.C.:

Q. That wouldn't have been your responsibility, I

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take it? Who would be responsible for doing that?

DR. LAING:

A. I'm not sure if it was Dr. Gardiner at the time or--I can't recall.

CHAYTOR, Q.C.:

Q. And as you continued to see the patients and they asked you questions about it, and you told them there was a retesting happening, I take it the patients would inquire as to whether or not they were part of it, and in those cases you would check their chart. Would you do that for all patients, or would it be if they inquired? So every patient coming through, would you check the chart to see if they, in fact, qualified for the retesting?

DR. LAING:

A. Oh, yes, we were--at this point we would be looking at their--you know, we would be looking at their pathology and seeing where they were because even at this point you'll recall that, although, the slides had been sent to Mount Sinai --

CHAYTOR, Q.C.:

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Q. The blocks.

DR. LAING:

A. The blocks had been sent to Mount Sinai, it was still--at that point if we had seen someone for any particular reason that we wanted to have the retesting results then, be it, you know, that they had metastatic disease or there was something about that patient, then we could certainly ask for retesting to happen as well.

CHAYTOR, Q.C.:

Q. And those were the ones sent as a consult, I understand?

DR. LAING:

A. That's correct.

CHAYTOR, Q.C.:

Q. And what criteria--other than the people with metastatic disease, I understand those you would pull and you sent as consults --

DR. LAING:

A. Yeah.

CHAYTOR, Q.C.:

Q. What other criteria did you use for determining who got sent as a consult as opposed to who stayed in the batch?

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DR. LAING:

A. I think that that would probably be the main one.

CHAYTOR, Q.C.:

Q. That's the only --

DR. LAING:

A. I'm trying to think of some other--I don't recall at that time having identified other people that were lobular histology. I had those few that we talked about before, but I think the metastatic disease is the only reason that I can think of right now that we would have asked for that to happen sooner than just in the queue with everybody else to be retested.

CHAYTOR, Q.C.:

Q. Okay. So the metastatic disease patients were given priority?

DR. LAING:

A. If we had someone who, for example, was being treated with chemotherapy for metastatic disease and we were thinking, okay, you've had however many cycles of such and such a treatment, and we were thinking about what to do next--certainly if we were at the treatment

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decision point for the patients with metastatic disease, then, yes, we would have sort of said, well, can we get this one done because we may--you know, this may be an option for us to offer this patient hormonal therapy at this point, again depending on where the disease was, you know.

CHAYTOR, Q.C.:

Q. And was that something then--and because that's like doing it on a priority basis because this person is running out of options, I take it?

DR. LAING:

A. That's right, and that was right from--you know, right from the index case, you know, some of the first few that we did retesting on were exactly that cohort of patients.

CHAYTOR, Q.C.:

Q. And was that communicated to the other oncologists so they would know --

DR. LAING:

A. Yes.

CHAYTOR, Q.C.:

Q. To pull the patients that most urgently needed to be retested?

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DR. LAING:
A. We would have--that would have been something that everybody would have--all the oncologists would have known that was available to them.
CHAYTOR, Q.C.:
Q. And did you send them an e-mail, a memo, how did they know to do that?
DR. LAING:
A. We would have communicated it at staff meetings.
CHAYTOR, Q.C.:
Q. At staff meetings, okay.
DR. LAING:
A. And, of course, because we're such a small group, you know, we would always be discussing things with each other, but they definitely-- I can tell you they definitely would have known that they could do that.
CHAYTOR, Q.C.:
Q. And pulling the charts or having the chart of a patient who is coming before you --
DR. LAING:
A. Uh-hm.
CHAYTOR, Q.C.:
Q. So every patient who would come in, you would

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check her--for the most part, her or his chart, and make sure--and determine whether or not they should be in the retest group or not?
DR. LAING:
A. Yes. So we would be--you know, so someone was coming in the clinic and they had breast cancer, you'd be sort of looking to see, you know, is this someone who's likely going to be in that retesting because of where they were. If they had asked the question, I'd say, yes, you will be retested and once we know that, we will give you the results. Patients who are on well follow-up are often seen about every six months by the medical oncologist. So, of course, there would have been a number of people who just simply would not have fallen into the time period to have a visit during that period of time. The people that we would have been seeing more frequently would have been the people who had metastatic disease, and, of course, the people who were having their adjuvant therapy currently.
CHAYTOR, Q.C.:
Q. Or the people who fell within--their six month visit fell within that Fall?

