

<p style="text-align: center;">COMMISSION OF INQUIRY ON HORMONE RECEPTOR TESTING</p> <p style="text-align: center;">BEFORE THE HONOURABLE JUSTICE CAMERON - COMMISSIONER</p> <p style="text-align: center;">September 15, 2008</p> <p>Appearances:</p> <p>Bernard Coffey, Q.C. . . . . Commission Co-counsel Sandra Chaytor, Q.C. . . . . Commission Co-counsel</p> <p>Rolf Pritchard/Jackie Brazil . . . . Her Majesty in Right of NL</p> <p>Peter Browne/Jane Hennebury . . . . . Doctors Kara Laing et al</p> <p>Daniel Simmons . . . . . Eastern Regional Integrated . . . . . Health Authority</p> <p>Ches Crosbie, Q.C./ Laura Brocklehurst. . . . . Members of the Breast Cancer Testing Class Action</p> <p>Mark Pike . . . . . NL Medical Association</p> <p>Jennifer Newbury . . . . . Canadian Cancer Society (NL Division)</p> <p>Blair Pritchett. . . . . Central, Western and Labrador-Grenfell Regional Integrated Health Authorities</p>	<p style="text-align: center;">LIST OF EXHIBITS</p> <p>Exhibits entered and marked P-2623 through to P-2628 . . . . . Pg. 68</p> <p>Exhibit entered and marked P-2621 . . . . . Pg. 109</p> <p>Exhibit entered and marked P-2622 . . . . . Pg. 109</p> <p>Exhibit entered and marked P-2629 . . . . . Pg. 109</p> <p>Exhibit entered and marked P-2630 . . . . . Pg. 292</p>
<p style="text-align: center;">TABLE OF CONTENTS</p> <p>DR. NEBOJSA (NASH) DENIC (CONT'D)</p> <p>Examination by Ms. Jennifer Newbury . . . . . Pgs. 4 - 53</p> <p>Examination by Chesley Crosbie, Q.C. . . . . Pgs. 54 - 60</p> <p>Examination by Mr. Peter Browne . . . . . Pgs. 61 - 91</p> <p>Re-Examination by Bernard Coffey, Q.C. . . . . Pgs. 91 - 100</p> <p>Examination by the Commissioner . . . . . Pgs. 101 - 108</p> <p>DR. DAVID JOSEPH DABBS (SWORN)</p> <p>Examination by Bernard Coffey, Q.C. . . . . Pgs. 108 - 292</p> <p>Certificate</p>	<p style="text-align: right;">Page 4</p> <p>1 THE COMMISSIONER:</p> <p>2 Q. Please be seated. Ms. Newbury.</p> <p>3 DR. NEBOJSA (NASH) DENIC, EXAMINATION BY MS. JENNIFER</p> <p>4 NEWBURY</p> <p>5 MS. NEWBURY:</p> <p>6 Q. Good morning. Good morning, Dr. Denic.</p> <p>7 Jennifer Newbury for the Canadian Cancer</p> <p>8 Society, Newfoundland and Labrador Division.</p> <p>9 I have a few questions for you this morning,</p> <p>10 dealing first with retesting of the positive</p> <p>11 ER/PR patients. And I believe that you'd</p> <p>12 mentioned last week that you had retested some</p> <p>13 of the patients recently?</p> <p>14 DR. DENIC:</p> <p>15 A. That's correct.</p> <p>16 MS. NEWBURY:</p> <p>17 Q. Okay, and was that done in 2008?</p> <p>18 DR. DENIC:</p> <p>19 A. That's correct, 2008. The latter group of the</p> <p>20 patients wanted to be retested.</p> <p>21 MS. NEWBURY:</p> <p>22 Q. Okay, and these are patients that identified</p> <p>23 themselves as wanting to have a retest done,</p> <p>24 is that correct?</p> <p>25 DR. DENIC:</p>

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<p>1 A. That's correct.</p> <p>2 MS. NEWBURY:</p> <p>3 Q. Okay, and about how many of these patients</p> <p>4 have been retested?</p> <p>5 DR. DENIC:</p> <p>6 A. I think the list that was given to me</p> <p>7 recently, it was around ten patients, and they</p> <p>8 come from the different years of original</p> <p>9 testing.</p> <p>10 MS. NEWBURY:</p> <p>11 Q. And is anyone at Eastern Health tracking the</p> <p>12 numbers and the results of those tests?</p> <p>13 DR. DENIC:</p> <p>14 A. That's correct. To best of my knowledge,</p> <p>15 actually, and I was being supplied basically</p> <p>16 by the risk and quality management department.</p> <p>17 MS. NEWBURY:</p> <p>18 Q. Okay, and they were from various years, is</p> <p>19 that correct?</p> <p>20 DR. DENIC:</p> <p>21 A. That's correct.</p> <p>22 MS. NEWBURY:</p> <p>23 Q. Okay, so these weren't random test results, as</p> <p>24 such, these were just patients that identified</p> <p>25 themselves?</p>	<p>1 DR. DENIC:</p> <p>2 A. - overall what has been done?</p> <p>3 MS. NEWBURY:</p> <p>4 Q. - positive test results?</p> <p>5 DR. DENIC:</p> <p>6 A. That's very small--oh, you mean--excuse me, I</p> <p>7 don't understand. The new ones that we</p> <p>8 received, ten patients statistic -</p> <p>9 MS. NEWBURY:</p> <p>10 Q. Well, the new--so far there have been a number</p> <p>11 of what have been called retroconversions or</p> <p>12 false positives.</p> <p>13 DR. DENIC:</p> <p>14 A. That's correct.</p> <p>15 MS. NEWBURY:</p> <p>16 Q. And there have been some other ER positive</p> <p>17 test results that were confirmed to be</p> <p>18 positive?</p> <p>19 DR. DENIC:</p> <p>20 A. That's correct.</p> <p>21 MS. NEWBURY:</p> <p>22 Q. And now you have a new group of about ten.</p> <p>23 And I believe that you indicated that those</p> <p>24 results, there were no retroconversions, there</p> <p>25 were no false positives in that group?</p>
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<p>1 DR. DENIC:</p> <p>2 A. That's correct.</p> <p>3 MS. NEWBURY:</p> <p>4 Q. And I assume that the patients would have been</p> <p>5 advised of the test results upon receipt?</p> <p>6 DR. DENIC:</p> <p>7 A. They were advised. Even one of the patients I</p> <p>8 called directly.</p> <p>9 MS. NEWBURY:</p> <p>10 Q. Okay, and would you consider this to be a</p> <p>11 sufficient sample size to draw conclusions</p> <p>12 about the ER positive group in its entirety?</p> <p>13 DR. DENIC:</p> <p>14 A. I think it's a good indicator, you know.</p> <p>15 Whether statistically is valid, it's difficult</p> <p>16 to say, but I think it's one of the good</p> <p>17 indicators that one should have in mind.</p> <p>18 MS. NEWBURY:</p> <p>19 Q. And do you know if anyone has done a</p> <p>20 statistical analysis or plans to do a</p> <p>21 statistical analysis of these results?</p> <p>22 DR. DENIC:</p> <p>23 A. You mean just these positive or -</p> <p>24 MS. NEWBURY:</p> <p>25 Q. Yes, just for the -</p>	<p>1 DR. DENIC:</p> <p>2 A. That's correct.</p> <p>3 MS. NEWBURY:</p> <p>4 Q. So you would have a number of samples now.</p> <p>5 And I'm just wondering if there is a plan or</p> <p>6 any discussion about doing an actual</p> <p>7 statistical analysis there to see if you can</p> <p>8 draw any conclusions about all of the ER</p> <p>9 positive test results done to date?</p> <p>10 DR. DENIC:</p> <p>11 A. I don't know to any organized way, but I'll</p> <p>12 let you--what I did recently since Dr.</p> <p>13 Makretsov came on board and he is very much a</p> <p>14 research oriented and he has a statistical</p> <p>15 analysis program in his computer. So I did</p> <p>16 draw some of the numbers, you know, just these</p> <p>17 are ball park figures, and I put like 2700</p> <p>18 tests as a denominator, then I put 380 tests</p> <p>19 that had a negative ER and that we have a</p> <p>20 problem with and then I put the number of</p> <p>21 false positives, which were four, but at that</p> <p>22 time I even put a little bit higher number</p> <p>23 because this was done looking into the</p> <p>24 thousands of patients, so I said, okay, let's</p> <p>25 give 15. So we give it a higher number, as</p>

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<p>1 such, so just to try to get any better</p> <p>2 statistics to all of this. And the remaining</p> <p>3 number are the positives, really. And based</p> <p>4 on the test that we did, the statistical</p> <p>5 analysis positive predictive value, which</p> <p>6 means what does it--how objective is the test</p> <p>7 to pick up the positives. That number is 99</p> <p>8 percent. So in 99 percent based of this rough</p> <p>9 analysis, I'm not saying that this is--you</p> <p>10 know, I think it should be done in a different</p> <p>11 way, but this is my rough analysis of this.</p> <p>12 So in 99 percent we should be able to pick up</p> <p>13 positives.</p> <p>14 MS. NEWBURY:</p> <p>15 Q. Okay, based on the results that you've</p> <p>16 received to date?</p> <p>17 DR. DENIC:</p> <p>18 A. That's correct.</p> <p>19 MS. NEWBURY:</p> <p>20 Q. Okay, and that's assuming that the data that</p> <p>21 you relied upon is appropriate and that</p> <p>22 instead of using the four, what you consider</p> <p>23 to be false positives, you used a figure of</p> <p>24 15?</p> <p>25 DR. DENIC:</p>	<p>1 the group of pathologists at St. Clare's or, I</p> <p>2 mean, Dr. Makretsov knows about it because he</p> <p>3 did that for me, really.</p> <p>4 MS. NEWBURY:</p> <p>5 Q. Okay. Nothing on a formal basis, anything</p> <p>6 shared -</p> <p>7 DR. DENIC:</p> <p>8 A. No, nothing on a formal basis.</p> <p>9 MS. NEWBURY:</p> <p>10 Q. Dr. Denic, it was Dr. Laing's evidence last</p> <p>11 week that it was her understanding that some</p> <p>12 of the retroconverters could be explained by</p> <p>13 over--by a pathologist overcalling a slide due</p> <p>14 to background staining. And she had indicated</p> <p>15 that the pathologists that were involved in</p> <p>16 looking at the retroconverters had taken out</p> <p>17 some of the original slides and reviewed them.</p> <p>18 And she thought the pathologists could speak</p> <p>19 better to that whole issue and, but her</p> <p>20 understanding was that they felt that the</p> <p>21 staining was more background staining than</p> <p>22 true staining of the cells and that lead to an</p> <p>23 overcalling of the slide. And I'm wondering</p> <p>24 if you were one of the pathologists involved</p> <p>25 in that review?</p>
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<p>1 A. Yes, I gave extra numbers just in case that we</p> <p>2 may encounter, but we may not.</p> <p>3 MS. NEWBURY:</p> <p>4 Q. Okay, and is this an analysis that you've kept</p> <p>5 a record of?</p> <p>6 DR. DENIC:</p> <p>7 A. Yes, I did.</p> <p>8 MS. NEWBURY:</p> <p>9 Q. Okay. I'm not sure, is that something that's</p> <p>10 been provided?</p> <p>11 DR. DENIC:</p> <p>12 A. No, that was done just by myself. I was</p> <p>13 interested--this was done in August. I just</p> <p>14 want to see what would be the--is there any</p> <p>15 statistical analysis can be done, but it</p> <p>16 hasn't been done, actually, and should be done</p> <p>17 more properly, I would say, by statistician,</p> <p>18 probably NLCHI or somewhere else.</p> <p>19 MS. NEWBURY:</p> <p>20 Q. Okay, and is this something that you've shared</p> <p>21 with any of your colleagues at Eastern Health,</p> <p>22 even your rough analysis and your thoughts</p> <p>23 that perhaps it could be done more formally?</p> <p>24 DR. DENIC:</p> <p>25 A. I don't think so I shared it. Maybe within</p>	<p>1 DR. DENIC:</p> <p>2 A. Yes, I was.</p> <p>3 MS. NEWBURY:</p> <p>4 Q. Okay, and Dr. Laing thought it was you and Dr.</p> <p>5 Cook and Dr. Carter. So is it the three of</p> <p>6 you that looked at that?</p> <p>7 DR. DENIC:</p> <p>8 A. I believe it was only me. I am not quite</p> <p>9 certain about Dr. Cook and Dr. Carter. They</p> <p>10 might have looked one or two cases, you know,</p> <p>11 because we looked at large number of cases. I</p> <p>12 cannot be stating this with absolute</p> <p>13 certainty, but I know I looked at these cases.</p> <p>14 MS. NEWBURY:</p> <p>15 Q. Okay, and do you know if anyone else, aside</p> <p>16 from Dr. Cook or Dr. Carter may have looked at</p> <p>17 these or did you do this on your own?</p> <p>18 DR. DENIC:</p> <p>19 A. That's what I am saying, I cannot be certain.</p> <p>20 I know that I looked at it.</p> <p>21 MS. NEWBURY:</p> <p>22 Q. You looked at it, okay. So you don't know if</p> <p>23 anyone else did for sure?</p> <p>24 DR. DENIC:</p> <p>25 A. No.</p>

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1 MS. NEWBURY:  
 2 Q. And if overcalling a slide due to background  
 3 staining occurred in some of those cases, can  
 4 you recall how many of the four  
 5 retroconversion cases fell into that category?  
 6 DR. DENIC:  
 7 A. Yeah, all four.  
 8 MS. NEWBURY:  
 9 Q. All four, okay. So if that occurred with  
 10 those four particular slides, how can you be  
 11 sure that it didn't occur with other slides,  
 12 other ER/PR positive test slides?  
 13 DR. DENIC:  
 14 A. Well, you cannot be absolutely sure about  
 15 anything, as such, that happened. You know,  
 16 these are some of the pitfalls in testing and  
 17 interpreting that it's recognized, you know.  
 18 But the literature states, really, that this  
 19 is not a common problem. This is not a  
 20 problem, as you can see, with the false  
 21 negatives, you know. So could we find one or  
 22 two more, we may or we may not, you know, so I  
 23 cannot state with any degree of certainty what  
 24 are there.  
 25 MS. NEWBURY:

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1 Q. Okay, you've indicated that the literature  
 2 says that this isn't a common problems. Now I  
 3 believe Dr. Banerjee had indicated that while  
 4 he saw no evidence that the Ventana system was  
 5 overcalling the--creating false positive  
 6 results, he had indicated that the system  
 7 still requires optimization to involve non-  
 8 specific staining. So you're aware that  
 9 that's something, that's a necessary step to  
 10 avoid non-specific staining?  
 11 DR. DENIC:  
 12 A. Any machine needs optimization.  
 13 MS. NEWBURY:  
 14 Q. Right.  
 15 DR. DENIC:  
 16 A. And validation. And that's been done in our  
 17 lab.  
 18 MS. NEWBURY:  
 19 Q. Okay, and that's something that Trish  
 20 Wegrynowski had also pointed out, that you  
 21 need to optimize your test results. And she'd  
 22 also indicated that you need to run negative  
 23 controls and that would help to ensure that  
 24 you're not getting any non-specific staining?  
 25 DR. DENIC:

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1 A. That's correct. And they have been run.  
 2 MS. NEWBURY:  
 3 Q. And in a decision whether or not to look at  
 4 false, possibility of false positive test  
 5 results or to do a review of some of the  
 6 positive test results, did you take into  
 7 account any possible flaws, I guess, or issues  
 8 that were apparent regarding optimization of  
 9 the systems that you had in place between '97  
 10 and 2005 and also the absence of negative  
 11 controls?  
 12 DR. DENIC:  
 13 A. I didn't take because obviously I didn't have  
 14 any kind of role and I didn't oversee  
 15 immunohistochemistry, so I really don't know  
 16 what was in place. And I think the people who  
 17 should know any kind of knowledge, as such,  
 18 would be Dr. Ejeckam, who overseen the  
 19 immunohistochemistry, Mr. Barry Dyer and Mr.  
 20 Gulliver and obviously the technologists who  
 21 were working on the system. So I wouldn't  
 22 have any kind of knowledge in that regard.  
 23 MS. NEWBURY:  
 24 Q. At the time, but do you think now that looking  
 25 back at it, now that you've had the reports of

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1 Ms. Wegrynowski and Dr. Banerjee, can you say  
 2 with confidence that there were no issues with  
 3 non-specific staining due to failure to  
 4 optimize the tests or that there were no  
 5 issues because of the lack of negative  
 6 controls, and have you taken that into account  
 7 into any decisions?  
 8 DR. DENIC:  
 9 A. With certainty of course I cannot say about  
 10 it. What I was thinking about my approach to  
 11 the, whether we should look into this group  
 12 was from the perspective that obviously  
 13 scientific road, as you can read now, try to  
 14 come to some kind of conclusion what would be  
 15 the error rate that one test may acquire  
 16 during performing. We are talking about,  
 17 what, minus five percent these days about it.  
 18 While we would all like to, for every test to  
 19 be 100 percent certainty and specific, we know  
 20 that this is not reality for any single test.  
 21 Any instrument you buy in your house, that  
 22 tells you a performance, plus, minus  
 23 confidentiality rate, 95, so you hear of plus,  
 24 minus five. So when I look all of this, as  
 25 well, and so a five percent is something that

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<p>1 even in Dr. Allan Gown's lab, he said 2 concurrence rate was 95 percent, I think he 3 stated that in Wall Street Journal, as well, 4 which is a high concurrence. So if you look 5 at these are four cases which were picked up 6 from 1000 of patients, they needed to be taken 7 off the Tamoxifen because they fell in a group 8 of false positive, that's far below even a 9 point five percent of the such. So that's one 10 way to look at it. The other ways to look at 11 it is these random patients that are coming up 12 and said that we would like our test to be 13 done, we did those ones where the number is 14 not big. Obviously, thankfully or luckily, 15 the results never changed. They were positive 16 then, they stayed positive now. The other 17 thing is that, as well, literature says that 18 this group may exist but is not even close 19 significant as a false negative. And the last 20 thing that I see that if there are still 21 patients out there that would like to be 22 retested, and I think Eastern Health did say 23 that, that we'll do it, we'll do it for the 24 benefit of them getting again the results, 25 confirming their results and for the benefit</p>	<p>1 much higher percentage. Perhaps you can 2 explain that? This is a document, an e-mail 3 that was sent to you. And I believe attached 4 to that there are lists--now, this is from 5 November, 2006, I believe. So it has total 6 retested. And I know that these numbers have 7 been updated - 8 DR. DENIC: 9 A. That's correct. 10 MS. NEWBURY: 11 Q. - since then. But just looking at this point 12 in time. They were confirmed negative 341, 13 patients panelled, 422. And if you go down 14 towards the bottom of the page, it says 15 "Confirmed positive, 12" and then a little 16 further down, "retroconverters, four." So it 17 would appear to me that the only positive test 18 results that were tested would be the 12 plus 19 the four, which is 16. And those are the 20 ones, the four out of the 16 are what 21 converted, so that would give an error rate of 22 25 percent. 23 DR. DENIC: 24 A. I think that's the very wrong way to look at 25 it, Ms. Newbury. I mean, we are doing against</p>
<p>1 of knowing the decision that we made was 2 right. While we did state it that we cannot 3 go onto the mass retesting because you can 4 only imagine, it's now we have another 1500 5 right away coming to the lab, I think the lab 6 would go to a halt and nothing would have been 7 performed and we still have hundreds and 8 hundreds of new patients that has to be done. 9 So this is a factor that I looked, and in my 10 opinion is how we should treat this issue. 11 MS. NEWBURY: 12 Q. A couple of points on your explanation, Dr. 13 Denic. I mean, first of all, you've indicated 14 that four patients had to have a change of 15 treatment because they were false positives 16 and you said that there were 1000 patients in 17 total, approximately. But wouldn't you have 18 to look at, when you're looking at the error 19 rate for the positive test results, wouldn't 20 you have to look at the positive test results 21 that converted as opposed to the whole group? 22 And I understand, perhaps we can bring up 23 Exhibit P-2662, please? I understand that the 24 total number of positives was actually 16, so 25 if you have four out of 16, that would be a</p>	<p>1 the 12, four, completing disregarding that 2 another how many, 1500 tests been done. 3 MS. NEWBURY: 4 Q. Um-hm. 5 DR. DENIC: 6 A. And these 12 patients, these patients' 7 original results were considered to be 8 positive by the treating clinician and treated 9 appropriately. There was slight change in the 10 patients' ER/PR status, but review by the 11 panel confirmed that ER/PR status are still 12 being positive. So they are being positive, 13 they stayed positive, so they should be put in 14 a group, really, of all of these remaining 15 positive which we didn't test it. But I don't 16 see that this is a good stat, that, you know, 17 just to look for over 12, no, I don't think 18 so, that isn't the right way to do it. 19 MS. NEWBURY: 20 Q. And I guess the point is is that it is a very, 21 very small number. You have only 16 positive 22 patients that were tested. So I guess the 23 point is that that is a very small sample 24 size, and wouldn't you have to do a much a 25 larger sampling size to be able to draw any</p>