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DR. LAING:
A. Yes.
CHAYTOR, Q.C.:
Q. So in terms of--so you pulled--their chart is pulled and you check and see that the person is ER negative, and do I understand you to say only if they asked am I part of the retest, you would tell them you're likely part of the retest or would you offer to them, look, I see that you're ER negative --
DR. LAING:
A. Oh, no, we'd offer that to them.
CHAYTOR, Q.C.:
Q. So you would talk to them?
DR. LAING:
A. Oh, yes.
CHAYTOR, Q.C.:
Q. So anyone that you had a chart before you and a person standing there with you, you would look and see, oh, you're ER negative, confirm that they hadn't been on anti-hormone therapy before that and say to them that you are part of the retest?
DR. LAING:
A. Yeah, when we see a patient in the clinic, we

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always have their chart.
CHAYTOR, Q.C.:
Q. Yes.
DR. LAING:
A. Even if somebody drops in, we, say, pick up the chart and then you go see the patient because, of course, that's where you have the information, and in the chart at the top of each progress note, we would have a summary of how they would be treated.
CHAYTOR, Q.C.:
Q. Yes.
DR. LAING:
A. So it would --
CHAYTOR, Q.C.:
Q. So it would be very easy to check because it's right up --
DR. LAING:
A. And if it wasn't clearly written there, then, you know, you could go to the pathology section and see if it was there, and, you know, see if this was someone who would be involved in the retest, and explain to them that when the results came back, we would look at that and discuss it and decide.

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CHAYTOR, Q.C.:
Q. So anyone who came to see you during that time period who was ER negative and had not been treated, you would have indicated to them that the retest is happening, they will be retested, and that we'll be back in touch with them?
DR. LAING:
A. Right, and even for some of those patients, you know, we wouldn't say that you are--this means that we are going to give you. We would say, well, we're going to look at that result and then see.
CHAYTOR, Q.C.:
Q. We'll be back to you.
DR. LAING:
A. Yeah.
CHAYTOR, Q.C.:
Q. So any patients that came to you would have been told that. How about the other oncologists, were they also told to do the same thing?
DR. LAING:
A. So they would have been--you know, they would have been doing the same thing. We would have

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had patients--you have to realize that we were getting phone calls not only from the breast cancer patients, but from many, many cancer patients. You know, you hear something in the news, you're not certain--all you hear is the word cancer; you've been a cancer patient, you're concerned, so we had phone calls from people with different malignancies, we had--you know, we had a lot of people coming into the clinic and saying, well, if this--okay, this is about breast cancer, then why is it--is it about my cancer too, and just trying to explain how this test was used as a predictive marker. We certainly had people who had breast cancer saying, well, do I still have cancer; we'd say, yes, you know, this doesn't change the diagnosis, and--so there was a lot of questions from patients.
CHAYTOR, Q.C.:
Q. And seemed to be a lot of confusion--from the kinds of questions that you're saying, there seemed to be a lot of confusion amongst the patients?
DR. LAING:
A. Yeah. You know, when--at this point, we're in

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October, 2005. We're dealing with this, this is all happening, and many things going on. I'm sure we'll talk over the next day about other times when letters came out, but, you know, each time this issue came and became a public issue again, be it at the times that we know about when we did the press release in 2006, be it, you know, May of 2007, be it the start of your work here just this last Spring, often every time this has come out, we would still get phone calls from patients to say can you tell me again now what this was about, and am I okay, and what does this mean.
CHAYTOR, Q.C.:
Q. Yes.
DR. LAING:
A. So it is somewhat of a complex issue and --
CHAYTOR, Q.C.:
Q. So, Doctor, my question about the other oncologists then, if the other oncologists are meeting with patients throughout that Fall while the retesting is going on, were they also told to do the same thing, what your practice was?
DR. LAING:

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A. Sure.
CHAYTOR, Q.C.:
Q. To check their chart, find out whether or not they are part of the group, speak to them about it, tell them someone will be in touch with them?
DR. LAING:
A. Yeah, this was something that all the oncologists--not only the medical oncologists, but the radiation oncologists who were seeing the patients, you know, people that were coming through the door would ask questions.
CHAYTOR, Q.C.:
Q. So everybody was told that's the practise, that's what we should do. What about then in terms of--you've identified through the chart that this is a person who likely should be part, in your opinion, should be part of the retest. Would you then do anything to make sure she, in fact, had been captured, for example, just put a Post-It note on her file for your assistant and say make sure this person is on the list? Would you do anything like that?
DR. LAING:

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A. No, I don't think at the time that we did. You know, I don't remember calling Nancy Parsons myself and saying can you make sure that this person is being retested. You know, I think that we just assumed that they were in that retest. We had made contact with them. Certainly if they hadn't heard anything as time went on, you know, many, many of these patients called us back and said have you heard anything yet, have you heard anything yet. So, you know, there was for many patients fairly regular contact between us and them during this process as they waited for their results.

CHAYTOR, Q.C.:

Q. And I take it at this point in time then, Doctor, as you're seeing those patients throughout the Fall, October, November, into December, did you have any concerns yourself that the list may not be thorough, the list from which the retest was happening? Did you have any concerns that there are people who aren't on the list that perhaps should be on the list?

DR. LAING:

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A. Not that I can recall in those early days, no.

CHAYTOR, Q.C.:

Q. If we could have, please, P-0432. Let's try 431. I think we just jumped ahead of my whole --

DR. LAING:

A. January, 2007.

CHAYTOR, Q.C.:

Q. I think I have the wrong date. That one looks like it's '07 too. I'm not going to ask you to try and read that because I don't even think that's a doctor's writing. Let's try 639, please. We'll come back to those. That's better. That's the--this is a meeting of October 13th, 2005, and it's an agenda, a meeting of senior management.

DR. LAING:

A. Of senior management.

CHAYTOR, Q.C.:

Q. Of the NCTRF at the time, and this indicates that there's--on business arising, "ER/PR testing", and the minutes then are attached and Dr. Gardiner is present, Dr. Ganguly, yourself, Ms. Pilgrim, Ms. Power, and Ms. Michelle Gregory, as the recording secretary,

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and under business arising it says, "ER/PR testing. Dr. Laing provided a brief update on the ER/PR testing. Results for the ER/PR testing are coming back and patients are being notified. Dr. Laing and Dr. Ganguly will be attending a tumour board rounds meeting this afternoon to review cases and discuss appropriate actions. It was noted that this is not a cancer clinic issue, but a lab issue, however, which affects our patients. Any calls that staff review", I think should be receive, "regarding ER/PR testing and reporting should be directed to Nancy Parsons at quality initiatives". So it appears at this point in time Nancy is indicated to be the contact?

DR. LAING:

A. Yes.

CHAYTOR, Q.C.:

Q. Appropriate contact person?

DR. LAING:

A. Yeah.

CHAYTOR, Q.C.:

Q. And it says you're going to be attending tumour board rounds meeting, and I take it

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October 13th would be the first day that the tumour board panel actually met?

DR. LAING:

A. Is this the same day as that? This is a Thursday?

CHAYTOR, Q.C.:

Q. That's right.

DR. LAING:

A. Yeah.

CHAYTOR, Q.C.:

Q. So it's the physician review panel.

DR. LAING:

A. Yes.

CHAYTOR, Q.C.:

Q. And sometimes that gets confusing because it is referred to as the tumour board as well.

DR. LAING:

A. Well, we try and--yeah, I mean, it was a tumour board, but we called it the panel to try and think about it as being separate, although the premise of it was the same.

CHAYTOR, Q.C.:

Q. Doctor, what did this mean, "It was noted that this is not a cancer clinic issue, but a lab issue"? What did that mean?

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DR. LAING:
A. I think that just simply referred to the fact that, you know, that this was a repot that came from the lab and that the retest and, you know, the list of patients who were being retested and all that was something that the lab people had and that was why, I think, a decision was made to forward inquiries to Nancy Parsons so that patients would be able to know directly from her whether or not they were being retested. This was--you know, this was minutes that were meant to reflect the discussion. You know, certainly this was always felt by the physicians at the cancer clinic to be an issue for us because, obviously, these were our patients and these were people that we were seeing. So, you know, it's--when I look at it written that way, you know, it certainly was an issue that was very important to us at the cancer clinic and one that we took very seriously.
CHAYTOR, Q.C.:
Q. And if we could have, please, P-0308, and I will take you to the tumour board panel, but I think we'll start that tomorrow because we're