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<p>1 conclusions one way or the other about 2 positive test results? 3 DR. DENIC: 4 A. So the question is how large sample should be 5 done and how this can be performed without 6 affecting helping the patients, as well, and 7 not affecting the regular daily service, as 8 such. That's why we came to that conclusion, 9 that let's offer this to the patients. 10 MS. NEWBURY: 11 Q. Yes. 12 DR. DENIC: 13 A. Because even as you understand the benefit of 14 Tamoxifen therapy in the patients who are 15 negative, there's some benefit of Tamoxifen, 16 as well, like preventing the breast cancer in 17 the opposite breast. 18 MS. NEWBURY: 19 Q. Um-hm. 20 DR. DENIC: 21 A. So not that some of these patients didn't 22 benefit and such. The other thing that's what 23 you should look at is probably there's a ten 24 percent of the chance, as the literature said, 25 that even if they're negative, they might be</p>	<p>1 negative. Wouldn't have been a clone of the 2 cells, one percent, in the billions of the 3 billions of the cells. And I think people 4 testified that even sometimes different clone 5 metastasis and they found the different clones 6 in the lymph nodes that can we absolutely 7 guarantee, absolutely guarantee, that there is 8 nothing positive even in this negative 9 patient. So these are my thoughts about the 10 process being done and this is my opinion. 11 MS. NEWBURY: 12 Q. Okay. I appreciate your opinion on that Dr. 13 Denic. I guess a couple of other points 14 arising from that. Was it your evidence last 15 week that when selecting the sample for the 16 ER/PR testing that you tried to select a 17 portion of the tumour that's well 18 differentiated, knowing that that would be the 19 most likely part that would be ER positive? 20 DR. DENIC: 21 A. Yeah, you're trying to do that from the tissue 22 already taken. 23 MS. NEWBURY: 24 Q. Sure. 25 DR. DENIC:</p>
<p>1 responding to Tamoxifen therapy. So there's 2 some benefit even of Tamoxifen to these four 3 patients, while they were taken off for the 4 various reasons, they could even have 5 benefitted because they're alive. And so I 6 think this is the way that to look at it. And 7 the other thing is that I think I brought that 8 on my last day last week is about how much we 9 know about the tissue, as such. I think that 10 some of the expert witness may have testified 11 about the heterogeneity of the estrogen 12 receptors into the tumour tissue. And what we 13 are examining is the five micrometres of the 14 one's tissue, while the tumour could be five 15 to six centimetres big. And we are taking 16 representative section because that's a part 17 of the standards of practice. So you would 18 take your three or four representative 19 sections from the tumour and thinking that you 20 have an appropriate sample. 21 MS. NEWBURY: 22 Q. Um-hm. 23 DR. DENIC: 24 A. So is there anybody going to say that in this 25 particular patients why we said they were</p>	<p>1 A. Because when you look at the tumour on the 2 gross bench as a gross specimen, you cannot 3 distinguish what part is well differentiated, 4 which part is moderately differentiated, which 5 one is poorly differentiated, because the 6 tumour looks the same. So only under the 7 microscope, so if you already sampled those 8 one and then when you look under the 9 microscope, you'll try to see is there any 10 areas that the tumour is well differentiated. 11 Again, this is a random sample of three to 12 four that we are obliged to take. Sometimes 13 we take more, depends what we are looking at. 14 If you are looking if the tumour is close to 15 the margin, surgical margin, of course you 16 take more tumour and the margin with it in 17 order just to identify whether or not the 18 tumour is crossing the surgical resection 19 margin, because it has clinical implications. 20 So obviously you cannot say that on a gross 21 bench, but when you're taking the slides, yes, 22 you can identify whether or not there are any 23 better differentiated area. 24 MS. NEWBURY: 25 Q. And that's with a view to trying to find out</p>

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<p>1 if there's any benefit at all to the patient</p> <p>2 in taking hormonal therapy?</p> <p>3 DR. DENIC:</p> <p>4 A. That's correct.</p> <p>5 MS. NEWBURY:</p> <p>6 Q. Such as Tamoxifen. So you try to overcome the</p> <p>7 problem about the tumour not being</p> <p>8 heterogenous and try to actually target those</p> <p>9 areas that you anticipate might be ER</p> <p>10 positive?</p> <p>11 DR. DENIC:</p> <p>12 A. Exactly. To try to--we anticipate, not</p> <p>13 necessarily, because biological makeup of the</p> <p>14 cells could be completely different from the</p> <p>15 various portions of the tumour. And that's</p> <p>16 something that you cannot even do on your</p> <p>17 regular microscope. That's what molecular</p> <p>18 geneticists do.</p> <p>19 MS. NEWBURY:</p> <p>20 Q. Dr. Denic, if there were to be further</p> <p>21 testing, at what point would you feel that</p> <p>22 there is value in, you know, looking at a</p> <p>23 further, broader sampling of ER positive test</p> <p>24 results? I'm assuming, you know, there is</p> <p>25 some value, obviously, into doing the ER/PR</p>	<p>1 identifying, it might be patients who are</p> <p>2 still alive, as an example, or perhaps</p> <p>3 patients that haven't done as well as they had</p> <p>4 hoped, and maybe by virtue of the fact that</p> <p>5 they are self-identifying rather than being</p> <p>6 randomly selected out of a database, then it</p> <p>7 may not be a true representation of all of the</p> <p>8 ER positive patients?</p> <p>9 DR. DENIC:</p> <p>10 A. But random sampling is usually a true</p> <p>11 representation rather than the direct going</p> <p>12 with--I understand your question, how many of</p> <p>13 the cases that we should be doing and that we</p> <p>14 would be satisfied that this is done right.</p> <p>15 Obviously, in order to be satisfied that this</p> <p>16 is done right, you have to do all of them, you</p> <p>17 know, and I believe that for the various</p> <p>18 reasons as I said, and herein mentioned, the</p> <p>19 biggest one that going through all of this,</p> <p>20 we're going to need a lot of human resources.</p> <p>21 I'm going to lose the manager, I'm going to</p> <p>22 lose the program director again, and I'm going</p> <p>23 to probably lose myself and the oncologists as</p> <p>24 well has to be dedicated through all of this,</p> <p>25 and thousand patients took us two years and</p>
<p>1 testing, otherwise it wouldn't be done. So</p> <p>2 even though there are some impediments due to</p> <p>3 the, you know, the heterogenous nature of the</p> <p>4 tumour, that there is a value in doing it and</p> <p>5 it's done for a purpose and it's done to give</p> <p>6 options to the physician and the patient for</p> <p>7 treatment. At what point would you have a</p> <p>8 lack of comfort about the PR positive test</p> <p>9 results?</p> <p>10 DR. DENIC:</p> <p>11 A. I believe there's going to be still patients</p> <p>12 around that are going to be coming asking to</p> <p>13 be retested, you know, and I'm going to be</p> <p>14 monitoring that--those ones as well, you know.</p> <p>15 So we have to give a period of time that</p> <p>16 patients come forward. As I said, we've been</p> <p>17 offering and some of them did come forward.</p> <p>18 So I think to me that's going to be the best</p> <p>19 indicator, as such, whether if we start seeing</p> <p>20 changes in the results, then I definitely</p> <p>21 would be alarmed myself.</p> <p>22 MS. NEWBURY:</p> <p>23 Q. Would you think there would be a value into</p> <p>24 doing some of those retests on a random basis,</p> <p>25 recognizing that if patients are self-</p>	<p>1 probably this going to take us another three</p> <p>2 or four years, and in the meantime, I think,</p> <p>3 we won't be able to sustain really the</p> <p>4 service, but what would be the number really.</p> <p>5 I think, if statistician comes with any kind</p> <p>6 of proper number that they say, then we can</p> <p>7 revisit that issue and look into it.</p> <p>8 MS. NEWBURY:</p> <p>9 Q. Would that be your only impediment in terms of</p> <p>10 doing a further larger sampling size? Is it</p> <p>11 only the financial and human resources?</p> <p>12 DR. DENIC:</p> <p>13 A. It's not financial as much as it cost--you</p> <p>14 know, I don't think so that anybody would put</p> <p>15 the dollar figure against the patient care.</p> <p>16 It is the human restraints as well.</p> <p>17 MS. NEWBURY:</p> <p>18 Q. Sure.</p> <p>19 DR. DENIC:</p> <p>20 A. And the other factors, as I stated, that</p> <p>21 influence decision whether we should go</p> <p>22 further on on additional 1500 patients for</p> <p>23 tests.</p> <p>24 MS. NEWBURY:</p> <p>25 Q. And you've made reference to literature and</p>

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<p>1 that your conclusion from the literature is</p> <p>2 that false positives are not likely to be the</p> <p>3 problem as compared to the false negatives?</p> <p>4 DR. DENIC:</p> <p>5 A. That's correct.</p> <p>6 MS. NEWBURY:</p> <p>7 Q. And I believe it was Dr. Mullen's evidence</p> <p>8 that he thought, as a concept, that it would</p> <p>9 be unlikely that you would get a false</p> <p>10 positive, but his qualifications on that is</p> <p>11 that if you had a properly validated antibody,</p> <p>12 he thought that a false positive would be</p> <p>13 unlikely, and Dr. Banerjee also had testified</p> <p>14 on the issue of false positive results, and</p> <p>15 his conclusion was that it shouldn't be--I</p> <p>16 believe he thought it wasn't likely because if</p> <p>17 a pathologist would see cytoplasmic staining,</p> <p>18 then that should be disregarded, and he would</p> <p>19 be surprised if a pathologist would interpret</p> <p>20 cytoplasmic staining as positive, but in light</p> <p>21 of the fact that the four retroconversions</p> <p>22 were, in fact, in that category, does that</p> <p>23 give you concerns that the pathologists did</p> <p>24 all, in fact, recognize that cytoplasmic</p> <p>25 staining should not be called a positive</p>	<p>1 tired, could be part of the day, as I said,</p> <p>2 you know, that's why we don't see a large</p> <p>3 number of these cases.</p> <p>4 MS. NEWBURY:</p> <p>5 Q. I think one of the physicians, I believe it</p> <p>6 was Dr. Mullen, had indicated that the problem</p> <p>7 with false positives is more likely with</p> <p>8 HER2/neu as opposed to ER, but even if factors</p> <p>9 such as a pathologist looking at a slide later</p> <p>10 in the day and being tired and not being able</p> <p>11 to distinguish cytoplasmic staining from</p> <p>12 nuclear staining, you know, those could very</p> <p>13 well have been factors between 1997 and 2005?</p> <p>14 DR. DENIC:</p> <p>15 A. It might have happened, and as I said, this is</p> <p>16 only four cases and if you just look what</p> <p>17 current opinion is about it, how much error</p> <p>18 rate one should allow this would have been</p> <p>19 plus/minus 5 percent because you have to give</p> <p>20 some kind of leverage in any test. So 4</p> <p>21 percent really is below in this group that had</p> <p>22 been done. It's very low.</p> <p>23 MS. NEWBURY:</p> <p>24 Q. But where does the 4 percent come from? That's</p> <p>25 what I don't understand. Where did you get</p>
<p>1 results?</p> <p>2 DR. DENIC:</p> <p>3 A. Well, this is the experience of what they</p> <p>4 have. I'm stating from the literature, which</p> <p>5 was not written by either of them in that</p> <p>6 regard, stating that you can find the issue--</p> <p>7 probably one of the issue would be because</p> <p>8 there is overstaining cytoplasmic versus</p> <p>9 nuclear, but that doesn't appear--when you</p> <p>10 look at the slide, it's not always</p> <p>11 straightforward as one would think it's black</p> <p>12 and white because even these days when they're</p> <p>13 reporting the, for example, HER2/neu, and if</p> <p>14 you just look at the statement of Dr. Gown's</p> <p>15 office, they're trained to subtract the</p> <p>16 background staining from the staining of</p> <p>17 everything else.</p> <p>18 MS. NEWBURY:</p> <p>19 Q. Uh-hm.</p> <p>20 DR. DENIC:</p> <p>21 A. So it's not always possible to clear up the</p> <p>22 background staining, which may--it depends on</p> <p>23 the date and the time that the pathologist</p> <p>24 might look at this and conclude, yes, this is</p> <p>25 positive, but eventually it's not. Could be</p>	<p>1 that figure?</p> <p>2 DR. DENIC:</p> <p>3 A. What 5 --</p> <p>4 MS. NEWBURY:</p> <p>5 Q. The 4 percent? Did you say 4 percent?</p> <p>6 DR. DENIC:</p> <p>7 A. No, no, four patients.</p> <p>8 MS. NEWBURY:</p> <p>9 Q. Four patients, but that's out of a total of</p> <p>10 how many positives?</p> <p>11 DR. DENIC:</p> <p>12 A. That we looked here, that we looked all of</p> <p>13 this cases that were picked up because there</p> <p>14 was the group of the patients, they fell in a</p> <p>15 group below 30, and I exactly don't know how</p> <p>16 many of them are below 30 cutoff. So they</p> <p>17 would have been considered positives today.</p> <p>18 MS. NEWBURY:</p> <p>19 Q. Uh-hm.</p> <p>20 DR. DENIC:</p> <p>21 A. So you can probably compare them against four</p> <p>22 as well, and you can compare them against</p> <p>23 those ones that we never retested.</p> <p>24 MS. NEWBURY:</p> <p>25 Q. But the ones that you haven't retested, you</p>



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1 have no idea how many of those might also  
 2 convert. So would it be appropriate to use  
 3 that as a denominator in figuring out what  
 4 your error rate is?  
 5 DR. DENIC:  
 6 A. While you say it's inappropriate, we have to  
 7 recognize that some patients are treated  
 8 right, and even in--we showed that even this  
 9 error, some patients stayed negative as well.  
 10 So while we didn't test them, you cannot just  
 11 assume they were not done right either.  
 12 MS. NEWBURY:  
 13 Q. And I agree, you can't make an assumption one  
 14 way or the other about that.  
 15 DR. DENIC:  
 16 A. That's correct.  
 17 MS. NEWBURY:  
 18 Q. Dr. Denic, another point on the literature and  
 19 what is expected in terms of false positive,  
 20 there were a number of PR results that  
 21 converted to negative, and perhaps we can  
 22 bring up Exhibit P-0720, please. I think the  
 23 focus in the false positives has been the ER  
 24 test results as opposed to the PR test  
 25 results. This is--I'm not sure if you're

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1 familiar with this document. These are  
 2 results that were provided to Mark Quinn  
 3 following an access to information request,  
 4 and these, I think, were compiled by quality  
 5 and risk management. Just looking down at  
 6 line 15, the original ER result was negative,  
 7 and the PR result originally was 50 to 60, and  
 8 then it converted to zero ER and 2 PR. So  
 9 would that be considered--it hasn't been  
 10 referred to in the group of retroconverters or  
 11 false positives, but would that essentially be  
 12 a false positive PR result?  
 13 DR. DENIC:  
 14 A. It's still positive as you can see. It's 2  
 15 percent, and if you recognize everything over  
 16 1 percent is positive, but --  
 17 MS. NEWBURY:  
 18 Q. Clinically is that your understanding?  
 19 DR. DENIC:  
 20 A. I don't know about this particular case. You  
 21 have to look at case by case.  
 22 MS. NEWBURY:  
 23 Q. Sure.  
 24 DR. DENIC:  
 25 A. Because the clinicians were treating the cases

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1 even then. It depends on the case as such.  
 2 Even below the cutoff, sometimes above the  
 3 cutoff, sometimes a patient would be--well  
 4 expressor of ER/PR, but wouldn't be treated  
 5 because of the various other reasons for.  
 6 MS. NEWBURY:  
 7 Q. Uh-hm, but that is a significant reduction in  
 8 the PR result?  
 9 DR. DENIC:  
 10 A. But I think since we have Dr. Dabbs here, I  
 11 think he would be better to give the overview,  
 12 but in my opinion, what I know about PR, PR is  
 13 more volatile antibody and you're going to see  
 14 a larger variability in the PR.  
 15 MS. NEWBURY:  
 16 Q. Uh-hm.  
 17 DR. DENIC:  
 18 A. While it has the clinical implications, as we  
 19 know, based even on a CIQC proficiency  
 20 testing, as you know, that's a new body that's  
 21 been developed in Saskatchewan they're doing,  
 22 you can see larger variability in the PR  
 23 testing among the labs than with ER. So this  
 24 is something that I wouldn't be surprised, and  
 25 if you had Dr. Brendan Mullen's retests for

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1 these positives, you can even see that in his  
 2 lab one of the tests changed from 5 to 30 on a  
 3 PR. I think that must be an exhibit here. So  
 4 it doesn't surprise me.  
 5 MS. NEWBURY:  
 6 Q. Okay.  
 7 DR. DENIC:  
 8 A. And still it could be a different level of  
 9 section expression, and the nature of the  
 10 beast is the PRE's.  
 11 MS. NEWBURY:  
 12 Q. And there are a number of these. I just  
 13 wanted to show those to you briefly. Line 20  
 14 --in fact, there are two line 20s. The first  
 15 line 20 was negative ER/75 PR, and that  
 16 changed to 2 and zero ER/PR respectively, and  
 17 on line 61--it's actually three lines 61. So  
 18 the third line, there was a result of zero ER,  
 19 50/60 PR originally, and that went to zero and  
 20 zero.  
 21 DR. DENIC:  
 22 A. Ms. Newbury, it doesn't surprise me.  
 23 MS. NEWBURY:  
 24 Q. It doesn't surprise you at all.  
 25 DR. DENIC:

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1 A. It doesn't surprise me.  
 2 MS. NEWBURY:  
 3 Q. And does it surprise you that not only did it  
 4 vary, but went from a high significant PR  
 5 result down to zero or very close to zero?  
 6 DR. DENIC:  
 7 A. As I stated, you can go even to the Mount  
 8 Sinai's results and you can see the  
 9 variability on the retests, the ER and the PR  
 10 as well. So if I want to compare us with a  
 11 gold standard lab, you're going to find that  
 12 this kind of changes may occur in anybody's  
 13 lab.  
 14 MS. NEWBURY:  
 15 Q. And isn't so much the fact that there is  
 16 variability because I can appreciate what has  
 17 been said to date, but it's the fact, number  
 18 one ,that there is a significant difference  
 19 there; number two, it goes from a positive  
 20 result down to a negative result, and does  
 21 that cause you any concern about the fact that  
 22 theoretically or according to the literature,  
 23 false positives are not likely to occur?  
 24 DR. DENIC:  
 25 A. Because we are talking here about PR,

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1 obviously, as I said. PR is more volatile and  
 2 not much even work up in the literature. We  
 3 know there's a positivity, but even if you  
 4 read the literature about the PR, they're  
 5 going to tell you that it is not as well shown  
 6 optimization, validation. We know there is  
 7 significance of patients who are PR positive  
 8 and ER positive appears to have better  
 9 responded to therapy. So I cannot explain all  
 10 of them because this kind of results you're  
 11 going to find in labs.  
 12 MS. NEWBURY:  
 13 Q. Dr. Denic, you testified last week a little  
 14 bit about the issue of tissue reprocessing, an  
 15 are you aware--you were aware, I understand,  
 16 that it was taking place at St. Clare's, and  
 17 I'm wondering if you're aware of the step by  
 18 step procedure that was used in the tissue  
 19 reprocessing at St. Clare's?  
 20 DR. DENIC:  
 21 A. While I don't do tissue reprocessing, tissue  
 22 reprocessing means trying to put tissue back  
 23 through the same process as it went the first  
 24 time, but before you do that, you have to take  
 25 the paraffin off. So the paraffin has to be

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1 melted off and then you put the tissue through  
 2 the same procedure. What reprocessing does is  
 3 not re-fixation.  
 4 MS. NEWBURY:  
 5 Q. Uh-hm.  
 6 DR. DENIC:  
 7 A. Reprocessing is moving the tissue again  
 8 through the solutions, such as alcohol, which  
 9 takes the water out of the breast tissue  
 10 because breast tissue is a fatty tissue and  
 11 has high content of water. So reprocessing  
 12 really harden the tissue in order to make more  
 13 suitable for cutting.  
 14 MS. NEWBURY:  
 15 Q. Okay, that's the purpose for it, and I think  
 16 you indicated last week as well that during  
 17 the process of reprocessing, the sample would  
 18 be exposed to alcohol?  
 19 DR. DENIC:  
 20 A. That is correct.  
 21 MS. NEWBURY:  
 22 Q. Part of taking the sample out of the paraffin.  
 23 You've referred also to an article of Clive  
 24 Taylor and Goldstein, I believe?  
 25 DR. DENIC:

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1 A. Yes, this is Dr. Dabbs actually ad hoc group.  
 2 MS. NEWBURY:  
 3 Q. I wonder if I could call up Exhibit P-1767,  
 4 please. I just want to confirm that this is  
 5 the article that you were referring to. If  
 6 you want to scroll through that, you can.  
 7 DR. DENIC:  
 8 A. Okay. I think if you have the questions and  
 9 answers in the back of this.  
 10 MS. NEWBURY:  
 11 Q. I believe there's a reference there on page  
 12 13.  
 13 THE COMMISSIONER:  
 14 Q. You're looking for page 13 on this exhibit?  
 15 MS. NEWBURY:  
 16 Q. Yes.  
 17 DR. DENIC:  
 18 A. Oh, I think we might have --  
 19 MS. NEWBURY:  
 20 Q. Did you want to go back a bit.  
 21 DR. DENIC:  
 22 A. I think this is--okay, I think this is Dr.  
 23 Badve, and this is the part which is marked  
 24 "Q", the middle column, first paragraph. He  
 25 said, "Standard processing protocols entail