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running short on time. So I'll just take you to a couple of other points. This is an e-mail Heather Predham wrote October 18th, 2005. Again it's to yourself, Ms. Pilgrim, Dr. Williams, and Susan Bonnell.
DR. LAING:
A. Is this the same one that we looked at earlier?
CHAYTOR, Q.C.:
Q. This is the same one, I think, that we did look at.
DR. LAING:
A. Yeah.
CHAYTOR, Q.C.:
Q. It is--oh, yes, it's without the copy, that's right, and I just wanted to--I didn't bring to your attention at the time, it is the same exhibit without the attachment, that's right.
DR. LAING:
A. Okay.
CHAYTOR, Q.C.:
Q. She indicates, "Before we send it out, we have to consider the following; the patients from St. Pierre, patients in nursing homes and personal care homes, will we send this letter

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out by registered mail through one central area, and I guess we also have to remember that we will get a negative reaction from the letters, everything from timing, upsetting people with no information, and, of course, we will send some unintentionally to people who have died. I guess we should compare the mailing list to the obituaries to ensure that we don't send letters to the recently deceased. Finally, I think we should be aware we will not be able to notify everyone. Several on the list have moved and we have no other contact information".
DR. LAING:
A. Uh-hm.
CHAYTOR, Q.C.:
Q. That's what I was just wondering, in terms of seeing people that were coming through and having these caveats spoken of by Ms. Pilgrim on the 18th, did it cause you any concern that --I'm sorry, Ms. Predham--did it cause you any concern that she--that they may be having difficulty trying to organize information or identify who the patients are and how they should be contacted?

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DR. LAING:
A. You know, that whole sort of issue about finding patients and identifying patients, and, you know, we know as time went on, and we know even to this day that there were people that were not found by various different means, and--but at that time, I think if anything, we had such a volume of people that we were seeing and dealing with, you know, back in those early days, that wasn't something that I can recall thinking about. I know that as time went on, there were some patients that--I remember talking about who had been my own patients, and we really didn't have a way that we could get in contact with them again and various different things had been tried, but that would have been just a very few people that I can remember at that time.
CHAYTOR, Q.C.:
Q. And, Doctor --
DR. LAING:
A. The whole issue about the deceased patients was one that we had talked about because even --as I said, even we wouldn't necessarily know

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that patients had died. I recall that when we would ask for the list for tumour board rounds, that after a while we realized that if patients were deceased, that their charts would be stored off site, and, you know, we could then recognize if a chart wasn't there, we'd think, oh, that might be someone who has died and subsequently their cancer clinic chart was stored off site, but to be able to go in right away, either to our OPUS system or whatever and readily identify a list of patients who were deceased at the time wasn't something that was easy to do, and, in fact, we did panel some patients who subsequently before the letter was sent out, we discovered that they were, in fact, through some queries had found that they were people who had actually died.

CHAYTOR, Q.C.:

Q. After you had already --

DR. LAING:

A. Yeah, discussed it. So we may not even have known when we talked about people that they had died.

CHAYTOR, Q.C.:

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Q. Doctor, what happened in that situation, what happened with the information or the recommendation that came out of--for that deceased patient or the--I think it happened a couple of times.

DR. LAING:

A. We didn't--if we knew before the letter was sent, then we didn't send the letter. And we put those patients into the side pile, if you will, for dealing with the patients who had been deceased after we had finished dealing with the patients that were alive.

CHAYTOR, Q.C.:

Q. And do you know ultimately what happened with the information, the opinion of the panel with respect to those people?

DR. LAING:

A. I'm not certain, no.

CHAYTOR, Q.C.:

Q. When people would call you in this time period in October and you were receiving calls from the patients, what did you do with that information? So, if somebody called you and had an inquiry, what did you do with the fact that you had received contact from a

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particular person?

DR. LAING:

A. Sometimes, I would have put a note in the chart, but not always. And if I had told the patient that, you know, when the results came available, that we would be in contact with them, then I would have just waited until they came through to me through the panel or through the process of the new results being sent out to us as the attending physicians.

CHAYTOR, Q.C.:

Q. So, in terms of passing on to the quality initiatives department, Heather Predham or anyone else, would you pass that information on?

DR. LAING:

A. That someone had called?

CHAYTOR, Q.C.:

Q. Yes, that you had received contact.

DR. LAING:

A. I know that as time went on we certainly did share that information, but I can't tell you exactly when it was that we would have started to do that.

CHAYTOR, Q.C.:

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Q. So, why did you start the practice? Was it suggested to you that that would be something you should or how is that you came to do that?