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<p>1 the use of alcohol out of the tissues fixed in 2 formalin. Alcohol is also fixative with a 3 relatively rapid penetration. So if unfixed 4 tissues are loaded onto a processor, they are 5 more likely to undergo significant alcohol 6 fixation which can lead to altered 7 immunohistochemistry and false positive 8 results".</p> <p>9 MS. NEWBURY: 10 Q. Okay. So that was the reference you made last 11 week?</p> <p>12 DR. DENIC: 13 A. That's correct.</p> <p>14 MS. NEWBURY: 15 Q. And so that was a concern, a potential concern 16 that you raised regarding the reprocessing?</p> <p>17 DR. DENIC: 18 A. My point is that we have 380 patients that 19 were false negative, and if alcohol 20 reprocessing does anything, it would be false 21 positive results.</p> <p>22 MS. NEWBURY: 23 Q. But you can't say --</p> <p>24 DR. DENIC: 25 A. So that doesn't really answer 380.</p>	<p>1 that there is evidence to support the fact 2 that there was alcohol being exposed to the 3 samples during the retesting. I think the 4 evidence of Les Simms said that to get the wax 5 out, you would soak it in xylene and rinse it 6 in alcohol and put it back in formalin. So 7 he's confirming your understanding that there 8 was exposure to alcohol, the samples?</p> <p>9 DR. DENIC: 10 A. The tissue was exposed to alcohol in the first 11 place.</p> <p>12 MS. NEWBURY: 13 Q. Right.</p> <p>14 DR. DENIC: 15 A. With the processing as well.</p> <p>16 MS. NEWBURY: 17 Q. Before it's fixed in formalin?</p> <p>18 DR. DENIC: 19 A. No. You first fix the tissue in formalin, as 20 I said, with this breast, except for the few 21 that fell out of--of the working hours of the 22 labs, and we know that some of tissue received 23 in lab had less formalin in. The tissue 24 eventually would be fixed 24 hours. So the 25 fixation wouldn't be any more affected in</p>
<p style="text-align: right;">Page 42</p> <p>1 MS. NEWBURY: 2 Q. Right.</p> <p>3 DR. DENIC: 4 A. Does it?</p> <p>5 MS. NEWBURY: 6 Q. Now the tissue reprocessing wasn't taking 7 place in all cases, though?</p> <p>8 DR. DENIC: 9 A. No.</p> <p>10 MS. NEWBURY: 11 Q. And there's no way to identify, as I 12 understand it, which samples had been subject 13 to tissue reprocessing?</p> <p>14 DR. DENIC: 15 A. No.</p> <p>16 MS. NEWBURY: 17 Q. Okay, and you don't know because there has 18 been very limited testing of positive 19 patients, you don't know if this, in fact, may 20 have played a role in some of the positive 21 test results?</p> <p>22 DR. DENIC: 23 A. No.</p> <p>24 MS. NEWBURY: 25 Q. Okay, and it was the evidence of Les Simms</p>	<p style="text-align: right;">Page 44</p> <p>1 terms of--the tissue comes fixed into the 2 tissue processor. So the fixation is done in 3 24 hours. So then you move the tissue from 4 one alcohol to another to take the water out 5 because fixation is one process. Moving the 6 water out of alcohol is a different process. 7 So again if you reprocess the tissue, fixation 8 is already done, but what he's talking here 9 about is most likely--so if unfixed tissues 10 are loaded onto the processor.</p> <p>11 MS. NEWBURY: 12 Q. Uh-hm.</p> <p>13 DR. DENIC: 14 A. So unfixed tissue, and there's testimony-- 15 actually the reports rather than testimony, 16 because most of them I didn't listen. 17 Fixation was taken as in account of as being 18 responsible for the false negative results.</p> <p>19 MS. NEWBURY: 20 Q. But the question, Dr. Denic, that arises from 21 this, what if a tissue had not been properly 22 fixed and then was later exposed to tissue 23 reprocessing, and there is evidence--Dr. 24 Banerjee had indicated in his first report 25 that there appeared to be inadequate attention</p>

<p style="text-align: right;">Page 45</p> <p>1 paid by grossing pathologists to the tissue 2 thickness, quality, and adequacy of fixation, 3 and that there was no standardized fixation 4 protocol, and Trish Wegrynowski also commented 5 in her report that prior to 2003, formalin 6 fixative was prepared in house and 7 distributed, but no documentation concerning 8 the pH of this fixative was found. So there's 9 some possible inadequacies here in fixation 10 and my question is whether or not there's been 11 any analysis or investigation of whether or 12 not an inadequately fixed specimen, then 13 subject to tissue reprocessing, could have led 14 to false positive results? 15 DR. DENIC: 16 A. But what you quoted here in Dr. Banerjee's 17 report he's talking about false negatives. 18 He's not talking about false positives in the 19 report as such. So from that perspective, Dr. 20 Banerjee--Ms. Wegrynowski has said--they said 21 just can be affected, they never stated how, 22 and obviously the whole point was about false 23 negative. None of them really, as I 24 understand, and I read this so many times, I 25 couldn't find that reference to the false</p>	<p style="text-align: right;">Page 47</p> <p>1 we know that could expose tissue samples to 2 alcohol. We also know there are problems with 3 fixation. Could those two combined factors 4 for some of the cases lead to problems with 5 false positives? 6 DR. DENIC: 7 A. I don't think so a significant problem, in my 8 opinion, and I don't consider myself an expert 9 in immunohistochemistry as such. I don't 10 think so it's a significant problem, and again 11 maybe more light is going to be shed by Dr. 12 Dabbs because I'm still seeking the right 13 answers too. 14 MS. NEWBURY: 15 Q. Sure. 16 DR. DENIC: 17 A. Obviously when Dr. Banerjee wrote all of this, 18 he found that the fixation was inappropriate, 19 and I agreed to the certain extent, and 20 whether the fixation was the real culprit, the 21 fixation or the processing as such, you would 22 expect--then the tissue went to Mount Sinai, 23 thousand tissue went to Mount Sinai, thousand 24 tissue came back with the results from Mount 25 Sinai.</p>
<p style="text-align: right;">Page 46</p> <p>1 positive results in neither of these reports, 2 but Dr. Banerjee was talking about false 3 negative, so if the tissue are unfixed, and 4 the other reference that they made is Sakura, 5 I couldn't find actually in the literature as 6 such. This is the first-- this was written in 7 2007 as such, reference to the alcohol and--so 8 they are conflicting statements really to me. 9 MS. NEWBURY: 10 Q. Dr. Banerjee, in writing his report, of 11 course, he was involved in a review that 12 resulted from an index patient that was ER 13 negative, and the focus all along has been on 14 the ER negative patients, and, you know, 15 granted the context there would be based on 16 that, however, Dr. Banerjee is pointing out 17 clearly that there are problems or concerns 18 that he had with fixation as did Ms. 19 Wegrynowski, and my question is whether or not 20 Eastern Health, or whether you or anyone else 21 has considered the implications of there being 22 inadequate fixation? It could affect the ER 23 positive--or negative test results clearly, 24 but has there been any consideration--we know 25 that we've had tissue reprocessing going on,</p>	<p style="text-align: right;">Page 48</p> <p>1 MS. NEWBURY: 2 Q. Uh-hm. 3 DR. DENIC: 4 A. So what happened--so there got to be some 5 other factors involved in all of this, that 6 Mount Sinai was using in 2005 that we were not 7 using, and we know that the technology 8 changed, we know that the protocol they were 9 using is completely different from the 10 protocol that we were using down there in '97, 11 '98, '99, up to 2004 when we using the DAKO. 12 So antigen retrieval obviously the one that 13 somebody should look into. The other thing 14 that I mentioned, I know that I still cannot 15 explain cases turning from zero to hundred, 16 and that's--since nobody has ever examined the 17 piece of equipment, and there is the evidence 18 in the other authorities, and even in UK that 19 equipment could have played some of the role, 20 I'm not saying the full role, but could have 21 been playing some role in all of this. I 22 think it's a complex process. I don't think 23 so it's straightforward, and we seen even in 24 Mount Sinai's results changing from one block. 25 We send the one block, zero, zero, internal</p>

<p style="text-align: right;">Page 49</p> <p>1 control positive, fixation adequate. Second 2 block, ER 50, internal control positive, 3 fixation adequate. So that makes all of this 4 very complex to me still. That's why I'm 5 saying I'm still seeking myself the answers 6 about all of this.</p> <p>7 MS. NEWBURY:</p> <p>8 Q. But does the fact that there was tissue 9 reprocessing going on, and the fact that there 10 was fixation, does that not at least raise a 11 question in your mind as to whether further 12 testing, a larger sample size, if not all of 13 the positive test results should be looked at, 14 just to satisfy yourself that there is not a 15 broader problem going on?</p> <p>16 DR. DENIC:</p> <p>17 A. Ms. Newbury, I need the evidence-based 18 literature in all of this to reflect and to 19 tell me exactly how was done, what is the 20 evidence about this, and then we can--we can 21 take some of the cases and we can experiment 22 with that.</p> <p>23 MS. NEWBURY:</p> <p>24 Q. So you're looking for evidence-based 25 literature to show that there is a problem?</p>	<p style="text-align: right;">Page 51</p> <p>1 A. So --</p> <p>2 MS. NEWBURY:</p> <p>3 Q. And you don't see that in the circumstances, 4 especially where there was no quality 5 assurance or quality control, that something 6 more than waiting for someone to provide 7 evidence-based literature that there could be 8 a problem, is enough to go back and do a 9 larger sample?</p> <p>10 DR. DENIC:</p> <p>11 A. It's not that I don't contemplating that, Ms. 12 Newbury. What we have done from 2005 never 13 been done anywhere. So we went with the same 14 thoughts, help the patients, as such. At this 15 particular moment, as I stated, why I'm not 16 contemplating further on, the various factors 17 in my mind why we cannot do this at this 18 particular--and that's why it was left to the 19 patient as well to identify themselves, to come 20 down, we do them--if we have to do them by 21 batch, you know, ten patients come forward as 22 such, we do them. So this is the best--at 23 this particular, the state that our lab is in, 24 that we can do that. Otherwise, we have to 25 stop all the processes, we won't be able to</p>
<p style="text-align: right;">Page 50</p> <p>1 DR. DENIC:</p> <p>2 A. Exactly.</p> <p>3 MS. NEWBURY:</p> <p>4 Q. How about looking for evidence-based 5 literature to show that there isn't a problem? 6 I'm wondering why you're assuming that there 7 is no problem unless there's some evidence out 8 there to show that there is, but perhaps there 9 hasn't been a lot out there that had a problem 10 with fixation at the same time that they had 11 tissue reprocessing? Maybe there is no 12 literature available to investigate that.</p> <p>13 DR. DENIC:</p> <p>14 A. I'm trying to run the laboratory on evidence- 15 based literature and everything has to be 16 supported. Whatever we do, we have to find 17 that--even pathologists are now advised if you 18 want something to be done in the lab, please 19 come up with a paper stating that this is it, 20 this has to be done, these are the 21 consequences, these are the benefits, in order 22 to do that.</p> <p>23 MS. NEWBURY:</p> <p>24 Q. Okay.</p> <p>25 DR. DENIC:</p>	<p style="text-align: right;">Page 52</p> <p>1 sustain a high workload and demand of the 2 cancer--new cancer patients. So this is my 3 answer really. I cannot shed any more light 4 on this.</p>

1 MS. NEWBURY:  
 2 Q. So it's primarily the lack of resources, as  
 3 opposed to your confidence that there isn't a  
 4 problem. Is that correct?  
 5 DR. DENIC:  
 6 A. I mean, I cannot say that we won't find one or  
 7 two patients as such.  
 8 MS. NEWBURY:  
 9 Q. Okay.  
 10 DR. DENIC:  
 11 A. I'm not stating that. I'm not absolutely  
 12 certain, but I believe, it's my opinion. It's  
 13 not even close as a problem as we had with the  
 14 false negative.  
 15 MS. NEWBURY:  
 16 Q. What if it's somewhere in between a five  
 17 percent error rate and the error rate that you  
 18 have with the ER negatives, would that be  
 19 worth--I'm just wondering where, at what point  
 20 -  
 21 DR. DENIC:

1 Q. No.  
 2 THE COMMISSIONER:  
 3 Q. Okay, Mr. Crosbie.  
 4 DR. NEBOJSA (NASH) DENIC, EXAMINATION BY CHESLEY CROSBIE,  
 5 Q.C.  
 6 CROSBIE, Q.C.:  
 7 Q. Thank you, Commissioner. Dr. Denic, we've  
 8 met. Ches Crosbie, I represent the members of  
 9 the class action. One or two things that  
 10 arose from your testimony on Friday afternoon.  
 11 This business about the refrigerator and the  
 12 cold section room, which is adjourning the OR.  
 13 There's one now installed in St. Clare's, but  
 14 not in the Health Sciences Centre. Is that  
 15 right?  
 16 DR. DENIC:  
 17 A. No, both of them have refrigerators.  
 18 CROSBIE, Q.C.:  
 19 Q. Oh, they both do?  
 20 DR. DENIC:  
 21 A. Both.  
 22 CROSBIE, Q.C.:  
 23 Q. Okay, and the theory behind that is if you--  
 24 ideally, you want to get the specimen down to  
 25 the lab and in fixation in 15 minutes or so.

1 A. I mean, that's purely speculation really. We  
 2 are speculating what if it's a five, but what  
 3 if it's a six percent? What if it's a four  
 4 percent? It's still a number of patients, as  
 5 such. I mean, I think I cannot speculate. I  
 6 think this is not the venue to speculate. I  
 7 think we should reconsider the stuff and try  
 8 to do anything what's best for the patient,  
 9 but it has to be somewhere, a certain way to  
 10 put on the argument on the benefits, on  
 11 expectations of such endeavour.  
 12 MS. NEWBURY:  
 13 Q. Thank you, Dr. Denic. Those are all the  
 14 questions I have.  
 15 DR. DENIC:  
 16 A. You're welcome.  
 17 CROSBIE, Q.C.:  
 18 Q. I have two minutes worth of questions.  
 19 THE COMMISSIONER:  
 20 Q. Yes, but before you go ahead, since there are  
 21 some changing of you this morning, Mr. Eaton,  
 22 does your arrival indicate a change of  
 23 position in respect of questions for this  
 24 witness?  
 25 EATON, Q.C.:

1 Is that right?  
 2 DR. DENIC:  
 3 A. That's correct. You want tissue, actually  
 4 tumour in particular, to be exposed within the  
 5 30 minutes.  
 6 CROSBIE, Q.C.:  
 7 Q. Sure. But if you can't do that, and  
 8 occasionally it doesn't happen according to  
 9 what you'd want to happen, then the ideal  
 10 thing--the second best thing is to put it in  
 11 the fridge, to try and slow decomposition?  
 12 DR. DENIC:  
 13 A. Mr. Crosbie, I would think so, you know, and I  
 14 accepted Ms. Fergrofski's (sic) argument for  
 15 that, we should have refrigerators, but when  
 16 you start digging now through the literature,  
 17 and I think that could have been a submission  
 18 in regard to the influence of refrigeration on  
 19 the tissue. One of the argument is that the  
 20 tissue can even stay on the bench in formalin  
 21 over weekend, and I think the other argument  
 22 about the refrigeration, that refrigeration  
 23 can have detrimental effect on fixation.  
 24 Furthermore, to overcome this issue, what we  
 25 do, we're still using the refrigeration -

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<p>1 CROSBIE, Q.C.:</p> <p>2 Q. I think we understand that, but the second</p> <p>3 best is to put it in the fridge, isn't it?</p> <p>4 Isn't that the reason for the recommendation?</p> <p>5 If you can't get it down and get it fixed?</p> <p>6 THE COMMISSIONER:</p> <p>7 Q. But isn't it in formalin in the refrigerator?</p> <p>8 DR. DENIC:</p> <p>9 A. Then in formalin. They have to be in</p> <p>10 formalin, and then if you put it in a</p> <p>11 refrigerator now and expose to the low</p> <p>12 temperature, penetration and fixation process</p> <p>13 is going to be retarded. It's going to be</p> <p>14 delayed, and at least that's the answer that</p> <p>15 CAP, which is College of American</p> <p>16 Pathologists, based on a QNA, said about it.</p> <p>17 But, to go furthermore, what we felt, and</p> <p>18 that's why we have pathology assistants,</p> <p>19 they're monitoring what's happening in the OR.</p> <p>20 CROSBIE, Q.C.:</p> <p>21 Q. We needn't dwell on it. I guess you're point</p> <p>22 is that you accepted the recommendation and</p> <p>23 you work with the fridge as a current best</p> <p>24 practice, I suppose.</p> <p>25 DR. DENIC:</p>	<p>1 possibility of clogging in the machine?</p> <p>2 DR. DENIC:</p> <p>3 A. That was my understanding from UK's</p> <p>4 experience.</p> <p>5 CROSBIE, Q.C.:</p> <p>6 Q. Have you read the 40, the 54-page DAKO</p> <p>7 troubleshooting manual to see if clogging is a</p> <p>8 recognized problem with the machine?</p> <p>9 DR. DENIC:</p> <p>10 A. No, I didn't.</p> <p>11 CROSBIE, Q.C.:</p> <p>12 Q. Have you inquired with the manufacturer to see</p> <p>13 if clogging is recognized as a machine failure</p> <p>14 issue?</p> <p>15 DR. DENIC:</p> <p>16 A. No, I didn't. This is the knowledge that I</p> <p>17 acquired recently.</p> <p>18 CROSBIE, Q.C.:</p> <p>19 Q. Did you review the maintenance records for the</p> <p>20 Eastern Health machine?</p> <p>21 DR. DENIC:</p> <p>22 A. No.</p> <p>23 CROSBIE, Q.C.:</p> <p>24 Q. And why is that?</p> <p>25 DR. DENIC:</p>
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<p>1 A. That's correct, but we are still revisiting</p> <p>2 stuff and we're going to do some consults as</p> <p>3 such and then maybe that's one of the things</p> <p>4 that I'm going to be after Dr. Dabbs -</p> <p>5 CROSBIE, Q.C.:</p> <p>6 Q. I'm sure, and that's -</p> <p>7 DR. DENIC:</p> <p>8 A. - has the money to talk about it.</p> <p>9 CROSBIE, Q.C.:</p> <p>10 Q. That's all part of ongoing quality assurance.</p> <p>11 DR. DENIC:</p> <p>12 A. That's correct.</p> <p>13 CROSBIE, Q.C.:</p> <p>14 Q. My other question has to do with this issue of</p> <p>15 machine error. You have training in forensic</p> <p>16 pathology, I believe.</p> <p>17 DR. DENIC:</p> <p>18 A. I do.</p> <p>19 CROSBIE, Q.C.:</p> <p>20 Q. And you're familiar with the process of</p> <p>21 weighing evidence, I guess?</p> <p>22 DR. DENIC:</p> <p>23 A. That's correct.</p> <p>24 CROSBIE, Q.C.:</p> <p>25 Q. I think you mentioned on Friday, the</p>	<p>1 A. The first--this is not something that I was in</p> <p>2 charge with.</p> <p>3 CROSBIE, Q.C.:</p> <p>4 Q. May I suggest there are no such records?</p> <p>5 DR. DENIC:</p> <p>6 A. I don't know what's in the -</p> <p>7 CROSBIE, Q.C.:</p> <p>8 Q. To the best of my knowledge, we have not found</p> <p>9 any such records in maintenance of machines,</p> <p>10 so that could be a reason why no one could</p> <p>11 review them.</p> <p>12 DR. DENIC:</p> <p>13 A. It's possible.</p> <p>14 CROSBIE, Q.C.:</p> <p>15 Q. You don't know anything to the contrary?</p> <p>16 DR. DENIC:</p> <p>17 A. It's possible. I heard that there's a lack of</p> <p>18 documentation and that would be the part of</p> <p>19 it. I agree with you.</p> <p>20 CROSBIE, Q.C.:</p> <p>21 Q. And you weren't able to perform a forensic</p> <p>22 examination of the DAKO autostainer in</p> <p>23 question, were you?</p> <p>24 DR. DENIC:</p> <p>25 A. That's correct.</p>

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1 CROSBIE, Q.C.:

2 Q. And that's because Eastern Health disposed of

3 it before you could do that?

4 DR. DENIC:

5 A. That's my understanding, and I was inquiring

6 myself to track down where the instrument

7 went, because I think before we put this

8 puzzle together, you need all pieces, and one

9 of the piece was missing and I was told that

10 nobody knows where this machine went and what

11 happened.

12 CROSBIE, Q.C.:

13 Q. And the reason the piece of the puzzle is

14 missing is that Eastern Health disposed of it.

15 DR. DENIC:

16 A. I really don't know who disposed of it, but

17 Eastern Health, did the managers do anything,

18 lab director, somebody did it.

19 CROSBIE, Q.C.:

20 Q. Well, maybe we'll find out when Mr. Gulliver

21 comes in. Thanks very much.

22 DR. DENIC:

23 A. You're welcome.

24 THE COMMISSIONER:

25 Q. Mr. Pike?

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1 MR. PIKE:

2 Q. No questions. Thank you very much.

3 THE COMMISSIONER:

4 Q. Mr. Browne?

5 DR. NEBOJSA (NASH) DENIC, EXAMINATION BY MR. PETER BROWNE

6 MR. BROWNE:

7 Q. Thank you, Commissioner. Good morning, Dr.

8 Denic.

9 DR. DENIC:

10 A. Good morning.

11 MR. BROWNE:

12 Q. A few areas I wish to cover with you, and I'd

13 ask you to cast your mind back to, I think,

14 the first day unfortunately, you gave evidence

15 here last week, and you were asked a question

16 by Mr. Coffey about your exposure to

17 immunohistochemistry during your residency and

18 my question is, specifically, in terms of your

19 understanding of who should understand about

20 the test and how the test was performed, what

21 was your understanding? Where did that

22 knowledge base lie?

23 DR. DENIC:

24 A. Pathologists, they don't perform the test, and

25 if you put me in the lab down there, I

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1 wouldn't know how to do it. You know, I know

2 the basics, you know, you apply the

3 antibodies, apply secondary antibodies. So

4 these are basics of all the tests as such, but

5 I wouldn't know how to perform.

6 MR. BROWNE:

7 Q. What is your understanding, who--what people

8 or persons would have had that understanding?

9 DR. DENIC:

10 A. The technologists.

11 MR. BROWNE:

12 Q. Now we've heard about fixation problems and

13 these have been mentioned by yourself, in

14 terms of questioning from Commission counsel

15 and others. Dr. Banerjee spoke to this. Dr.

16 Mullen spoke to this, as well as others.

17 Today, Doctor, if you noticed a problem with

18 fixation of a particular tissue specimen, what

19 would, if any, corrective action would you

20 take?

21 DR. DENIC:

22 A. Today, we have check and balances and quality

23 controls and assurance on every step,

24 including pre-analytical, analytical and post

25 analytical phase of this. So, on our

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1 requisition, the time when the tissue was put

2 in the formalin is recorded and that time

3 comes directly from the OR. So we can

4 identify the time when the tissue is exposed

5 to the formalin. We know the time when the

6 tissue comes to the lab because the book has

7 been signed and receive of the specimen is

8 done because--and then it's been attended

9 immediately by the pathology assistants who

10 are on call all the time. Then the tissue, we

11 know that the tissue, by protocol, is left in

12 the formalin for 24 hours, at least, to be

13 fixed. Been sliced at that time and left in

14 the formalin to be fixed, so that's all

15 recorded and we exactly know the time when the

16 tissue was sampled, then we know the time when

17 the tissue is submitted to the tissue

18 processor. This is all pre-analytical phases,

19 and the tissue processor, we know the times

20 when the solutions were changed as well. So

21 if anything can go wrong, you can go back and

22 see when the solutions were changed. We even

23 have the templates, because the various

24 containers of the solutions sometimes can be

25 confusing, there's even a picture of the



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1 tissue processor showing you the set up of the  
 2 container, so that you can always cross check  
 3 that. So we exactly know when processor  
 4 starts, because by default it's always 6:00.  
 5 So you know the time in the processor. You  
 6 know the time how long tissue stays in the  
 7 formalin, because the first chamber is still  
 8 formalin and you can add that time to the time  
 9 of fixation from the OR. Then we know the  
 10 people who are cutting the tissue.  
 11 MR. BROWNE:  
 12 Q. So Doctor, just to--I guess, the focus of my  
 13 question perhaps is a little bit more pointed.  
 14 There are a number of steps that you have in  
 15 place and where you can now go back and target  
 16 if there's a particular problem which led to  
 17 that fixation that you identified? Is that -  
 18 DR. DENIC:  
 19 A. Exactly. We can go to the root cause analysis  
 20 with no time and check it out every single  
 21 station.  
 22 MR. BROWNE:  
 23 Q. And that's through the policies that you have  
 24 in place?  
 25 DR. DENIC:

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1 A. That's correct.  
 2 MR. BROWNE:  
 3 Q. In terms of the timing and so on, that allows  
 4 you to pinpoint a particular problem, if you  
 5 were to go look back to see where it may be,  
 6 as you say, the root cause?  
 7 DR. DENIC:  
 8 A. That's correct.  
 9 MR. BROWNE:  
 10 Q. You were asked about educational memos and you  
 11 referenced Dr. Khalifa's memo in 1998, Dr.  
 12 Ejeckam's memo in May 2003. Going back to Dr.  
 13 Khalifa, when you were--I think you were  
 14 around during his time, you were doing your  
 15 residency, do you recall Dr. Khalifa  
 16 distributing any documentation surrounding  
 17 synoptic reporting?  
 18 DR. DENIC:  
 19 A. Yes, he was actively working on synoptic  
 20 reporting of various tumour sites, so he made,  
 21 I think, he almost addressed all tumour sites.  
 22 MR. BROWNE:  
 23 Q. And he had documents that he distributed with  
 24 that?  
 25 DR. DENIC:

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1 A. That's right, and they've been printed at  
 2 Health Sciences at that time and distributed  
 3 to the attending physicians, pathologists. So  
 4 we all had that on our desk, so that we can  
 5 fill up the synoptic reports.  
 6 MR. BROWNE:  
 7 Q. And the purpose of that was to move away from  
 8 then the inconsistent narrative reporting to a  
 9 detailed checklist that would have helped  
 10 clinicians, oncologists, on the other end?  
 11 DR. DENIC:  
 12 A. That's correct, and these are CAP based  
 13 practices.  
 14 MR. BROWNE:  
 15 Q. You were also asked about Dr. Fontaine's--  
 16 there was a--you were shown an exhibit which  
 17 had a meeting note where Dr. Fontaine  
 18 suggested to his colleagues at the Health  
 19 Sciences about availing of Dr. Carter's  
 20 services for rereads of ER/PR. Was that type  
 21 of approach necessary at St. Clare's, given  
 22 that Dr. Carter shared the same offices?  
 23 DR. DENIC:  
 24 A. You didn't need any memo. I mean, Dr. Carter  
 25 was there and we utilized her services

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1 whenever we could, you know, especially for  
 2 the breast specimens.  
 3 MR. BROWNE:  
 4 Q. Okay. Now there are a number of articles,  
 5 Doctor, that I just want to reference and I  
 6 should enter right now. You had mentioned in  
 7 your testimony last week a couple of  
 8 Ackerman's, Rosai Ackerman's textbooks where  
 9 you cited about the--I think a particular  
 10 passage concerning, I guess, the relationship  
 11 between--statistical relationship between  
 12 ductal and lobular and I think you also  
 13 mentioned Tavassoli. So perhaps we can,  
 14 Registrar, enter those two exhibits, beginning  
 15 first with P-2623 and 2624.  
 16 THE COMMISSIONER:  
 17 Q. 2623 and 2624? There are others as well, are  
 18 there not?  
 19 MR. BROWNE:  
 20 Q. Yes, and perhaps why don't we just enter them  
 21 all at this point, Commissioner. The next is  
 22 the Tavassoli reference, which is P-2625, and  
 23 the Royal College of Pathologists Recognition  
 24 Roles of Specialists, Pathologists, P-2626.  
 25 Requirements of a Specialist Breast Unit, P-

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<p>1 2627, and then lastly, the UK NEQAS Journal, 2 which is P-2628. 3 THE COMMISSIONER: 4 Q. All right, entered. 5 EXHIBITS ENTERED AND MARKED P-2623 THROUGH P-2628 6 MR. BROWNE: 7 Q. Thank you, Commissioner. Doctor, going back 8 to the first of these exhibits, P-2623, and we 9 can probably deal with 2623 and 2624 as a 10 package, and I'll--one is, I think, if we look 11 at--I'll follow down here. This is the 2004 12 version, it seems, and I think the other 13 exhibit is a previous, an earlier version of 14 that textbook, looks to be 1996. 15 Nevertheless, Doctor, I think the passage 16 remains the same in both. Is that, from your-- 17 and the passage you were referencing, if we 18 could just look at it, is this one right here? 19 It's under the section "Hormone Receptors." 20 It's the second paragraph, and in terms of 21 giving your evidence, the other day, you were 22 referencing the comment "not much correlation 23 exists between the cyto architectural type of 24 breast cancer carcinoma and the presence of 25 hormone receptor protein. Specifically no</p>	<p>1 DR. DENIC: 2 A. That's correct. 3 MR. BROWNE: 4 Q. So the purpose of these articles, Doctor, is 5 just to confirm the source of your evidence 6 the other day? 7 DR. DENIC: 8 A. That's correct. 9 MR. BROWNE: 10 Q. Now there are a couple of other articles that 11 you've asked to be entered, Doctor, and I'll 12 begin with the first of these. Registrar, can 13 we look at--and I think some of these come out 14 of requests that Mr. Coffey made to you, I 15 think, on Friday. Is that correct? 16 DR. DENIC: 17 A. That's correct. 18 MR. BROWNE: 19 Q. Okay. The first of these, Doctor, is P-2626, 20 and this is from the United Kingdom. It's 21 from the Royal College of Pathologists, and it 22 talks about the recognition and roles of 23 specialist cellular pathologists. Now is this 24 from Dr. Makretzov? 25 DR. DENIC:</p>
<p>1 statistically significant difference has been 2 found between ductal type and lobular type 3 tumours." Is that the reference you were 4 referring to? 5 DR. DENIC: 6 A. That's correct. 7 MR. BROWNE: 8 Q. Okay, and then, but nevertheless, you did 9 qualify that later on by saying, look, there 10 was Tavassoli which actually did give a 11 reference, and Registrar, if we can have 2625? 12 And again, this is under the section "Hormone 13 Receptors" and is that ploidy? 14 DR. DENIC: 15 A. Yeah, ploidy. 16 MR. BROWNE: 17 Q. Just as a matter of curiosity, what is ploidy? 18 DR. DENIC: 19 A. This is a chromosomal abnormality. It's an 20 abnormal number of chromosomes. 21 MR. BROWNE: 22 Q. Okay, and the reference again, Doctor, that 23 you gave in evidence is at the first line. It 24 says "about 70 to 92 percent of lobular 25 carcinomas are ER positive."</p>	<p>1 A. No, this is something, that was a document 2 that was shown to me by Mr. Coffey when 3 explaining the benefit of subspecializing to 4 pathologists, and some of their recommendation 5 I took out. At the time I quoted, I thought 6 that this article is really coming from the 7 article from the Board of Directors in 8 Anatomical Pathology, but it's rather the 9 Royal College of - 10 MR. BROWNE: 11 Q. Okay, and - 12 DR. DENIC: 13 A. I think this is UK, Royal College. 14 MR. BROWNE: 15 Q. - the passage you're looking at, I think it 16 may be at page four, and that's under Section 17 5, the attributes of a specialist pathologist. 18 Is that the passage you were referencing 19 there? 20 DR. DENIC: 21 A. That's correct. 22 MR. BROWNE: 23 Q. Okay. 24 DR. DENIC: 25 A. It could have been slight revisions, but this</p>

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1 is the gist of it.

2 MR. BROWNE:

3 Q. The next document, Doctor, is P-2627,

4 Registrar. And again, this is entitled the

5 requirements of a specialist breast unit.

6 Doctor, this is something Dr. Makretzov

7 brought to your attention about the UK

8 experience?

9 DR. DENIC:

10 A. That's correct. This is a position paper and

11 they are working towards creation of the

12 specialist breast unit.

13 MR. BROWNE:

14 Q. And this is, I think, so we're clear on this

15 point, this was the notion of having like

16 stations where the patient can go see a

17 pathologist, oncologist, radiologist, all in

18 sort of a one clear area?

19 DR. DENIC:

20 A. That's right. One unit or to be close by, so

21 they could be available to the patient.

22 MR. BROWNE:

23 Q. Right, for immediate consultation?

24 DR. DENIC:

25 A. That's right, so that the people work together

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1 on the same patient really.

2 MR. BROWNE:

3 Q. And then lastly, Doctor, there is, Registrar,

4 P-2628, and this is from the UK NEQAS

5 publications and this is 154. There's a

6 comment section at page 12. I'll just bring

7 it to your attention now, Doctor, which is

8 highlighted there, and it says, "as a very

9 high ER positive case is likely to stain

10 strongly, even when the sensitivity of the

11 assay is relatively low. Similarly, due to

12 the limited number of nuclei frequently

13 staining in normal glands, it is difficult to

14 detect changes in day-to-day assay sensitivity

15 by relying totally on this material for

16 quality control." There was a point, I think,

17 you wanted to draw out to the Commissioner's

18 attention from this commentary section?

19 DR. DENIC:

20 A. I mean, I think I stated, and that's why I was

21 puzzled with some of these cases turning from

22 zero to 100, you know, and it is quite clear

23 that any kind of really of test, as they state

24 here, with the low sensitivity test, while low

25 sensitivity test can tell that probably the

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1 test wasn't optimized well. So that, so even

2 then, some nuclear staining would have been

3 positive, and in some of the cases that we've

4 seen, they change from zero to 100. So even

5 thinking that the test wasn't validated, the

6 test wasn't optimized, you would think that

7 applying at that time would pick up any type

8 of staining in the nuclei, but it didn't. So

9 that's why I also stated it could be something

10 more. Is it something that the antibody never

11 even touched the tissue.

12 MR. BROWNE:

13 Q. So you raise this as a possible contributing

14 factor?

15 DR. DENIC:

16 A. That's right. Although there's another point

17 there, although they're talking in regards of

18 the controls here, if you can see they're

19 talking about staining in normal glands,

20 frequency of staining in normal glands.

21 Normal glands we see as internal control as

22 well. While they're probably referring, not

23 quite certain, to the external control using

24 normal glands, they tell you that the limited

25 number of nuclei frequently staining in normal

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1 glands, it is difficult to detect changes in

2 day-to-day assay sensitivity by relying

3 totally on the material for the quality

4 control. So while we recognize value of

5 internal control today more than we did and

6 we're putting stuff, that's why we still

7 seeing the cases where internal control not

8 going to be positive, but the stain's going to

9 work based where the stain is present. If a

10 stain is present in the nuclei and you have

11 external control which is well done, then you

12 know that the test works, and these are the

13 experiences as well that you can pull out from

14 Dr. Mullen's list that he also reported the

15 cases where internal control was positive, but

16 not staining.

17 MR. BROWNE:

18 Q. Now Doctor, Ms. Newbury asked you about an

19 exhibit that was previously entered under Dr.

20 Pritzker and that's P-1767. I just want to

21 reference that. That's the recommendations

22 from approved standardization of

23 immunohistochemistry, and attached to that was

24 another exhibit, P-1727, where these

25 individuals, some of these individuals, Dr.

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<p>1 Taylor, Dr. Hewitt, among some of the 2 committee members, were asked several 3 questions, and I'm going to ask you to--I 4 think there's a particular section, page 5 seven, that you want to offer or point out to 6 the Commissioner. I think it's this one right 7 here. It's the question "despite popularity 8 of antigen retrieval AR techniques, the 9 precise molecular mechanism underlying the 10 process remains an enigmatic, what is the most 11 AR technique?" and there's a couple comments 12 there I think you wanted to draw out and 13 potentially comment on?</p> <p>14 DR. DENIC: 15 A. Where I see the complexity in all of this, and 16 again, I'm just looking at this as a 17 practising pathologist and again, I'm not the 18 expert in immunohistochemistry, but the 19 complexity and why that things are going as 20 they're going, not only in our lab, but 21 worldwide is as well, as it states here about 22 antigen retrieval, which is the one of crucial 23 part as well of this process. It states here 24 that in three of them, even four, says--Dr. 25 Taylor says about antigen retrieval, "don't</p>	<p>1 DR. DENIC: 2 A. Yes. Probably that's why we are manipulating 3 to a certain degree, exposing to various 4 temperatures, trying to standardize fixation, 5 that we all control certain parameters in 6 order to get certain colour. But we really 7 don't know how that works on the tissue. 8 MR. BROWNE: 9 Q. Just following on that point, Dr. Denic, you 10 were asked by Mr. Coffey, I'm not sure if it 11 was Thursday or Friday, your reasons for test 12 failure and you indicated there were no single 13 factors. You recognized fixation. You 14 recognized antigen retrieval. You recognized 15 the possibility of the machine itself, and I 16 think you made a statement, something to the 17 effect, I made a note here, "fixation, to my 18 opinion, not to a great extent" and you wanted 19 to explain that, I think, but you didn't come 20 back to it. Is there--do you want to explain 21 that further now? 22 DR. DENIC: 23 A. I think I did touch bases with Ms. Newbury 24 when she was asking about it. If fixation is 25 the main culprit as was portrayed, fixation</p>
<p>1 think anyone is most understood." Dr. Yaziji 2 said, like you said, "they are mostly 3 speculations without solid evidence. The 4 cross linking hypothesis is most popular one, 5 but again, without solid proof." Dr. Hewitt 6 said "it is certainly shrouded in mystery. I 7 view it as a simple heat time and pressure, go 8 back to physical chemistry." And Dr. Badve 9 said "akin to fixation, the processes 10 associated with antigen retrievals are poorly 11 understood. All of the changes seems to be 12 different for the various protein. The 13 overall process seems to be relatively 14 specific for the given protein." So we're 15 applying pretty much science that we really 16 don't know how it works. 17 MR. BROWNE: 18 Q. And you're referring both to the antigen 19 retrieval and the fixation? 20 DR. DENIC: 21 A. Fixation. Actually, that's what they are 22 referring to, and that's, to me, as a 23 practising pathologist, again taking - 24 MR. BROWNE: 25 Q. An interesting observation?</p>	<p>1 processing, then Mount Sinai wouldn't report 2 them. You wouldn't think that results would 3 come down reported. If the tissue is not 4 readable, if the tissue is badly affected, I 5 wouldn't report it. 6 MR. BROWNE: 7 Q. So that's the point you were trying to make on 8 that? 9 DR. DENIC: 10 A. That's right. If I identify fixation, while I 11 believe it did play a role, I seen the cases 12 that were not well fixed, I seen those ones, 13 but the question is obviously due to the 14 various techniques they were using, they were 15 satisfied that obtained results are real 16 results and they can report on them. 17 MR. BROWNE: 18 Q. Registrar, P-1373, please? Doctor, I just 19 want to ask you a question surrounding the 20 retroconverters and the false positives. Ms. 21 Newbury had a number of questions with respect 22 to that. This is an e-mail from Ms. Predham 23 to you and it says--and others. It says "Hi, 24 Kara and I reviewed the retro list and here is 25 the final list that will need to be reviewed</p>

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<p>1 at the panel next Thursday, given the results 2 from Mount Sinai." We'll see here, Doctor, 3 these are the numbers. Was this, just have a 4 look at this, the situation here, is this one 5 where these were patients where 30 percent or 6 less became an issue and this question of 7 coming under 30 percent and then one of these 8 was, in fact, a weakly positive case. So is 9 this sort of an interpretation issue, in terms 10 of the application of the 30 percent? 11 DR. DENIC: 12 A. When I reviewed the slides, there were 13 interpretation issues. 14 MR. BROWNE: 15 Q. Right. But in terms of the numbers here, are 16 these all cases where 30 percent or less? 17 DR. DENIC: 18 A. Some of them were already, yes, 25 to 30, 19 that's why that case came into the equation, 20 and the other one was 30. There's one from 21 Carbonear that were negative, negative from 22 Gander, and from Gander, ten percent was a 23 case, and from Western, we have a weak 24 positive. So that was put as such, because 25 without explanation what a weak positive</p>	<p>1 was staining positive, and fixation wasn't 2 even recognized with Dr. Mullen as well. He 3 put that the fixation was adequate. So she 4 falls in the group of these patients that 5 internal control could be negative, but a 6 tumour is well positive and shown nuclear 7 staining positivity, variability of the 8 staining, so which tells me that the test did 9 work and subsequently we know that it was 10 retested and showed positivity. So she was 11 positive then. She was positive now. 12 MR. BROWNE: 13 Q. And what would then be your opinion as to the 14 likely reason behind the change in the result? 15 DR. DENIC: 16 A. The reason behind the change in her results is 17 first, that it was different technology that 18 the tissue had been done at Mount Sinai in 19 2005, in this case from '98, for different 20 antibodies, different procedures, and also 21 this is not the same level that the tissue was 22 sectioned from. So I have the block here, 23 just I don't know that Commissioner ever seen 24 the block. It looks--you did see the block? 25 THE COMMISSIONER:</p>
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<p>1 means. 2 MR. BROWNE: 3 Q. Right. So it's a question of this 30 percent 4 as opposed to, you know, an actual conversion 5 because of potentially fixation issues or - 6 DR. DENIC: 7 A. That's right, that's right, because fixation 8 was adequate in most, except of two cases. 9 MR. BROWNE: 10 Q. Doctor, you were shown an exhibit by Mr. 11 Coffey and asked about your discussions. I 12 think the particular exhibit involved a 13 meeting you had with a husband of a deceased 14 patient and what you recalled around that. I 15 understand you've subsequently had a look at 16 that slide of that particular patient and 17 again, looking at the issues of fixation, was 18 fixation an issue for that particular patient? 19 DR. DENIC: 20 A. No. 21 MR. BROWNE: 22 Q. Was internal control an issue, internal 23 control as a an issue for that patient? 24 DR. DENIC: 25 A. Internal control was negative, but the tissue</p>	<p>1 Q. I have seen one. 2 DR. DENIC: 3 A. Okay, so this is the block where the tissue is 4 embedded in paraffin. So what you see here, 5 in the middle, is the piece of tissue embedded 6 in paraffin. So when they're putting on a 7 machine for cutting, they strip a surface with 8 razor sharp blade and they take five micron of 9 it. So not necessarily if when they are 10 stripping, they're taking the ribbons off this 11 and they're putting on a glass slide and 12 produce the glass slides and so the Mount 13 Sinai never got the surface that we got read, 14 so that their section would be somewhere 15 underneath. So it's not even the same 16 section. So different procedures, different 17 depth of the block. It could be some 18 variability of the staining, and again, you 19 have inter observer variability, so that 20 pathologist said 10-15. 21 MR. BROWNE: 22 Q. So those would be the reasons you would see? 23 DR. DENIC: 24 A. Those would be the reasons as well. 25 MR. BROWNE:</p>