DR. LAING:

A. I think it was because we, you know, as the tumour panel started, Heather was part of that and so, we would have spent a lot of time, you know, sitting in a room and going over the list of patients. And you know, if we knew that someone had notified us or vice versa, if they had gotten a query from a patient and they didn't feel they were able to answer the question, then they would have sent us an e-mail or a note that the patient, or a phone call that the patient had called. But I don't recall in the early days, that we had a direct sort of, communication back and forth between people. And I think at the end of the day that we should have had a keeper of a list and that that person should have, you know--I think that what was happening is that a bunch of very, very well intentioned people were dealing with their little pieces of this and then I think that when I look back, that if there had been one person who was co-

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ordinating that and was a central, you know, place -

CHAYTOR, Q.C.:

Q. Central registry for all the information.

DR. LAING:

A. - for registry for all the patients' contact, I think that would have been much, much better. But we were dealing with the issue, with what we had and -

CHAYTOR, Q.C.:

Q. So, nobody had that role? To your knowledge, nobody had that role?

DR. LAING:

A. No.

CHAYTOR, Q.C.:

Q. So, if we look at the names of the people in this e-mail, by the middle of October, why are you still being included in any decision making around patient contact?

DR. LAING:

A. I guess because I had given opinions and this is something that I had discussions in right back from August, July and August, but -

CHAYTOR, Q.C.:

Q. And did you consider yourself still to be part

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of the committee that was managing the issue?

DR. LAING:

A. I didn't consider myself to be a big part of that because I'd felt I had moved on to chairing the tumour panel and to the roles and responsibilities associated with that.

CHAYTOR, Q.C.:

Q. And so that's where you saw you piece to be in the whole thing by this point in time.

DR. LAING:

A. Yes.

CHAYTOR, Q.C.:

Q. And Ms. Pilgrim, what did you understand her role to be?

DR. LAING:

A. Well, she was taking over as the--this is 2005, we're still in our transition into Eastern Health and cancer care was her responsibility. So, she was involved at that time as a senior person to help co-ordinate this.

CHAYTOR, Q.C.:

Q. And Dr. Williams, what was his role?

DR. LAING:

A. Well, I mean, as you know, he had been

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involved with this issue for quite some time and continued to be one of leads. And you know, really it was him who, through Allan Kwan, had come up with the idea of having the tumour panel, be a tumour board for this issue and he was the one who had asked me to chair it. And so he was still very much a lead person involved in this for sure.

CHAYTOR, Q.C.:

Q. Okay. And in the fall then of 2005, are you involved in any further meetings with government on the issue?

DR. LAING:

A. In the fall of 2005? No.

CHAYTOR, Q.C.:

Q. Okay. Were you involved in meetings with government on other issues, for example, the Herceptin issue?

DR. LAING:

A. Yes.

CHAYTOR, Q.C.:

Q. Do you recall attending meetings regarding that?

DR. LAING:

A. Yes. So, at that same time, you know, as you

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can imagine, the day-to-day running of a cancer care program continues, we're in this transition period, we have a lot of issues related to drug coverage. We had made a presentation and had written, looking for funding for Herceptin for the Trastuzumab. And one of the things that that really struck home for us--because that meeting was in June of 2005, the American Society of Clinical Oncology meeting that showed such a tremendous benefit to this treatment. Some provinces were, sort of, lined up and ready to go and had funding secured by that summer and we were one of the last provinces to secure funding. And we felt that we would really like to, on a go forward basis, be able to say, look these are the things that are coming down the line and, in fact, that's what we did with Avastin and Folfox. So, yes, you know, we continued to--we had a presentation with government and subsequently, I did meet again with Minister Ottenheimer just prior to the press release that announced, around this time, I believe it was, some time in October of 2005, that indeed the government did fund and continue to fund

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this very important treatment for our patients.

CHAYTOR, Q.C.:

Q. And in those meetings, do you recall any issues of ER/PR coming up? Do you recall the minister or anybody on his staff or anyone in the Department of Health asking you anything about the ER/PR issue?