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<p>1 Q. Okay. Doctor, I want to--one last area I want 2 to just cover with you. The Commissioner 3 spent some time, I think, with you asking 4 about lines of communications and today, 5 Doctor, I just want to--and perhaps you'd give 6 an example of each. Do you view that there 7 are good lines of communication that exist 8 between pathologists and technologists? 9 DR. DENIC: 10 A. I really think that good lines of 11 communication exist. We work one on one more 12 frequently, and we have worked one on one, you 13 know, we were always at their disposal and it 14 was just a telephone call away. We meet each 15 other to these various rounds, such as breast 16 disease site group, lymphoma tumour, where 17 they will meet with the hematological 18 oncologist as well. 19 MR. BROWNE: 20 Q. Now are you referring to technologists or 21 oncologists? 22 DR. DENIC: 23 A. Oncologists. 24 MR. BROWNE: 25 Q. Oncologists, okay.</p>	<p>1 technologists, Doctor, again, your views on 2 this? 3 DR. DENIC: 4 A. This is something, this is evolving. We start 5 inviting them on our rounds, especially on our 6 Friday rounds, which are pathology updates, 7 and they are also presenters on those rounds. 8 So the pathologists come and they present to 9 the pathologists, especially the experiences 10 they acquired for the meeting they attended 11 recently, and other way around. So they are 12 attending. Those rounds are attended by 13 t e c h n o l o g i s t s , m o s t l y f r o m 14 immunohistochemistry and pathology assistants. 15 MR. BROWNE: 16 Q. And lastly, Doctor, between pathologists? 17 DR. DENIC: 18 A. Between pathologists, of course, we are 19 meeting, as we said, on our monthly meetings 20 where every single issue of interest can be 21 discussed. Pathologists, as a group, they are 22 still meeting separately, pathologists from 23 Health Sciences and pathologists from St. 24 Clare's, but one of the reasons that I would 25 like to have all the pathologists on the same</p>
<p>1 DR. DENIC: 2 A. Then the other rounds, tumour rounds, chest 3 tumour board, urology oncology rounds, and on 4 top of this, when we have somebody coming for 5 the workshop, we invite oncologists too. So 6 the last time, in June, I already mentioned 7 Dr. Srigley was invited. I invited Dr. 8 Srigley to come and do the workshop for the 9 group that does uropathology and we invited 10 oncologists too. So they have attended from 11 the oncology group. 12 MR. BROWNE: 13 Q. What about - 14 DR. DENIC: 15 A. And we were working together as a part of NAP, 16 which is Newfoundland Association of 17 Pathologists, on synoptic reporting. 18 MR. BROWNE: 19 Q. Okay, and that's with the oncologists as well, 20 to try to develop a template for synoptic 21 reporting? 22 DR. DENIC: 23 A. That's right. 24 MR. BROWNE: 25 Q. What about between pathologists and</p>	<p>1 site is that we're going to be physically 2 closer and going to be easier to organize all 3 of this. So this is pretty much - 4 MR. BROWNE: 5 Q. Doctor, that's it in terms of the formal part 6 of my questioning of you. As other witnesses 7 have been given the opportunity, I'd offer you 8 the opportunity to speak to the Commissioner 9 on any comments, observations, or 10 recommendations you may wish to make at this 11 time. 12 DR. DENIC: 13 A. I brought - 14 MR. BROWNE: 15 Q. You have a statement, I understand. 16 DR. DENIC: 17 A. Right, I have a statement. I want to thank 18 the Commission for the opportunity to 19 participate in this important process, thank 20 you. We have heard a lot about the issues 21 affecting the laboratory medicine program 22 during the course of this Inquiry and you have 23 already heard from many of my colleagues. I 24 want to echo the sentiments of my colleagues 25 by saying that I and all the other</p>

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1 pathologists care deeply about patient care.  
 2 The issues around the problems with ER/PR  
 3 testing had had a profound impact in raising  
 4 public awareness of the importance of  
 5 pathology to patient care. More importantly,  
 6 I believe Government now appreciates the  
 7 necessity to ensure that the laboratory  
 8 medicine program is properly resourced and  
 9 funded to ensure the circumstances which  
 10 brought us to this point are never repeated.  
 11 When my colleagues became aware of  
 12 problems with hormone receptor testing in  
 13 2005, their first thoughts were for our  
 14 patients. The decision to undertake a  
 15 retrospective review of ER/PR tests was  
 16 necessary, but at the same time,  
 17 unprecedented, certainly in Canada, and I  
 18 believe unprecedented worldwide. We know  
 19 about these problems today because physicians  
 20 in our lab and in the Cancer Centre put  
 21 patients first by going through this important  
 22 and necessary process. Our only goal in  
 23 launching the review was to improve patient  
 24 care. Today, I believe we are playing an  
 25 important role in moving toward the need for

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1 standardization of ER/PR and thereby reducing  
 2 the potential for error. The complexity and  
 3 scope of the issues around ER/PR testing  
 4 problem are significant, as I am aware all  
 5 realize through the process of this Inquiry.  
 6 It is important to know that the review  
 7 encompassed the work of some 50 pathologists  
 8 representing a broad cross section of our  
 9 specialty North America wide, at least. When  
 10 you review the literature, you realize that  
 11 this is a worldwide problem. I hope that  
 12 findings and recommendations from the  
 13 Commission will have implications for labs  
 14 around the globe who are paying close  
 15 attention to this Inquiry. I am please with  
 16 the steps and accomplishments that we have  
 17 taken in the aftermath of discovering the  
 18 problem with ER/PR. In my view, our lab has  
 19 risen from the ashes.  
 20 I would also like to say that while there  
 21 were deficiencies identified with ER/PR, our  
 22 labs perform 11 million tests each year, tests  
 23 that can be trusted.  
 24 Our goal now is to make our laboratory  
 25 medicine program one of the best in Canada.

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1 As physicians our number one priority will  
 2 always remain to ensure our patients receive  
 3 the best possible care. That sometimes can  
 4 prove to be frustrating when you feel  
 5 constrained by a system that lack resources to  
 6 do this important work. As we attempt to  
 7 address the problems in our health care  
 8 system, it is vital that we don't let  
 9 laboratory medicine fall off the radar. We  
 10 must ensure that we have the resources  
 11 necessary for proper operation of our labs.  
 12 The laboratory leadership and Eastern  
 13 Health are actively working to strengthen our  
 14 program. We are also working to assist  
 15 laboratory medicine problems in the other  
 16 health regions to strengthen their programs.  
 17 I know it will take time to accomplish our  
 18 goals. It will also take resources and  
 19 manpower to address any weaknesses in the  
 20 system. Furthermore, I think these efforts  
 21 can be strengthened by ensuring that  
 22 certification and accreditation of laboratory  
 23 services in Canada are pursued through  
 24 appropriate provincial and national bodies.  
 25 I would like to conclude by saying that

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1 today we are dealing with the consequences of  
 2 the ER/PR, but not the cause. I hope that the  
 3 Commission will address these causes, starting  
 4 with the lack of funding, under staffing,  
 5 under resourcing for the laboratory medicine  
 6 program and the lack of standardization of  
 7 immunohistochemistry testing.  
 8 To our patients and their families, I  
 9 would like to express my deepest sympathies  
 10 for the pain that this caused them. We are  
 11 committed to ensure that this never happens  
 12 again and we are dedicated to ongoing care.  
 13 Thank you.  
 14 MR. BROWNE:  
 15 Q. Thank you, Commissioner.  
 16 THE COMMISSIONER:  
 17 Q. Mr. Coffey, is there anything arising?  
 18 COFFEY, Q.C.:  
 19 Q. Yes, Commissioner, just a--things.  
 20 DR. NEBOJSA (NASH) DENIC RE-EXAMINATION BY BERNARD  
 21 COFFEY, Q.C.  
 22 COFFEY, Q.C.:  
 23 Q. Doctor, Mr. Browne asked you about Dr.  
 24 Khalifa's synoptic reporting guidelines back  
 25 when he was here and introduced them here. In

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<p>1 your experience was there anybody monitoring 2 whether pathologists were actually following 3 those? 4 DR. DENIC: 5 A. Not that I know of, but now we do. 6 COFFEY, Q.C.: 7 Q. Yeah. And, Doctor, you did, I believe, in 8 answering the question from Mr. Simmons, make 9 a reference to yourself and Dr. Carter having 10 looked at all of the slides relating to the 11 deceased patients? 12 DR. DENIC: 13 A. That's correct. 14 COFFEY, Q.C.: 15 Q. Did you and Dr. Carter, or Dr. Carter make any 16 notes on those observations at the time? 17 DR. DENIC: 18 A. What we did, Mr. Coffey, is we had printouts 19 of the patients' reports, and on the printouts 20 I marked which block and I marked internal 21 control present, staining, that kind of stuff, 22 but not any general notes but those ones. 23 COFFEY, Q.C.: 24 Q. And you were, at that point, in making these 25 notes, were noting your observations of the</p>	<p>1 A. Certainly. 2 COFFEY, Q.C.: 3 Q. A copy, okay, be passed on to the Commission, 4 thank you. Doctor, as well, you in answering 5 a question for Mr. Simmons you referred in the 6 context of interlab variability, you were just 7 talking, you were being asked about that, you 8 referred to low expressors are known to be 9 problematic in studies of interlab 10 variability. In that context a low expressor 11 is what percentage range? 12 DR. DENIC: 13 A. From one to ten. 14 COFFEY, Q.C.: 15 Q. One to ten, thank you. Clarify that. And, 16 Doctor, there was--Ms. Newbury asked you about 17 this whole issue about false positives, okay. 18 So I just want to clarify something for the 19 Commissioner here. The four retroconverters, 20 okay, that were finally judged to be 21 retroconverters, do I understand you correctly 22 that it was your view or understanding that 23 ultimately this was attributable to a mistaken 24 interpretation of cytoplasmic staining for 25 nuclei staining?</p>
<p>1 original slides? 2 DR. DENIC: 3 A. In terms of internal controls. 4 COFFEY, Q.C.: 5 Q. Yes. So - 6 DR. DENIC: 7 A. Yes, I did. 8 COFFEY, Q.C.: 9 Q. And do you know if they have been passed on, 10 like, a photocopy of those sheets, do they - 11 DR. DENIC: 12 A. They're not sheets, they are just - 13 COFFEY, Q.C.: 14 Q. The pathology reports, yes. 15 DR. DENIC: 16 A. - the report itself. 17 COFFEY, Q.C.: 18 Q. Do the pathology reports that you wrote on 19 still exist? 20 DR. DENIC: 21 A. They do. 22 COFFEY, Q.C.: 23 Q. And could I ask if that hasn't been done, that 24 they be passed on to Mr. Browne? 25 DR. DENIC:</p>	<p>1 DR. DENIC: 2 A. That's right. And some background staining. 3 COFFEY, Q.C.: 4 Q. Background staining. 5 DR. DENIC: 6 A. Yes. 7 COFFEY, Q.C.: 8 Q. Doctor, in relation to that, then, you arrived 9 at that view or conclusion based upon an 10 examination of the original slides for those 11 four patients? 12 DR. DENIC: 13 A. That's correct. 14 COFFEY, Q.C.: 15 Q. So to your knowledge in this regard, okay, in 16 this entire review to date, are you aware of 17 any instance of nuclei staining that was 18 false? 19 DR. DENIC: 20 A. No. 21 COFFEY, Q.C.: 22 Q. Okay. Just to be clear on that. And in the 23 context of false positive in its pure sense, 24 that would involve, in fact, a nuclei stain 25 inappropriately, wouldn't it, a false</p>



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<p>1 positive? It could be a misinterpretation 2 issue, but as well, a false positive in a 3 sense of a nuclei has stained and it shouldn't 4 have, you haven't seen a case of that here, 5 have you? 6 DR. DENIC: 7 A. What I have seen in those cases is like you 8 see it's almost like a blob of the antibodies 9 covering this stuff, so then you know that's 10 not just nucleus protruding from the 11 background stain, no, this is - 12 COFFEY, Q.C.: 13 Q. Every, everything is staining? 14 DR. DENIC: 15 A. Just a smear. 16 COFFEY, Q.C.: 17 Q. In effect, everything is - 18 DR. DENIC: 19 A. And this came like partially like a blob. 20 COFFEY, Q.C.: 21 Q. Sure. 22 DR. DENIC: 23 A. And that's why I say that could have been 24 misinterpreted. 25 COFFEY, Q.C.:</p>	<p>1 it physically actually take you to do it? 2 DR. DENIC: 3 A. Again, depends on the slide to slide. 4 COFFEY, Q.C.: 5 Q. Yes, and that - 6 DR. DENIC: 7 A. And intensity of the staining, because as you 8 heard, intensity of the staining could be very 9 weak. 10 COFFEY, Q.C.: 11 Q. Yes. 12 DR. DENIC: 13 A. And still positive. So not necessarily have 14 to be very bright in order--and this is 15 experience if you seen from our new staining 16 and as I reported on that particular case from 17 Mount Sinai where the discrepancy, so every 18 lab has a weak staining. So those cases 19 require more time and thorough review, 20 especially--and also you have to track down 21 for the internal controls. 22 COFFEY, Q.C.: 23 Q. Yes. 24 DR. DENIC: 25 A. You know, so it might take you ten minutes per</p>
<p>Page 97</p> <p>1 Q. So, Doctor, in terms of this issue of false 2 positives, okay, that Ms. Newbury has been 3 asking you about, if someone was to identify 4 all the positive patients, I think the figure 5 you used, there'd be about 1500, roughly? 6 DR. DENIC: 7 A. Roughly. 8 COFFEY, Q.C.: 9 Q. Rough. And that would be the ER positive 10 patients, 1500 of them. And if someone was to 11 identify them and was to locate all of their 12 original slides, then one could have a 13 pathologist or pathologists simply review the 14 1500 slides, ER, 1500 PR and determine whether 15 in those pathologists' view there was nuclei 16 staining not attributable to background 17 staining? 18 DR. DENIC: 19 A. They could. 20 COFFEY, Q.C.: 21 Q. Okay, could do that. Doctor, just again so 22 the Commissioner understands or appreciates 23 this, in a typical case how long does it 24 actually take you to view an ER slide? You 25 have the slide right here, and how long does</p>	<p>Page 99</p> <p>1 slide. And also to appreciate them, sometimes 2 you need a second pair of eyes just to see 3 what would be the percentage that somebody 4 would call at the time. 5 COFFEY, Q.C.: 6 Q. So it would be ten minutes per slide or per 7 pair of slides? And again, I appreciate, the 8 Commissioner will - 9 DR. DENIC: 10 A. If the slides are--if the slides are pre- 11 stained and you have a bright slide, it could 12 take a couple of minutes. 13 COFFEY, Q.C.: 14 Q. Okay, so - 15 DR. DENIC: 16 A. You know, but depends on the intensity and you 17 never know what you're going to find, okay, 18 and how long you're going to spend on each 19 slide. 20 COFFEY, Q.C.: 21 Q. And again, I want the Commissioner to have 22 some sense of if the slides were all kind of 23 stacked up in order for the pathologist or a 24 group of pathologists, then one could go 25 through them, some would be straightforward,</p>

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<p>1 take a minute or two minutes, and some you're</p> <p>2 saying could take ten or 15 or 20 minutes?</p> <p>3 DR. DENIC:</p> <p>4 A. Yes, but you have to put in equation what</p> <p>5 would be the comfortable level of somebody,</p> <p>6 how many slides per day should they read.</p> <p>7 COFFEY, Q.C.:</p> <p>8 Q. Yes, okay.</p> <p>9 DR. DENIC:</p> <p>10 A. Because it's very tiring, exhausting process</p> <p>11 looking for the nuclear staining and searching</p> <p>12 for the internal controls and making the</p> <p>13 assumptions of the percentage.</p> <p>14 COFFEY, Q.C.:</p> <p>15 Q. Has there been any estimate performed as to</p> <p>16 how much time might be required to do this, to</p> <p>17 look at the original slides, original</p> <p>18 positives?</p> <p>19 DR. DENIC:</p> <p>20 A. Not that I know of.</p> <p>21 COFFEY, Q.C.:</p> <p>22 Q. Thank you. Doctor, there are my questions.</p> <p>23 Thank you, Commissioner.</p> <p>24 DR. NEBOJSA (NASH) DENIC, EXAMINATION BY THE COMMISSIONER</p> <p>25 THE COMMISSIONER:</p>	<p>1 play a role. And I learned that from Dr.</p> <p>2 Carter, as well, and she would never report</p> <p>3 the intensity of the staining. And again, to</p> <p>4 our experiences seeing the slides and the</p> <p>5 reports coming in from Mount Sinai, the weak</p> <p>6 is taken off of the list, as such. Because</p> <p>7 one should wonder what intensity of the stain</p> <p>8 going to tell to the oncologist, what does it,</p> <p>9 weak 30 means for the oncologists.</p> <p>10 THE COMMISSIONER:</p> <p>11 Q. Okay.</p> <p>12 DR. DENIC:</p> <p>13 A. Is it positive or negative, are you claiming</p> <p>14 this patient is positive or negative. So</p> <p>15 while still again some of the people are using</p> <p>16 Allred Score, I think it's the various schools</p> <p>17 reflecting on this issue.</p> <p>18 THE COMMISSIONER:</p> <p>19 Q. What about intensity of the stain for</p> <p>20 controls, is that a question that should be</p> <p>21 examined?</p> <p>22 DR. DENIC:</p> <p>23 A. Intensity of the controls, we are using</p> <p>24 actually as external control we are using</p> <p>25 three types, one good expressor, intermediate</p>
<p>Page 101</p> <p>1 Q. Dr. Denic, there were just a couple of points</p> <p>2 that I hope you can clarify for me. Mr.</p> <p>3 Simmons asked you a question on Friday and</p> <p>4 you've referred to it again and that's the</p> <p>5 matter of the intensity of the stain not being</p> <p>6 a question when you're trying to determine</p> <p>7 whether the percentages within the nuclei, is</p> <p>8 that correct?</p> <p>9 DR. DENIC:</p> <p>10 A. That's correct. What the pathologists, some</p> <p>11 of the pathologists use so called Allred</p> <p>12 Score.</p> <p>13 THE COMMISSIONER:</p> <p>14 Q. Um-hm.</p> <p>15 DR. DENIC:</p> <p>16 A. In Allred Score the score reflects to the</p> <p>17 intensity of the stain and the number of</p> <p>18 nuclei. And that has been utilized in some of</p> <p>19 the centres. And however, there's various</p> <p>20 schools these days and some people utilize</p> <p>21 intensity of the stains only if the case goes</p> <p>22 in a group of weak expressors, from one to ten</p> <p>23 that you can say, okay, weak, five percent.</p> <p>24 But if you have a higher percentage of the</p> <p>25 cells, the intensity of the stains doesn't</p>	<p>Page 103</p> <p>1 expressor and low expressor or no expressors.</p> <p>2 I haven't read the meaning if your stain is</p> <p>3 moderately weak, what does that mean. You're</p> <p>4 trying to use your best expressor, best</p> <p>5 expressor you would expect intensity of the</p> <p>6 staining to be very good, should be brown.</p> <p>7 THE COMMISSIONER:</p> <p>8 Q. And would the normally the external control be</p> <p>9 in that classification?</p> <p>10 DR. DENIC:</p> <p>11 A. That's right.</p> <p>12 THE COMMISSIONER:</p> <p>13 Q. Okay.</p> <p>14 DR. DENIC:</p> <p>15 A. And about internal control, as such, I really</p> <p>16 don't know what does that mean. If you see a</p> <p>17 weak positivity in internal control and you</p> <p>18 see your positivity in your tumour, I think</p> <p>19 it's very safe to conclude that the tumour is</p> <p>20 expressor of estrogen receptors regardless of</p> <p>21 the intensity. These are only my experience</p> <p>22 that I seen working with Dr. Carter at that</p> <p>23 time.</p> <p>24 THE COMMISSIONER:</p> <p>25 Q. Okay.</p>

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1 DR. DENIC:  
 2 A. And I don't know anything else.  
 3 THE COMMISSIONER:  
 4 Q. Now, you've mentioned, switching off to  
 5 another topic now, and that is that the  
 6 development of the new policies and procedures  
 7 within the lab. And one of the things that I  
 8 took from your evidence last week was that has  
 9 been valuable in this process is that it has  
 10 caused you, in effect, to review what you're  
 11 doing and to concentrate on the details of  
 12 what you're doing. Can you tell me whether or  
 13 not the existence of or the development of  
 14 policies and procedures has been beneficial or  
 15 otherwise in other respects?  
 16 DR. DENIC:  
 17 A. Oh, definitely it was beneficial. You have  
 18 your guidelines. You know, without guidelines  
 19 difficult to practice. While we did practice  
 20 based on professional standards of practice at  
 21 that time, we realized and we know, really,  
 22 that this is not enough and it's not the way  
 23 to go. So that's why all of these policies  
 24 and procedures, they should define in most  
 25 instances every single step that's being done

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1 in the lab so that everybody can follow. And  
 2 we are trying to put this on intranet and some  
 3 of them already been lifted on intranet. So  
 4 not everybody has to know about every single  
 5 policy what's written, but at least you have  
 6 the ability to go back and just search and  
 7 find it. So it's very valuable thing that we  
 8 have done.  
 9 THE COMMISSIONER:  
 10 Q. Well, one of the things that has occurred to  
 11 me is that particularly in light of the  
 12 description that I've gotten from you and  
 13 other witnesses about a fairly good sized  
 14 turnover in pathologists, as well as  
 15 oncologists, as far as that's concerned, at  
 16 Eastern Health is that the existence of  
 17 policies and guidelines at least enables those  
 18 who are new to your organization to know where  
 19 to go to find the standard that you are using?  
 20 DR. DENIC:  
 21 A. That's absolutely correct.  
 22 THE COMMISSIONER:  
 23 Q. All right. And the final point is that you on  
 24 a couple of occasions have referred to the  
 25 fact that you view this as a worldwide

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1 problem?  
 2 DR. DENIC:  
 3 A. That's correct.  
 4 THE COMMISSIONER:  
 5 Q. Or a global problem I think was used, not by  
 6 you, but by one of the other witnesses, at  
 7 least, in communication. And when you say  
 8 it's a worldwide problem, what aspect of this  
 9 are you saying is worldwide problem?  
 10 DR. DENIC:  
 11 A. False negatives are worldwide problem.  
 12 THE COMMISSIONER:  
 13 Q. Okay.  
 14 DR. DENIC:  
 15 A. And no standardization--again I believe myself  
 16 as well I'm going to learn more through Dr.  
 17 Dabbs testimony. We read in the United  
 18 States, and there the article is as well, in  
 19 the United States this is a problem too. We  
 20 seen that through the works of Dr. Rhodes and  
 21 his paper as well because he was conducting  
 22 the studies on over 200 labs across the world  
 23 and he found the problem there. So that's  
 24 what I'm referring to. I think this is not  
 25 isolated one.

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1 THE COMMISSIONER:  
 2 Q. Uh-hm.  
 3 DR. DENIC:  
 4 A. What's isolated in this case, that we embarked  
 5 on this process and went back to look in every  
 6 single case that fell in that category. So  
 7 that's what difference is. You know, there's  
 8 one of the attempts as well through Dr.  
 9 Banerjee's paper, they went--when they  
 10 introduced the new antibody which was SP1, and  
 11 they tested 4000 patients actually tissue,  
 12 they found complete conversion from zero to  
 13 the number using new antibody in 6 percent, it  
 14 was 240 patients. So what we did, nobody has  
 15 done to this extent to identify the patients,  
 16 try to help them out, to go back regardless of  
 17 the consequences that we were facing, and the  
 18 public scrutiny that we were exposed to.  
 19 THE COMMISSIONER:  
 20 Q. Thank you, and thank you for participating and  
 21 providing us with your insights into this  
 22 issue. I very much appreciate it.  
 23 COFFEY, Q.C.:  
 24 Q. Commissioner, on the point of the remark  
 25 involving Dr. Gown's report, I've told my

1 fellow counsel that I'm going to defer that  
 2 for now, and if I'm going to come back to it,  
 3 I'll let them know.  
 4 THE COMMISSIONER:  
 5 Q. All right then. Why don't we take the morning  
 6 break and then we can prepare for the next  
 7 witness.  
 8 (BREAK )  
 9 THE COMMISSIONER:  
 10 Q. Mr. Coffey.  
 11 COFFEY, Q.C.:  
 12 Q. Dr. David Dabbs, Commissioner.  
 13 DR. DAVID JOSEPH DABBS (SWORN) EXAMINATION-IN-CHIEF BY  
 14 BERNARD COFFEY, Q.C.:  
 15 REGISTRAR:  
 16 Q. Would you please state and spell your complete  
 17 name for the Commission?  
 18 DR. DABBS:  
 19 A. David Joseph Dabbs, D-A-B-B-S.  
 20 COFFEY, Q.C.:  
 21 Q. Commissioner, there are three new exhibits I'm  
 22 going to ask to be entered, and they are P-  
 23 2621, 2622, and 2629.  
 24 THE COMMISSIONER:  
 25 Q. Entered.

1 EXHIBIT ENTERED AND MARKED AS P- 2621  
 2 EXHIBIT ENTERED AND MARKED AS P- 2622  
 3 EXHIBIT ENTERED AND MARKED AS P- 2629  
 4 COFFEY, Q.C.:  
 5 Q. Thank you, Commissioner. Registrar, could we  
 6 open, please, P-2622. Doctor, this is your  
 7 curriculum vitae?  
 8 DR. DABBS:  
 9 A. Yes.  
 10 COFFEY, Q.C.:  
 11 Q. Okay. Doctor, I'm going to ask you perhaps if  
 12 you could just to take the Commissioner  
 13 through your educational background and your  
 14 professional background, okay.  
 15 DR. DABBS:  
 16 A. Yes, certainly. I attended the University of  
 17 Pittsburg, Undergraduate School. I  
 18 subsequently went to Graduate School and  
 19 obtained a Masters Degree in Chemistry at  
 20 Cleveland State University. I subsequently  
 21 went to Medical School at the Medical College  
 22 of Ohio in Toledo, Ohio. Did my residency  
 23 training in anatomic pathology at the  
 24 University of Washington in Seattle.  
 25 COFFEY, Q.C.:

1 Q. That's your educational background, Doctor.  
 2 What about your professional background, your  
 3 career?  
 4 DR. DABBS:  
 5 A. In terms of the positions that I've held, my  
 6 very first position was at East Carolina  
 7 University, School of Medicine, in Greenville,  
 8 North Carolina, where I was Assistant  
 9 Professor. I subsequently spent a couple of  
 10 years at the Case Western Reserve University  
 11 Hospital at Metro Health and Medical Centre in  
 12 Cleveland, and then I subsequently went into  
 13 private practice for about four years in  
 14 Oakland, California, at Samuel Merit Hospital.  
 15 I subsequently moved back to Pennsylvania as  
 16 Associate Professor of Pathology at Penn State  
 17 University in Hershey, Pennsylvania, and then  
 18 when the opportunity called to go to  
 19 Pittsburg, I went to Allegheny General  
 20 Hospital where I was Associate Professor in  
 21 Pathology associated with the Medical College  
 22 of Pennsylvania, Hahnemann School of Medicine  
 23 there. Due to some issues that occurred in  
 24 Pittsburg at that institution, I then moved on  
 25 to private practice for a period of one year

1 at St. Agnes Health Care in Baltimore, and  
 2 when the opportunity came forward to move back  
 3 to Pittsburg as Director of Anatomic Pathology  
 4 at Magee Women's Hospital, and that was in  
 5 September of 2001, I was subsequently named  
 6 Chief of Pathology at the same institution in  
 7 April of 2003 and have been there since.  
 8 COFFEY, Q.C.:  
 9 Q. Doctor, you're certified by?  
 10 DR. DABBS:  
 11 A. I'm certified by the American Board of  
 12 Pathology and Anatomic Pathology.  
 13 COFFEY, Q.C.:  
 14 Q. And that was November 15th, 1983?  
 15 DR. DABBS:  
 16 A. Yes, sir.  
 17 COFFEY, Q.C.:  
 18 Q. And also by the American Board of Pathology,  
 19 Anatomic Pathology, and Cytopathology,  
 20 November 16th, 1989?  
 21 DR. DABBS:  
 22 A. Yes.  
 23 COFFEY, Q.C.:  
 24 Q. Doctor, while we're on the point, what's the  
 25 difference between cytopathology and anatomic

<p style="text-align: right;">Page 112</p> <p>1 pathology?</p> <p>2 DR. DABBS:</p> <p>3 A. Cytopathology basically is the study of</p> <p>4 individual cells as opposed to tissues.</p> <p>5 Surgical pathology is largely dealing with</p> <p>6 tissues, tissue sections. Cytology is mostly a</p> <p>7 specimen that is collected as a fluid or as an</p> <p>8 aspirate specimen and is composed of small</p> <p>9 bits of cells, if you will.</p> <p>10 COFFEY, Q.C.:</p> <p>11 Q. Doctor, as well on page three of your CV,</p> <p>12 professional society memberships are set out</p> <p>13 there, and editorial board appointments.</p> <p>14 Doctor, have you been involved in the</p> <p>15 preparation of any textbooks?</p> <p>16 DR. DABBS:</p> <p>17 A. Yes, I have. I have a textbook on diagnostic</p> <p>18 immunohistochemistry that was originally</p> <p>19 published by Elsevier as a first edition, I</p> <p>20 believe, in October, 2002. It went on to</p> <p>21 second edition about three or four years later</p> <p>22 and is currently in preparation for a third</p> <p>23 edition.</p> <p>24 COFFEY, Q.C.:</p> <p>25 Q. And, Doctor, your role in that is what?</p>	<p style="text-align: right;">Page 114</p> <p>1 Q. Doctor, could you tell the Commissioner,</p> <p>2 please, about your own introduction to and</p> <p>3 experience with immunohistochemistry, perhaps</p> <p>4 going back to the beginning and take us</p> <p>5 through?</p> <p>6 DR. DABBS:</p> <p>7 A. Certainly. I was fortunate in being at the</p> <p>8 epicentre of immunohistochemistry at the</p> <p>9 University of Washington during my residency,</p> <p>10 and that was the period from 1980 to 1980.</p> <p>11 There was a fair amount of</p> <p>12 immunohistochemistry going on at that time</p> <p>13 that was pretty much avant garde, and that's</p> <p>14 where I acquired my interest in this</p> <p>15 discipline. When I moved to my first position</p> <p>16 in Eastern North Carolina, I developed an</p> <p>17 immunohistochemistry laboratory there as well,</p> <p>18 and basically continued my interest, attending</p> <p>19 meetings, societies, and all of these venues.</p> <p>20 When I subsequently ended up going up to the</p> <p>21 Hershey is when I developed a further interest</p> <p>22 in breast pathology. It wasn't until when I</p> <p>23 was in my position at Allegheny General</p> <p>24 Hospital in Pittsburg, beginning around 1997,</p> <p>25 that I was somewhat frustrated with the state</p>
<p style="text-align: right;">Page 113</p> <p>1 DR. DABBS:</p> <p>2 A. My role in that book is as a contributor as</p> <p>3 well as an editor of the book.</p> <p>4 COFFEY, Q.C.:</p> <p>5 Q. And, Doctor, the book is intended for what</p> <p>6 audience?</p> <p>7 DR. DABBS:</p> <p>8 A. The book is intended for anyone who is</p> <p>9 involved in the practice of</p> <p>10 immunohistochemistry and that includes</p> <p>11 pathologists, pathologists in training, anyone</p> <p>12 in the laboratory who may be using</p> <p>13 immunohistochemistry for any reason, and as a</p> <p>14 reference book for oncologists as well.</p> <p>15 COFFEY, Q.C.:</p> <p>16 Q. And in relation to the two editions of the</p> <p>17 book that have been published to date, did you</p> <p>18 contribute any particular chapters to it?</p> <p>19 DR. DABBS:</p> <p>20 A. Yes, I did, I contributed the chapter on</p> <p>21 breast immunohistochemistry as well as the</p> <p>22 chapter on tumours of unknown primary, also</p> <p>23 known as metastatic carcinomas of unknown</p> <p>24 primary.</p> <p>25 COFFEY, Q.C.:</p>	<p style="text-align: right;">Page 115</p> <p>1 of affairs of immunohistochemistry in that</p> <p>2 there really weren't many good references, a</p> <p>3 go to place, if you will, for information</p> <p>4 regarding immunohistochemistry. There were a</p> <p>5 few textbooks out at that time. They were</p> <p>6 quite dated, each more than five years old,</p> <p>7 and so it was my plan at that time to create a</p> <p>8 resource that I felt was badly needed, and I</p> <p>9 basically wrote a proposal to one of the</p> <p>10 publishers in the States and they accepted</p> <p>11 this and that's how the book became where it</p> <p>12 is.</p> <p>13 COFFEY, Q.C.:</p> <p>14 Q. Doctor, are there other immunohistochemistry -</p> <p>15 diagnostic immunohistochemistry text available</p> <p>16 in North America?</p> <p>17 DR. DABBS:</p> <p>18 A. In North America there are some other books</p> <p>19 that are available. One is written by Clive</p> <p>20 Taylor and Richard Coady. That book just came</p> <p>21 out, I believe, approximately two years ago.</p> <p>22 Dr. Taylor, of course, had published books</p> <p>23 previously on immunomicroscopy and</p> <p>24 immunohistochemistry, and--so his is a new</p> <p>25 edition about two years. Dr. Mehrdad Nadji</p>

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1 from Miami also has a book out by the ASCP  
 2 Press, that's very popular as well. Of  
 3 course, there are other surgical pathology  
 4 textbooks out that do have sections on  
 5 immunohistochemistry and relevant chapters.  
 6 COFFEY, Q.C.:  
 7 Q. Doctor, I understand that you have prepared a  
 8 presentation for the Commissioner. If we  
 9 could open, please, Registrar, Exhibit P-2621  
 10 and I take it, Doctor, this is it. Perhaps  
 11 then, Doctor, I'll leave you with control of  
 12 the mouse for the slides, and if you could  
 13 take the Commissioner and the rest of us  
 14 through this. This is entitled "Best  
 15 Practices for Hormone Receptor Testing by  
 16 Immunohistochemistry".  
 17 DR. DABBS:  
 18 A. Yes, certainly. Basically, what I would like  
 19 to discuss and ultimately get to is the  
 20 consensus recommendations on estrogen receptor  
 21 testing of breast cancer by  
 22 immunohistochemistry. This is a paper that is  
 23 in press in "Applied Immunohistochemistry and  
 24 Molecular Morphology". This is a popular  
 25 journal for our discipline. This paper

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1 basically was generated from ad hoc group of  
 2 pathologists and laboratory scientists and  
 3 technical experts representing academia  
 4 community hospitals, industry and reference  
 5 laboratories. We conducted a full day  
 6 consensus meeting in Santa Barbara,  
 7 California, January 27th of this year, to  
 8 discuss these critically important issues in  
 9 an effort to develop rational evidence-based  
 10 guidelines for best practices in the  
 11 assessment of estrogen receptor by  
 12 immunohistochemistry. Now ultimately before I  
 13 get to this paper, what I wanted to do is what  
 14 steps led up to this particular meeting at  
 15 Santa Barbara, and what does history of this  
 16 topic tell us. Way back as far as 1889, there  
 17 was a Dr. Schinzingler who suggested that  
 18 endocrine ablation was important in the  
 19 treatment of breast cancer, and this actually  
 20 panned out further by Dr. Beatson in 1896, who  
 21 performed the first operation to remove  
 22 ovaries in a patient with inoperable breast  
 23 cancer, and his quote was that "eight months  
 24 after the operation the disease in this  
 25 patient had disappeared". Boyd was the first

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1 actually to do a controlled study some four  
 2 years later on 54 patients, and patients who  
 3 had advanced breast cancer. He removed the  
 4 ovaries and 35 percent of these patients went  
 5 into complete remission of their disease. Now  
 6 there was a large hiatus that subsequently  
 7 ensued over the next several decades, and the  
 8 question that was battered around at the time  
 9 was should removal of ovaries in patients with  
 10 breast cancer be prophylactic or therapeutic  
 11 based on advanced stage. So up until 1960,  
 12 this information was controversial in the  
 13 oncology literature and it wasn't until 1960  
 14 that Jensen and Jacobsen actually demonstrated  
 15 that radioisotopic or radioactive estrogen  
 16 accumulates in target tissues in the body in  
 17 the pituitary gland, in the vagina, and in the  
 18 uterus, and that these radioisotopes were  
 19 found in cytoplasm and nucleus of these  
 20 targeted cells, and it suggested that ablation  
 21 of the pituitary gland which controls the  
 22 ovary or adrenal gland, which is also  
 23 controlled by the pituitary, may be a  
 24 treatment to eliminate these sources of  
 25 estrogen in the body. So in essence then in

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1 the next few years, from 1965 to 1970, I chose  
 2 these articles as sort of exemplifying what I  
 3 called the prelude to estrogen receptor  
 4 testing. Paper by Lewison entitled  
 5 "Castration in the Treatment of Advanced  
 6 Breast Cancer" that was published in Cancer in  
 7 1965, a paper by Sander, "The In Vitro Uptake  
 8 of Oestradiol", that's also known as estrogen,  
 9 and biopsies from 25 breast cancer patients,  
 10 the first time that anyone ever demonstrated  
 11 that, in fact, tumours from breast cancers can  
 12 take up estrogen and bind to it. Then  
 13 Korenman, from the Journal of Clinical  
 14 Endocrinology and Metabolism, discussing  
 15 specific estrogen binding sites of the  
 16 cytoplasm of human breast cancer. So these  
 17 were all really sentinel papers that  
 18 demonstrated that breast cancers do, in fact,  
 19 take up estrogen. Now McGuire in the early  
 20 '70s, late '60s, demonstrated in his  
 21 laboratory a method of showing, in fact, that  
 22 the estrogen that binds in breast tumours can  
 23 be measured. This test became known as the  
 24 dextran coated charcoal ligand binding method.  
 25 Initially it was the ligand binding method

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<p>1 exclusively, and the principle of this test  2 was the measurement of available cytoplasmic  3 estrogen receptor binding proteins measured as  4 a fraction of the total sample protein content  5 of that cell. Just a couple of years later,  6 Ferherdy showed that the dextran coated  7 charcoal step in the ligand binding method  8 aided in reducing non-specific estrogen  9 receptor binding receptors. He discovered  10 that there were more receptors found in post-  11 menopausal women than in pre-menopausal women  12 and suggested that it may have a prognostic  13 value for treatment regiments. Now I wanted  14 to take you through these steps in the DCC or  15 dextran coated charcoal/ligand binding method  16 that was initially published by McGuire.  17 Basically you take a piece of tissue and you  18 homogenize it and put it in a centrifuge and  19 isolate what is called the cytosol, which  20 presumably represents the cytoplasmic content  21 of whatever cells that you have. You then  22 take that and you fractionate it through what  23 is called the sucrose density, and you then  24 isolate those specific fractions and expose  25 them to radioisotopic label estrogen, and the</p>	<p>1 COFFEY, Q.C.:  2 Q. That's how small a quantity?  3 DR. DABBS:  4 A. That's how small a quantity, exactly,  5 femtomoles.  6 COFFEY, Q.C.:  7 Q. Doctor, you just in passing referred to the  8 fact this was done in relatively few or very  9 few laboratories?  10 DR. DABBS:  11 A. Yes.  12 COFFEY, Q.C.:  13 Q. Why was that?  14 DR. DABBS:  15 A. Well, I was going to--the next slide here, is  16 that this was a very high tech procedure that  17 required very exotic, if you will, laboratory  18 instrumentation that was very expensive and  19 required very great technical skill,  20 laboratory science type technologists, not the  21 type of typical technologists that you find in  22 a usual hospital laboratory.  23 COFFEY, Q.C.:  24 Q. And, Doctor, while I'm on the topic, this  25 would have been--would this have been in use</p>
<p>Page 121</p> <p>1 principle here is that that estrogen which is  2 radioactive will bind to estrogen receptors  3 that were present in the cytoplasm of that  4 cell. Then this mixture is exposed to a  5 slurry of charcoal, dextran coated charcoal,  6 which removes unbound estrogen, and then  7 what's left is estrogen receptors bound to  8 radioactive estrogen and it is exposed or  9 counted in a scintillation counter to see how  10 much radioactivity there is. The exposure to  11 estrogen--the specimen is then exposed to  12 estrogen to determine non-specific binding.  13 In other words, estrogen will displace  14 anything that is binding to the remaining  15 receptors in a much tighter fashion and knock  16 out any non-specific binding, and then it's  17 counted again. I know this is--you know,  18 seems very laborious and time consuming and  19 difficult to interpret, and it is. It's a  20 very laborious procedure performed in few  21 laboratories. The final result then was  22 expressed in femtomoles of estrogen receptor  23 protein per milligram of cytosol protein. Now  24 to put this in perspective, femtomole means 10  25 to the minus 15. So that 14 zeros and a one.</p>	<p>Page 123</p> <p>1 when you first started your residency?  2 DR. DABBS:  3 A. This was in use and was the preferred method  4 of testing as I started my residency in the  5 year 1980.  6 COFFEY, Q.C.:  7 Q. Doctor, at that time was there any  8 certification regime or licensing regime  9 related to who could perform this sort of  10 test?  11 DR. DABBS:  12 A. Well, to my knowledge, the laboratories that  13 performed this operated under the aegis of the  14 usual kinds of quality control standards that  15 were prevalent at the time. The issues  16 regarding quality control and everything are  17 pretty much the same as they are now for  18 immunohistochemistry, the same issues, and, in  19 fact, one of the first slides that I  20 demonstrated there was the first step was  21 homogenizing the tissue. Well, that became an  22 issue when it became evident that laboratories  23 were getting different results for ER by this  24 method, depending on how tissue was  25 homogenized. So every step of the way had to</p>

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<p>1 become somewhat standardized as time moved 2 forward with this test. 3 COFFEY, Q.C.: 4 Q. Thank you, Doctor. Go ahead then, please. 5 DR. DABBS: 6 A. So the DCC ligand binding method required a 7 large amount of fresh tissue. It required 8 immediate freezing of fresh tissue when 9 removed from the patient, and I can tell you 10 that there was one evening when I was on call 11 and I got called in and specifically for the 12 reason of collecting tissue. What it meant 13 was as soon as the breast tissue was 14 devitalized at the time of surgery, that 15 tissue was handed off. The pathologist took 16 it right to the laboratory and froze it 17 immediately. That's the kind of immediate 18 care that was required for that, and I'll show 19 you an important reference in a few moments as 20 to why that is so. So this method required 21 radioactive reagents. Some of those reagents 22 were actually estrogen compounds, DES, 23 diethylstilbestrol. Those are known 24 carcinogens. Expensive laboratory equipment 25 not usually found in hospitals. The other</p>	<p>1 challenging and again a test to the tedious 2 and scientific method involved was so called 3 "scatchard plot analysis" which basically was 4 a determination of binding coefficients, how 5 tight the estrogen receptor that was present 6 bound to the estrogen that it was exposed to. 7 That related to specificity issues for the 8 actual test. So again the quality assurance 9 issues were the same, quality control test 10 results were standardized test specimens. It 11 wasn't until 1978 when Pertschuk published in 12 Cancer, "The immunofluorescent detection of 13 estrogen receptors in breast cancer", and this 14 is really a sentinel paper. One of the other 15 authors on this was David J. Brigatti. He was 16 the person who actually developed the very 17 first automated immunostainer that was ever 18 put together. He also was a faculty member at 19 Hershey at Penn State. So basically what 20 these authors did was using an estrogen 21 polymer labelled with something that they 22 could see under a special microscope called 23 fluorescein. The principle here was that this 24 polymer would bind to the estrogen receptor in 25 the cell cytoplasm and you could see where it</p>
<p>Page 125</p> <p>1 main issue with this test was what's referred 2 to as blind sampling, and basically samples 3 for the assay are largely independent of what 4 is actually examined histologically, so while 5 there was some attempt at taking a sample that 6 was representative of the tumour, whatever 7 tissue was sent for this assay was really 8 blind, people really never knew 100 percent 9 what was in it, how much normal tissue might 10 have been in there. If the sample, for 11 example, had only a few tumour cells and a lot 12 of stroma, it could affect the result; if 13 there was any devitalized totally dead tumour 14 tissue in there, you really would never know. 15 So that was considered to be one of the main 16 drawbacks of that particular testing, non 17 tumour area sampled and no direct 18 visualization of the assay sample. Not to 19 mention that if this testing, for example, 20 were to be done in Toronto and wasn't being 21 done in St. John's just for an example, you 22 would have to transport, expense of sending 23 this on dry ice in a very rapid way over to 24 Toronto. Another issue associated with this 25 that made it very tedious and mathematically</p>	<p>Page 127</p> <p>1 bound by putting these cells under a 2 microscope, a fluorescence microscope. So 3 this fluorescein that was present on the 4 polymer would show up when placed under a 5 fluorescent microscope. Receptors were found 6 in the cytoplasm and in the nucleus, and what 7 they did was they found that there was a 90 8 percent correlation with the dextran coated 9 charcoal ligand binding method with this 10 immunofluorescence procedure, and in this 11 paper he comments that the technique can be 12 performed by the average surgical pathology 13 laboratory in general. Tumours with less than 14 10 percent positive cells were negative by DCC 15 ligand binding and those with 11 to 20 percent 16 positive were borderline by DCC ligand 17 binding. I think this is one of the first 18 mentions of this magic number, 10 percent, 19 that tended to permeate the rest of ER testing 20 literature if you follow that throughout time. 21 Then just a year later, Antoniadis in the 22 American Journal of Clinical Pathology looked 23 at correlation of estrogen receptor levels 24 with histology and cytomorphology in breast 25 carcinoma, and this really was the first paper</p>