DR. LAING:

A. When we had had the meeting and made the case for the Herceptin, just prior to announcing the funding, Minister Ottenheimer asked if I would come by and have a look at the media briefing or the press release or whatever you would call it that he had prepared with his assistant. And I can't remember her name, maybe it was Tanis or -

CHAYTOR, Q.C.:

Q. Tansy Mundon?

DR. LAING:

A. Tansy, that's right. And so I had gone by the Department of Health and had looked at that with the Minister and really, he was very pleased that--it was a big deal to get funding in the tune of a million dollars for a drug at

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not budget time. So, we were very pleased with their decision to give us the funding to get things going right away. And at that time, one of his assistants, I believe it was Mr. Hynes was there, and I would have said, yes, we have started the panel, the results are coming back and that would have been a very brief discussion only that we would have had about that at the time, that I can recall.

CHAYTOR, Q.C.:

Q. Okay. So, you recall Mr. Hynes asking you about it?

DR. LAING:

A. I think they both did. He happened to be there as well. And me saying that, you know, we've decided to do this tumour panel and results are coming back and we're reviewing it and making recommendations.

CHAYTOR, Q.C.:

Q. Do you recall him asking whether or not there are people who could have been impacted by this delay in having had the treatment and in particular, whether or not anyone who was deceased could have been impacted by not having had the treatment?

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DR. LAING:

A. Yeah. Do I recall having that conversation with him specifically, no, but I've been asked about this subsequently, and I certainly would have said to him, you know, this is a treatment that in the adjuvant setting is given to try and reduce the risk of the cancer coming back and reduce the risk of mortality. So yes, there would have been people that, you know, had been said to be negative who would not have received these therapies, and it is potential that those patients may have had a relapse that could have been avoided by having had Tamoxifen, and I certainly would have said that type of thing to him and to many other people subsequent, or people who would ask me today the same question.

I don't recall having a specific--you know, subsequently, we did have discussions around the deceased patients, but that's not something that I remember, you know, strongly from that interaction. I remember it as being a very pleasant visit and mostly because of the significance of the funding for the Herceptin.

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CHAYTOR, Q.C.:

Q. Okay, and -

THE COMMISSIONER:

Q. Ms. Chaytor, it's past the 5:00 time, so wherever it's a convenient spot. If you're in the middle of something, complete it, but.

CHAYTOR, Q.C.:

Q. Sure, yes. That's fine. Just before I leave that then, on the Herceptin proposal or the meetings around the Herceptin and what you saw in terms of the media proposal on it, were you ever aware of any linkage being made in terms of the decision to fund the Herceptin and that having anything to do with offsetting any negativity messaging about the ER/PR issue?

DR. LAING:

A. Oh no, absolutely not. I mean, this was because of, at that time, three large international phase three trials that showed a tremendous benefit in terms of decreased disease free survival and improved--or improved, sorry, disease free and overall survival. I think it's a mere coincidence that it happened at the same time, and I never ever felt at all that the two were linked in

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any way.
CHAYTOR, Q.C.:
Q. And any document suggesting anything in terms of -
DR. LAING:
A. Absolutely not.
CHAYTOR, Q.C.:
Q. - negativity in the messaging?
DR. LAING:
A. No.
CHAYTOR, Q.C.:
Q. And offsetting that, you've never seen anything along those lines?
DR. LAING:
A. No, no.
CHAYTOR, Q.C.:
Q. And perhaps if we could just bring up then, P-1533, page 19? And then that'll be it, I promise, for today. The story, and it's referring to "the ER/PR story has received national media attention," and it goes on and quotes a recent CBC story, what it was titled, warning that "medical technology expert warned that a lab problem that occurred in Newfoundland and Labrador could be repeated

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across the country. Given the negative coverage of this story and the resulting lack of confidence among breast cancer patients and the reliability of testing procedures in the province, it is important that government respond with positive messages about the introduction of Herceptin to the provincial systemic therapy, chemotherapy program." So anything of that nature, that wasn't brought to your attention in what you saw, in terms of media releases or whatever?
DR. LAING:
A. No. No, and again, I stress the timing was because it was the same timing in the rest of the country, and in fact, in the world. You know, this was when--the summer and fall of 2005 is when everybody was coming out with their recommendations. It was in fact when we as a group in Atlantic Canada wrote our very first Atlantic Canada guideline with the oncologists in the rest of Atlantic Canada addressing adjuvant Herceptin and those issues.
CHAYTOR, Q.C.:
Q. Okay. Thank you, Doctor. Thank you,

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Commissioner.
DR. LAING:
A. Okay.
THE COMMISSIONER:
Q. All right then, we'll meet at 9:30 in the morning. Thank you.
Upon conclusion.

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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 16th day of September, 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 16th day of September, A.D., 2008

Judy Moss

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