<p style="text-align: right;">Page 128</p> <p>1 that had a critical look at what did tumours  2 look like when they expressed estrogen  3 receptor. Prior to this, there were few  4 papers that only tangentially addressed this  5 issue, and in my opinion didn't really do a  6 very good job of it because what they said  7 was, you know, we're looking at these tumours  8 and the way they look doesn't really correlate  9 with what we're seeing by the dextran coated  10 charcoal method. These authors, using strict  11 criteria from what was then the National  12 Surgical Adjuvant Breast Project, which has  13 been and always was centred in Pittsburg,  14 showed a very strong correlation with better  15 differentiated tumours, especially tubular  16 cancers and lobular cancers, so called high  17 expressors. So this was the first paper that  18 discerned what tumours looked like when they  19 express high amounts of estrogen receptor.  20 Then this paper by Eusebi and others actually  21 increased sensitivity by showing that a two  22 stage method for estrogen receptor analysis  23 correlated with morphological parameters of  24 breast cancer as well. It showed an enhanced  25 sensitivity over direct methods. It</p>	<p style="text-align: right;">Page 130</p> <p>1 Then what they did, they compared that result  2 for estrogen receptor with the mastectomy  3 specimen that came hours later and sat around  4 in the laboratory, and showed that there were  5 huge differences, that the estrogen receptor  6 content markedly fell off with time, and  7 suggested that, in fact, because of that a low  8 expressor--if there was a patient who had a  9 low expressing tumour initially, it may, in  10 fact, become negative because of this issue  11 with disconnecting the blood supply and  12 causing this devitalized tissue lag time.  13 COFFEY, Q.C.:  14 Q. It may become negative in the sense that when  15 it's analyzed as a mastectomy specimen --  16 DR. DABBS:  17 A. Correct.  18 COFFEY, Q.C.:  19 Q. It would be analyzed as negative?  20 DR. DABBS:  21 A. Yes, and this was the call to arms that it was  22 critically important to be there when the  23 surgery was done and the surgeon was actually  24 disconnecting the blood supply from the  25 tumour, that that's when you had to obtain the</p>
<p style="text-align: right;">Page 129</p> <p>1 demonstrated for the first time that nuclear  2 expression dominates and not cytoplasmic, and  3 that it correlates well with morphology. In  4 other words, better differentiated tumours,  5 those that do not look really aggressive under  6 the microscope, have the most estrogen  7 receptor content. This paper, you'll notice  8 it's basically one--almost two pages by Hasson  9 et al in Cancer from 1981 right when I was a  10 resident. Comparison of estrogen receptor  11 levels in breast cancer samples from  12 mastectomy and frozen tissue samples, they  13 demonstrated that devitalized tissue may give  14 a false negative result, that the comparison  15 of fresh frozen tissue in the subsequent  16 mastectomy specimens was really the culprit  17 here, that there were markedly lower ER  18 results obtained in the mastectomy specimen as  19 opposed to a fresh frozen tissue section. In  20 other words, what they were saying was that if  21 they were called for a consult to determine  22 whether this was cancer and they got fresh  23 tissue in their hands, they did a documented  24 frozen section that it was cancer, and they  25 stowed some away right away and froze it.</p>	<p style="text-align: right;">Page 131</p> <p>1 tissue and freeze it immediately to get an  2 optimal result. Then Shimada and colleagues  3 just a few years later showed that the  4 immunocytochemical staining of estrogen  5 receptor in paraffin sections by the use of  6 monoclonal antibodies was comparable to that  7 of frozen section, and this was one of the  8 first papers that compared frozen section with  9 paraffin and using two different methods,  10 immunoperoxidase, and another more sensitive  11 technique, the Avidin-Biotin method for  12 immunohistology, and also corroborated  13 previous other studies that all of these  14 correlated very well with the results that  15 were obtained by dextran coated charcoal  16 ligand binding method. This paper by McCarty  17 and others that described estrogen receptor  18 analysis correlation of immunohistochemical  19 and biochemical methods was the first paper to  20 really quantitate, attempt to quantitate  21 estrogen receptor results by  22 immunohistochemistry and actually compare them  23 with dextran coated charcoal methods and  24 patient outcome, and this had never been  25 previously performed. What he devised was</p>

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1 something called the H score, H simply meaning  
 2 histochemical, and the H score which is still  
 3 used today in some institutions including ours  
 4 is the sum of the proportion of cells by  
 5 immunohistology with nuclear staining times  
 6 the intensity of staining. So, for example,  
 7 if you have 100 percent of cells by this  
 8 scheme that stained 4 plus, your H score is  
 9 400 and that's the maximum it can be. If you  
 10 have a completely negative result, 100 percent  
 11 of cells stain zero, your H score is zero. If  
 12 you have 10 percent of cells that stain 1  
 13 plus, 10 percent of cells that stain 2 plus,  
 14 10 percent of cells that stain 3 plus, and 70  
 15 percent of the remainder stain 4 plus, what  
 16 you do is you add up all those four numbers by  
 17 taking 70 times 4, plus 10 times 3, plus 10  
 18 times 2, plus 10 times 1, and that's your H  
 19 score, okay. It worked very well and  
 20 correlated with outcome and the desirable  
 21 aspect of this is that our clinician  
 22 colleagues do like to have a quantitative  
 23 measure put to this test result as opposed to  
 24 it being reported just as positive or  
 25 negative. It is possible to report it as just

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1 positive or negative, but what the  
 2 quantitation does is it gives you a reasonable  
 3 number for the clinician to tell the clinician  
 4 how much impact the patient may get from  
 5 antihormonal therapy. For example, a patient  
 6 with a H score of 350, I can tell you several  
 7 things about that; that patient almost  
 8 certainly is also PR positive. We know that  
 9 from our metrics. They're going to get a good  
 10 impact out of anti-hormonal therapy. Whereas  
 11 if someone has a H Score of 60, the patient  
 12 may have an impact, but it will be  
 13 substantially less than the patient who has  
 14 one of 350. So the importance of this  
 15 quantitation is is dialled into one of the  
 16 other factors that deal with individual  
 17 patients. Some patients may do well on  
 18 therapy, some patients may be frail or have  
 19 other relative contraindications to anti-  
 20 hormonal therapy, so this is a judgment call.  
 21 This number helps the clinician, the  
 22 oncologist and the patient determine what  
 23 course of action they want to take.  
 24 This same study actually compared the  
 25 only antibody at the time, when I was a

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1 resident was used on frozen tissue H22 by  
 2 Abbott. And you can see here that the  
 3 quantitative comparison with the biochemical  
 4 method had a sensitivity of 93 percent and a  
 5 specificity of 89 percent based on clinical  
 6 outcome alone. A very important paper.  
 7 Now, the quality issues with the dextran-  
 8 coated charcoal and ligand binding method were  
 9 exemplified very nicely in this paper by  
 10 Thorpe from 1987. And I mentioned some of  
 11 these already: the biopsy composition and  
 12 inability to really distinguish normal from  
 13 tumour in some instances, the concept of  
 14 homogenization was a variable, incubation time  
 15 with radioisotopes, there could be unwanted  
 16 absorption of the Ligand on free surfaces of  
 17 the glass tubes, there could be absorption of  
 18 free steroid by Dextra-Coated Charcoal. In  
 19 other words, this was not an easy test to do.  
 20 There were far more steps and far more things  
 21 that could go wrong, in actuality, than with  
 22 immunohistology. And again, variation in  
 23 scintillation counting.  
 24 So in 1989 Berger came out with the first  
 25 introduction of an antibody to progesterone

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1 receptor. This was the first time that this  
 2 actually allowed for routine analysis of  
 3 progesterone receptor. Progesterone receptor  
 4 was not routinely done with the dextran-coated  
 5 charcoal method simply because it required so  
 6 much tissue. Estrogen receptor itself  
 7 required a great deal of tissue. And I can  
 8 tell you that back then many times it was not  
 9 difficult getting adequate tissue because back  
 10 then mammographic screening was not what it is  
 11 today and tumours were larger, regrettably,  
 12 patients presented with larger tumours, so  
 13 there was, in many instances, adequate tissue  
 14 but progesterone receptor was not routinely  
 15 done because it required so much additional  
 16 tissue. So the introduction of the PR  
 17 antibody was a very important step for  
 18 immunohistology.  
 19 These authors then demonstrated that, in  
 20 fact, PR is an independent prognostic factor  
 21 and ER positive, PR positive patients respond  
 22 better as a group to endocrine therapy. What  
 23 it turns out is if you look at metrics, and by  
 24 metrics I mean for any given laboratory the  
 25 overall percent of patients who are ER

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<p>1 positive and then you can break that down into 2 the category that's ER positive and PR 3 positive, there will be a category that's ER 4 positive and PR negative, there will be a 5 category that's ER negative and PR positive, 6 and then there will be the double negatives, 7 the ER negatives and PR negatives. What they 8 demonstrated here was that when PR is also 9 positive, these patients get the best bang out 10 of the treatment, they get the most impact 11 with anti-endocrine therapy, presumably 12 indicating that the--at least some of the 13 physiology of those tumour cells is still 14 intact. Estrogen receptor in normal cells 15 induces the presence of progesterone 16 receptors, that's in normal cells. So it's 17 heartening in this group of tumours to see 18 that ER positive and PR positive, that 19 physiology axis is still working and so these 20 patients who are--and these are almost always 21 strong positive ERs or moderate positive ERs 22 who also have PR, they respond best. And 23 these papers, each one of these four here 24 document this, the paper by Thorpe, McGuire, 25 the two papers by McGuire, and Pertschuk, as</p>	<p>1 that there may be not sufficient number of 2 tumour cells, for example, to actually be 3 assayed by DCC, given what we know now about 4 these tumours. So he nicely demonstrated that 5 DCC was not necessarily the gold standard that 6 everyone had previously thought. 7 One of the first calls to standardization 8 of hormone receptor testing by 9 immunohistochemistry was done by Jose Eseban 10 et al. And actually, in the very same 11 supplement Pertschuk, whose name I've 12 mentioned several times now, did the same 13 thing. Basically they've recognized that 14 immunohistochemistry was rapidly becoming the 15 test of choice for multiple reasons. It was 16 it can be performed in any surgical pathology 17 laboratory, it could be--it was much more cost 18 effective, it was reproducible and the studies 19 to date had demonstrated that, in fact, the 20 outcomes were as good or better, in some 21 instances, in some papers, than what was seen 22 with the dextran-coated ligand binding method. 23 And, in fact, Pertschuk, in 1996, using 24 the ER1D5 antibody demonstrated, in fact, that 25 the endocrine response was better compared to</p>
<p>Page 137</p> <p>1 well. So this was an very important milestone 2 to recognize that if someone needs to have 3 this anti-hormonal therapy, which is not 4 without side effects, it's nice to know that 5 these are the patients who will get the most 6 out of that treatment. 7 This paper then by Shousha in 1990 showed 8 something that no one had ever demonstrated 9 before and that was he took 60 cases that were 10 negative for estrogen receptor by dextran- 11 coated charcoal and he reassessed them by 12 immunohistochemistry and found six to be 13 weakly positive, that's ten percent of the 14 cases. He also found three that were 15 moderately positive, and these were tubular 16 and lobular cancers and should have been 17 positive by DCC. But again, with all of those 18 items that I showed you and some of the 19 weaknesses of the DCC Ligand Binding in that, 20 sometimes you really never knew what sample 21 you were submitting. And I can tell you that 22 with lobular cancers are notorious in that 23 they tend to be tumour cell poor and have a 24 lot of stroma. So it's conceivable that on 25 sampling and with the processing of tissue</p>	<p>Page 139</p> <p>1 cytosol methods, compared to the DCC method or 2 the frozen tissue method. And he found, in 3 fact, that the percent of cell staining, ten 4 percent was as good as naming the intensity 5 and percent of cells. So in other words he 6 was saying if you just use the percent of cell 7 staining, that seems to be as good as naming 8 the percent of cells staining as well as the 9 intensity of cells staining. 10 And at about this time there was another 11 paper that I don't mention here, and the 12 author was Mascarelli, that also used the 1D5 13 antibody and in doing so they used cutoffs of 14 five percent and ten percent just arbitrarily 15 and the outcomes were the same. The patients 16 who had five percent did as well as the ten 17 percent. So that was the 1D5 certainly had 18 been worked out well with outcomes as low as 19 five percent. So you can see where some of 20 these numbers of ten percent keep popping up 21 in the ER literature over time. 22 This sort of takes us up to about the 23 year 2000. And I wanted to point this out 24 because this had a significant impact on me. 25 I had moved to Mcgee Women's Hospital in</p>

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1 September of 2001, approximately a year after  
 2 this statement came out. And in fact, I  
 3 noticed this statement when it came out. I  
 4 was in Baltimore at the time. And this  
 5 statement did have an impact on me and the way  
 6 we reported estrogen and progesterone  
 7 receptors.  
 8 Basically this consensus conference  
 9 stated the following, "The decision whether to  
 10 recommend adjuvant hormonal therapy should be  
 11 based on the presence of hormone receptors as  
 12 assessed by immunohistochemical staining on  
 13 breast cancer tissue. Adjuvant hormonal  
 14 therapy should be recommended to women whose  
 15 breast tumours contain hormone receptor  
 16 protein, regardless of age, menopausal status,  
 17 involvement of axillary nodes or tumour size.  
 18 While the likelihood of benefit correlates  
 19 with the amount of hormone receptor protein in  
 20 tumour cells, patients with any extent of  
 21 hormone receptor in their tumour cells may  
 22 still benefit from hormonal therapy. Hormonal  
 23 adjuvant therapy should not be recommended to  
 24 women whose breast cancers do not express  
 25 hormone receptor protein."

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1 So what I did when I--whenever this  
 2 statement came out is we changed our method of  
 3 reporting at St. Agnes to the following: we  
 4 would semi-quantitate it as we did before, but  
 5 we also considered any result--rather, a  
 6 positive result as any nuclear expression.  
 7 And the way--the reason why we did that is if  
 8 you read, you know, from here, "Patients with  
 9 any extent of hormone receptor in their tumour  
 10 cells may still benefit." Okay. My reading  
 11 of that is that you want to report that  
 12 because a patient may benefit from it and  
 13 therefore my threshold became zero for a  
 14 negative result.  
 15 And when I moved to Magee Women's  
 16 Hospital a year later, I brought this up at  
 17 one of our interdisciplinary tumour boards,  
 18 you know, presented this same information to  
 19 our tumour board and oncologists and they  
 20 concluded that this would be an acceptable  
 21 method of expressing the reports, but they  
 22 were also very much interested in continuing  
 23 semi-quantitation. And the reason for that  
 24 was, as I mentioned before, they want to know  
 25 how much hormone there is so that they can

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1 assess on an individual patient how much  
 2 efficacy they will get from the medicine,  
 3 because these medicines are not all 100  
 4 percent benign, they have side effects.  
 5 So I thought that this was an absolutely  
 6 key event, a sentinel event, this statement.  
 7 It has not changed since. If you Google this  
 8 statement, it will say something to the effect  
 9 that the statement is seven years old and if  
 10 you Google further, you will find nothing else  
 11 follow up, it hasn't been changed, it hasn't  
 12 been amended, it hasn't been struck down, so  
 13 it's still there. And I think as I move on to  
 14 other items you will be able to put this into  
 15 perspective in that I still strongly believe  
 16 that this does have a role in hormone receptor  
 17 reporting.  
 18 COFFEY, Q.C.:  
 19 Q. Doctor, when you say semi-quantification, why  
 20 -  
 21 DR. DABBS:  
 22 A. When I say semi-quantitation, basically at a  
 23 minimum you report the percent of cells that  
 24 stain weakly, moderately and intensely, so  
 25 that they all add up to 100 percent.

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1 COFFEY, Q.C.:  
 2 Q. Okay.  
 3 DR. DABBS:  
 4 A. The following paper by Fisher, actually, I was  
 5 a co-author on this, and we reported this in  
 6 Cancer in 2005. This paper is titled,  
 7 "Solving the Dilemma of the  
 8 Immunohistochemical and Other Methods Used for  
 9 Scoring ER and PR in Patients With Invasive  
 10 Breast Cancer." We basically compared the ER  
 11 and PR results by comparing the dextran-coated  
 12 charcoal method to immunohistochemistry in an  
 13 NSABP group, that's the National Surgical  
 14 Adjuvant Breast Project, protocol B09, that  
 15 basically had 402 patients. This was a  
 16 randomized study in which patients were  
 17 treated with Tamoxifen or not treated based on  
 18 hormone receptor status. Our criteria, when  
 19 we went into this, was we were going to report  
 20 any or none and we were going to then attempt  
 21 to assess the intensity and percent of cell  
 22 staining. And we also had a separate group of  
 23 people who did a fancy computer assisted image  
 24 analysis of this same material. And basically  
 25 what we concluded was that the presence of any

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<p>1 nuclear estrogen receptor expression is 2 related significantly to overall survival of 3 five and ten years regardless of the scoring 4 method. In other words, if there was any 5 expression whatsoever, that was clinically 6 important, it was important because those 7 people responded to therapy and it was 8 prognostically significant at five and ten 9 years regardless of the scoring method. In 10 other words if there was any expression 11 whatsoever, that was clinically important. It 12 was important because those people responded 13 to therapy and it was prognostically 14 significant at five and ten years regardless 15 of the scoring method. So you could analyze 16 your tissue section by a fancy computer 17 assisted image analysis, you could eyeball it 18 by percentages, you could create an H Score or 19 you can say present or absent, all those were 20 equivalent.</p> <p>21 This does not diminish the semi- 22 quantitation in my mind because when you 23 report the semi-quantitation, you're talking 24 about the care of an individual patient and 25 because no two patients are alike, some</p>	<p>1 course, we were all mindful of our CLIA 88 2 responsibilities, the Clinical Laboratory 3 Improvement Act of 1988 regarding items that 4 were necessary to be present in our laboratory 5 reports.</p> <p>6 And basically to sort of start off with, 7 these are the items that we all grappled with, 8 that there are different procedures intra and 9 intra laboratory items that can potentially 10 compromise standardization. If you just 11 consider the preparation phase or the pre- 12 analytic phase, the IHC staining as part of 13 the pre-analytic and analytic phase and the 14 interpretation phase as part of the analytic 15 phase, you'll notice that for the preparation 16 phase there's biopsying, fixation, 17 preparation, sectioning and drying. In the 18 second step there's deparaffination, 19 pretreatment, meaning antigen retrieval, the 20 antibody, the detection method and the 21 counterstain. And then for the interpretation 22 phase, what are your controls, what are your 23 cutoff values, what is the tumour entity, and 24 what sort of things do you need to put on your 25 report? If you take these three steps and</p>
<p>Page 145</p> <p>1 patients may have relative contraindications 2 to the medicine, if you want to give them that 3 medicine, in my mind and I think most 4 oncologists, you'll want to have a real good 5 reason to give it to them. You wouldn't want 6 to give it to someone who has relative 7 contraindications and has a very weak 8 expression, for example.</p> <p>9 So this takes us right now to 10 recommendations for improved standardization 11 in immunohistochemistry. This paper was 12 published in 2007 in The Applied 13 Immunohistochemistry and Molecular Morphology 14 Journal. This was, this paper represents the 15 fruits of the same ad hoc group committee 16 meeting, we even had met the year before 17 somewhere in the Florida Keys and came upon 18 these recommendations.</p> <p>19 First what I'll--my first line here is to 20 basically reference that all of these items 21 were taken into account by this committee. 22 There was a person present at this meeting who 23 was a representative of the CLSI, Clinical and 24 Laboratory Standards Institute, people from 25 the College of American Pathologist and of</p>	<p>Page 147</p> <p>1 these 14, you can see that there can be a 2 myriad of potential items competing with each 3 other that are not in the best interest of 4 standardization. So what we have tried to do 5 in this meeting was standardize these items 6 the best way that we could.</p> <p>7 I take this chart from this paper by Dr. 8 Clive Taylor, from Archives Pathology of 9 Laboratory Medicine, where he talks about the 10 total test for immunohistochemistry, and this 11 is immunohistochemistry in general, the 12 elements of testing in this column, the QA 13 issues and the responsibility. You know, the 14 clinical question, what test is ordered? 15 That's the pathologist, the clinician and the 16 technologist all have responsibility. The QA 17 issues are getting the specimen properly 18 fixed, collected and fixed. What are the 19 indications for the stain? What are the 20 stains? This is within the realm of the 21 pathologist. What is the technology and 22 methodology? What are the reagents and the 23 protocols? What's your specificity and 24 sensitivity? What are the qualifications? 25 What are the proficiency testing profiles for</p>

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<p>1 that particular test? What about your 2 results? What are your criteria for a 3 positive and negative report? What should be 4 in your report content? And then finally, the 5 interpretations, what are the qualifications 6 of the person who is doing this, and how does 7 this all integrate into everything else? And 8 overtime, I think that Dr. Taylor's total test 9 concept was really critically important in 10 pushing us all in the right direction of 11 standardization.</p> <p>12 So basically, the items that we discussed 13 in Florida were tissue acquisition. Again, 14 this harkens back to the paper by Hassen. We 15 need to get the tissue as soon as possible and 16 into our fixative, which our preferred 17 fixative is ten percent neutral buffered 18 formalin. Tissue sections need to be cut 19 thin, and this is especially important for 20 breast tissue, where you obtain the specimens 21 fresh from the operating room. They have to 22 be cut as thin as humanly possible and placed 23 into fixative. Tissue fixation, there should 24 be minimum and maximum fixation times for 25 predictive and prognostic markers, and this</p>	<p>1 DR. DABBS: 2 A. Yes.</p> <p>3 COFFEY, Q.C.: 4 Q. - there was, as you put it, such a line in the 5 sand drawn?</p> <p>6 DR. DABBS: 7 A. Correct.</p> <p>8 COFFEY, Q.C.: 9 Q. In terms of regarding tissue minimum fixation 10 time for particular type of tissue?</p> <p>11 DR. DABBS: 12 A. Exactly, and this was referring to breast 13 tissue, in fact. So the other items in best 14 practice, you want to make sure that your 15 tissue gross sections are nice and thin and 16 that your tissues for microtomy are, you know, 17 in the realm of four to five millimetres 18 thick, which has been the standard of tissue 19 sectioning ever since immunohistochemistry has 20 been practised.</p> <p>21 The pre-analytical factors, in your 22 tissue processor, it has to be formalin. 23 There's a need to change the solutions, 24 especially for formalin, daily, and probably 25 weekly, and replenish solutions as necessary.</p>
<p>Page 149</p> <p>1 actually came up as a first time ever, if you 2 will, recommendation by the College of 3 American Pathologists and ASCO where they 4 addressed HER2 testing. Where, for the very 5 first time, there was an organization that 6 said "you must fix your tissue a minimum of 7 six hours if you're going to do HER2 testing, 8 and not longer than 48 hours," and this was 9 completely new to anatomic pathologists 10 worldwide. Never before had anyone drawn a 11 line in the sand and said this is what you 12 have to do if you're going to do this type of 13 testing.</p> <p>14 COFFEY, Q.C.: 15 Q. That was HER2? 16 DR. DABBS: 17 A. HER2, yes, that was the CAP ASCO guidelines 18 that came out just a couple of years ago.</p> <p>19 COFFEY, Q.C.: 20 Q. So it was just a couple of years ago? 21 DR. DABBS: 22 A. Yes.</p> <p>23 COFFEY, Q.C.: 24 Q. For the first time, to your knowledge, 25 anywhere -</p>	<p>Page 151</p> <p>1 No solutions in the processor should exceed 37 2 degrees Celsius. Paraffin should not exceed 3 60 degrees Celsius. Blocks should not be 4 allowed to sit in heated paraffin for any 5 extended period of time, and embedding has to 6 be done in accordance with standard embedding 7 procedures without using excessively hot 8 paraffin.</p> <p>9 Tissue microtomy, tissues are sectioned 10 to four to five microns. Tissue has to be 11 able to adhere to the slide and it sounds like 12 a sticking point here, but just simply having 13 your tissue sections adhere to a slide is 14 critically important. You can do this several 15 ways. You can have it sit on the slide and 16 dry overnight or you can have it in a 17 controlled oven to bake so that all of the 18 water is taken out of that section. It's 19 critical, because if you have water in that 20 section and you put it through an 21 immunohistochemistry stainer, what will happen 22 is that the tissue will lift off and it will 23 partially degenerate, so that you can end up 24 with holes and folds and part of it will be 25 missing. Okay, if it's not--just something</p>

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1 this simple can kill the whole system.  
 2 Everything has to be done very methodical.  
 3 You cannot short change any method.  
 4 Tissue has to be de-waxed, de-  
 5 paraffinized appropriately, and if you--so if  
 6 you change anything in your system, if you  
 7 change a paraffin, for example, you need to  
 8 re-optimize your process and make sure that  
 9 the result that you have been getting is the  
 10 same result that you got before. Probably no  
 11 two paraffins have the same melting point.  
 12 Some paraffins come nowadays with polymers in  
 13 it to help histotechs cut tissue better. So  
 14 you have to make sure that you're properly de-  
 15 waxing your paraffin. You have to make sure  
 16 that the technical--the person who is  
 17 performing the immunohistochemistry knows what  
 18 they're doing, knows the fine detail that has  
 19 to be attended to every one of these steps,  
 20 because without proper preparation, putting it  
 21 in the machine is--if you don't have it  
 22 properly prepared, putting it in any automated  
 23 machine is not going to fix it. It's sort of  
 24 like if you're going to have your house  
 25 painted, you don't just paint over big peeling

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1 areas and whatnot. You have to properly  
 2 prepare the surface in order for the new paint  
 3 to stick, and it's critically important for  
 4 the technician to have the competence to  
 5 recognize that and also recognize when things  
 6 aren't working quite well.  
 7 Additional pre-analytic processes is  
 8 antibody optimization. The antibody package  
 9 insert is there for a reason. It comes with  
 10 every product, whether it be an item approved  
 11 by FDA for use or in vitro device or analyte  
 12 specific reagent. They tell you what the item  
 13 is, how it was generated, what it has reacted  
 14 to and their experience, and in some  
 15 instances, on those package inserts, it will  
 16 recommend a dilution, and what you want to do  
 17 is, at the minimum, work one above and below  
 18 that dilution, and just a word about  
 19 dilutions. Many antibodies nowadays come as  
 20 ready-to-use reagents. You open a vile and  
 21 you take that reagent and you put it on the  
 22 machine. But in the early days of  
 23 immunohistochemistry, and even nowadays, there  
 24 are laboratories that basically make their own  
 25 dilutions. They buy antibody as a

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1 concentrate. It's cheaper and as effective,  
 2 but the critical item there is being able to  
 3 make those dilutions and titre those dilutions  
 4 appropriately. It requires intricate  
 5 equipment, pipettes that are properly  
 6 calibrated. One slight mistake in a dilution  
 7 can give you a false negative or a false  
 8 positive result. So these are items that are  
 9 highly dependent on the skill of the tech who  
 10 is doing the procedure, and the fact of the  
 11 matter is, at least in the States nowadays,  
 12 it's difficult to find technical people with  
 13 that kind of skill from scientific  
 14 laboratories. They're difficult to find and  
 15 they don't usually work in hospitals. They  
 16 work in other scientific laboratories. So  
 17 this is one reason why there's a move towards  
 18 automation and standardization, the  
 19 development of ready-to-use reagents has come  
 20 about, reagent that's already predetermined  
 21 how it will react and the dilution is already  
 22 made, so that that step is just another step  
 23 that doesn't have to be dealt with. So  
 24 dilutions, again, it's an absolute critical  
 25 item that one has to deal with.

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1 In working up antibody optimization, AR  
 2 stands for antigen retrieval, you have to work  
 3 this up at at least a low and a high pH and  
 4 see how the characteristic of your test  
 5 responds to each. You should use at least two  
 6 different detection systems, and for  
 7 categorical results, for example, something  
 8 that's just positive or negative like a  
 9 keratin stain, it's recommended that one use  
 10 25 samples. Ten are expressors, ten are  
 11 intermediate expressors and at least five are  
 12 negative for the item in question. So this is  
 13 the overall high view of antibody  
 14 optimization, according to the recommendations  
 15 of this committee.  
 16 One test battery that you might, you  
 17 know, consider just the complexity of it is  
 18 you have your buffer here and you have various  
 19 temperatures, and different pHs and you have  
 20 different slides holding the same tissue. So  
 21 that, for example, in this one, 100 degrees C,  
 22 you have this breast tumour at pH one to two.  
 23 This one is seven to eight, this 10 to 11, and  
 24 you run it through these antigen retrieval  
 25 processes and then continue with your test and

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1 see which works best for your antibody and  
 2 your tissue in question. This is just one of  
 3 many ways, and this actually was taken from  
 4 the same paper on the total test by Dr. Clive  
 5 Taylor.  
 6 So what about antibodies that come into  
 7 the laboratory. New antibody lots come in all  
 8 the time. Do you have to do this all over  
 9 again? Not really. If you just take three  
 10 samples, one a high expressor, one an  
 11 intermediate and one a negative, and just test  
 12 the new lot that comes in and make sure that  
 13 you're getting the same result as you were  
 14 before. If you're not, you might want to call  
 15 the company and say "you know what, I used  
 16 this the same way. Is there something new  
 17 about this lot?" You might have to change the  
 18 conditions of your test. The lot might have  
 19 changed to some degree. So this is another  
 20 item that should be carried out with new  
 21 antibody lots.  
 22 In addition, in the pre-analytic step, if  
 23 one is using a technique that is crucial for  
 24 blocking endogenous peroxidase, and most of  
 25 them are, and antigen retrieval, these items

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1 have to be worked out.  
 2 The IHC procedure itself requires primary  
 3 antibody application to a slide, followed by a  
 4 secondary antibody, usually with a detection  
 5 agent. Then there's a localization with a  
 6 colour reaction that's developed and the slide  
 7 is then counterstained and cover slipped.  
 8 So what about the analytic process then?  
 9 It's recommended that pathologists document  
 10 the immunostaining, where it is, what is  
 11 positive and what is negative, semi-quantitate  
 12 it to some degree, comment on appropriate  
 13 positive and negative internal controls, and  
 14 comment on appropriate positive and negative  
 15 external controls.  
 16 Post-analytic. On your report, you  
 17 should tell how you've dealt with the tissue.  
 18 You should document the fixative and the  
 19 fixation. You should document the antibody  
 20 source, the clone and targeted antigen, and by  
 21 the way, these are items which are on the  
 22 College of American Pathologists checklist.  
 23 When they come to inspect your laboratory,  
 24 they will look at your reports to see if these  
 25 items are present.

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1 One of the items that I pushed for with  
 2 this most recent meeting, which I'll go over  
 3 in a few minutes, is the need for metrics for  
 4 predictive and prognostic markers. Now by  
 5 metrics, I mean what are the results for  
 6 estrogen and progesterone receptor or whatever  
 7 other antibody, for HER2, in our laboratory?  
 8 How many positive--what's our percent  
 9 positive? What does the literature say?  
 10 What's the percent positive for estrogen  
 11 receptor? If you look at the literature, it  
 12 says 70 to 80 percent. If you look at your  
 13 metrics and see that you're 45 percent, you  
 14 have a real problem. If you have 95 percent  
 15 positive, you have a real problem. If you're  
 16 between 70 and 80 percent, that's a bird's eye  
 17 view that you're probably doing okay. So in  
 18 my opinion, and I pushed for this in the new  
 19 paper, right now that's in press, that metrics  
 20 are highly desirable for any laboratory. That  
 21 way, if something is changing--and things do  
 22 change, some vendors disappear and you have to  
 23 pick up new antibodies or new detection  
 24 systems or whatever. You want to know where  
 25 you have been and what has happened in your

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1 metrics so that you have a complete grip on  
 2 what this test is doing in your laboratory,  
 3 because the impact is incredible. You're  
 4 talking about therapies that affect patients'  
 5 lives. So you want to be able to compare to  
 6 other testing methods outside the laboratory,  
 7 whether it be for HER2, immunohistochemistry,  
 8 HER2 by fluorescent in situ hybridization,  
 9 ER/PR, or whatever.  
 10 And then, this brings us lastly to the  
 11 section that I was going to talk about on the  
 12 current consensus recommendations on ER  
 13 testing for the paper that's in press.  
 14 COFFEY, Q.C.:  
 15 Q. Doctor, I should apprise the Commissioner,  
 16 there are some things in some of these slides  
 17 that we've looked at that I will be taking you  
 18 back to this afternoon, but if we could  
 19 continue then.  
 20 DR. DABBS:  
 21 A. Okay. Tissue fixation.  
 22 COFFEY, Q.C.:  
 23 Q. Or perhaps -  
 24 THE COMMISSIONER:  
 25 Q. I'm just going to raise the question of



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1 whether you want to do the luncheon break -  
 2 DR. DABBS:  
 3 A. Yeah, perhaps we -  
 4 THE COMMISSIONER:  
 5 Q. - at this point, which perhaps is a good point  
 6 to make the break, since we normally break at  
 7 quarter to one.  
 8 COFFEY, Q.C.:  
 9 Q. Yes, because otherwise we'll be only three or  
 10 four slides into it. Thanks, Doctor.  
 11 THE COMMISSIONER:  
 12 Q. All right then. We'll break until two.  
 13 COFFEY, Q.C.:  
 14 Q. Thank you.  
 15 (LUNCH BREAK)  
 16 THE COMMISSIONER:  
 17 Q. Please be seated. Mr. Coffey.  
 18 COFFEY, Q.C.:  
 19 Q. Thank you, Commissioner. Exhibit P-2621,  
 20 which is up here on the screen. Doctor, we  
 21 had gotten as far as the consensus  
 22 recommendations, I believe, on estrogen  
 23 receptor testing in breast cancer by  
 24 immunohistochemistry, and the first slide is  
 25 tissue fixation. You go ahead, Doctor.

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1 DR. DABBS:  
 2 A. Yes, thank you. So the critical issues began  
 3 with communication and coordination with  
 4 operating room personnel and clinics, where  
 5 tissue is acquired, be they biopsies on core  
 6 biopsies or actual resection specimens. The  
 7 first recommendation is that resection  
 8 specimens must be sectioned fresh, as soon as  
 9 possible, preferably 0.5 centimetres, placed  
 10 in fixative as quickly as possible, in less  
 11 than one hour, and that the time in formalin  
 12 should be recorded. Tissue sections must be  
 13 immersed in an adequate volume of fixative  
 14 with a ratio of tissue to fixative of about  
 15 one to 20, within a maximum of one hour from  
 16 removal and acquisition. It's desirable to  
 17 include normal tissue with tumour in the same  
 18 cassette, if that is possible, from resection  
 19 specimens.  
 20 The second recommendation is that breast  
 21 core biopsy should be fixed and processed in  
 22 an identical manner to excision specimens.  
 23 Specimen acquisition time into formalin should  
 24 be recorded.  
 25 The third recommendation is that only ten

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1 percent aqueous phosphate buffered formalin,  
 2 pH7 to 7.4, ten percent, should be used as  
 3 fixative for breast tissue samples. The  
 4 reason for this is that accrued data on  
 5 hormone receptor testing and clinical outcomes  
 6 have been performed on formalin fixed paraffin  
 7 embedded tissues. Alternative fixatives are  
 8 possible, but a formal cross validation study  
 9 requires a minimum of 100 samples that are  
 10 fixed in both the alternative fixative and ten  
 11 percent neutral phosphate buffered formalin.  
 12 The fourth recommendation is that the  
 13 time that the samples spend in ten percent  
 14 phosphate buffered formalin should be  
 15 standardized for all breast specimens, to help  
 16 ensure adequate and uniform fixation. Minimum  
 17 fixation times of at least eight hours, not to  
 18 exceed 72 hours, unless validated by the  
 19 medical director, and what this does is it  
 20 avoids alcohol fixation and promotes antigen  
 21 retrieval standardization. The key reference  
 22 for this is the paper by Goldstein, which is  
 23 mentioned here.  
 24 Recommendation number five, alcohol fixed  
 25 fine needle aspirates, if there is a clinical

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1 suspicion of breast cancer that may need ER  
 2 analysis and an FNA is performed, then all  
 3 efforts should be made to collect a portion of  
 4 the cytology specimens in formalin. Validation  
 5 is required with appropriate alcohol fixed  
 6 cytology specimens. In other words, it's okay  
 7 to use alcohol as a primary fixative, but it  
 8 must be validated within the laboratory with  
 9 appropriate positive controls, and that is not  
 10 easy to do. At our institution, we mandate  
 11 that if we know we're going to be collecting a  
 12 sample on a patient with a history of breast  
 13 cancer, specifically for hormone receptors or  
 14 HER2 analysis, that we go equipped with  
 15 formalin to collect the specimen as such, so  
 16 that it's properly fixed.  
 17 Tissue processing. Breast cancer  
 18 specimens should be processed in conventional  
 19 processors. If alternative processors, such  
 20 as those that are microwaved enhanced, need to  
 21 be validated by the medical director on 100  
 22 samples.  
 23 Number seven, the first formalin  
 24 containers in the tissue processor should  
 25 always be newly replenished, and that means on

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<p>1 a daily basis. The time in formalin includes</p> <p>2 the processor exposure to formalin. So that</p> <p>3 eight-hour minimum time that I was talking</p> <p>4 about, that would include the time in formalin</p> <p>5 on the tissue processors. Formalin normally is</p> <p>6 the first liquid that the tissue is exposed to</p> <p>7 on a tissue processor and that may vary from</p> <p>8 minutes to an hour, hour and a half. That can</p> <p>9 be included as the eight-hour minimum exposure</p> <p>10 time.</p> <p>11 COFFEY, Q.C.:</p> <p>12 Q. So I take it, Doctor, implicit in what you've</p> <p>13 just said, that tissue processors at times, in</p> <p>14 terms of the first step, the first fluid into</p> <p>15 which the sample is placed, can vary with</p> <p>16 time, from minutes to up to an hour and a</p> <p>17 half?</p> <p>18 DR. DABBS:</p> <p>19 A. It depends on what the tissue processor</p> <p>20 program is and probably would vary at each</p> <p>21 possible laboratory.</p> <p>22 COFFEY, Q.C.:</p> <p>23 Q. Okay.</p> <p>24 DR. DABBS:</p> <p>25 A. Recommendation number eight, it is strongly</p>	<p>1 solutions, so I take it if for some reason the</p> <p>2 solutions, solution or solutions to be used in</p> <p>3 the tissue processor are changed?</p> <p>4 DR. DABBS:</p> <p>5 A. Yes.</p> <p>6 COFFEY, Q.C.:</p> <p>7 Q. I don't mean like changed routinely, but as in</p> <p>8 the type of solution used?</p> <p>9 DR. DABBS:</p> <p>10 A. The type of solution. For example, as far as</p> <p>11 processor solutions go, some people may be</p> <p>12 using xylene substitutes. They would need to</p> <p>13 make sure that those xylene substitutes give</p> <p>14 the same result as xylene. There are also</p> <p>15 some green initiatives that involve recycling</p> <p>16 of solutions that are characteristically found</p> <p>17 on a tissue processor, including alcohols and</p> <p>18 xylenes. They're basically stills that</p> <p>19 recover the native solution, and so, if one is</p> <p>20 going to use recycled materials in a tissue</p> <p>21 processor, you have to make sure that they are</p> <p>22 pure solutions and make sure that you're</p> <p>23 getting the same results as you had</p> <p>24 previously.</p> <p>25 COFFEY, Q.C.:</p>
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<p>1 recommended that none of the tissue processor</p> <p>2 solutions, excluding paraffins, should exceed</p> <p>3 37 degrees Celsius if the processor contains</p> <p>4 breast tissue for potential ER and other</p> <p>5 biomarker testing. Revalidation is required</p> <p>6 if significant changes in processor solutions</p> <p>7 or paraffin types are changed.</p> <p>8 COFFEY, Q.C.:</p> <p>9 Q. Doctor, in relation to that, what is the</p> <p>10 potential downside or negative effects of</p> <p>11 exceeding that temperature?</p> <p>12 DR. DABBS:</p> <p>13 A. Exceeding temperature basically, we're going</p> <p>14 into the realm of the unknown, and so what we</p> <p>15 do not want to do is damage the tissue by</p> <p>16 exceeding temperatures that we are already</p> <p>17 known and comfortable with, in terms of the</p> <p>18 way specimens have been handled in the past.</p> <p>19 So rather than go into an unknown zone, it was</p> <p>20 felt that these temperatures would be best</p> <p>21 controlled as to what is usual standard and</p> <p>22 operating procedure in hospital laboratories.</p> <p>23 COFFEY, Q.C.:</p> <p>24 Q. And here, you noted that revalidation is</p> <p>25 required if significant changes in processor</p>	<p>1 Q. Which is the revalidation process?</p> <p>2 DR. DABBS:</p> <p>3 A. Exactly.</p> <p>4 COFFEY, Q.C.:</p> <p>5 Q. Doctor, you've referred to this already, the</p> <p>6 paraffin types. So I think--don't know if the</p> <p>7 Commissioner has really heard this before, and</p> <p>8 if she has, I apologize. Not all paraffin, I</p> <p>9 take it, are the same?</p> <p>10 DR. DABBS:</p> <p>11 A. Correct.</p> <p>12 COFFEY, Q.C.:</p> <p>13 Q. Here, routinely, there have been just</p> <p>14 references to paraffin embedded tissue.</p> <p>15 DR. DABBS:</p> <p>16 A. Yes.</p> <p>17 COFFEY, Q.C.:</p> <p>18 Q. I take it, there are different types of</p> <p>19 paraffin?</p> <p>20 DR. DABBS:</p> <p>21 A. There are different types of paraffin and</p> <p>22 they're marketed differently, and some of them</p> <p>23 have polymers in them to enhance tissue</p> <p>24 structure, so that when the technician cuts</p> <p>25 them on a microtome that they are easier to</p>

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<p>1 handle and easier to handle on their water 2 bath and whatnot, and that's fine, but it has 3 to be made clear that because of the complex 4 testing requirements that we need to make sure 5 that if there's a change in the paraffin, that 6 there's not going to be a change in the 7 immunohistochemistry result, because of 8 melting point change or something of that 9 manner. I would imagine that if you put the 10 polymer in with plain wax, that it will change 11 the melting point. So if you're going to try 12 to de-paraffinize and clear it with xylene, it 13 may have an effect there as well. Basically, 14 what we're saying is if you're introducing an 15 unknown, it's the responsibility of the 16 medical director of the laboratory to make 17 sure that the results that they're getting 18 with the changed solutions or paraffins are 19 the same as what happened before the change.</p> <p>20 COFFEY, Q.C.: 21 Q. Thank you, Doctor. Go ahead, recommendation 22 nine, I believe.</p> <p>23 DR. DABBS: 24 A. Yes. Paraffin and tissue processors or 25 embedding centres should not be warmed over 60</p>	<p>1 marker for that is when the tissue processor 2 begins. In our laboratory, we have seven or 3 eight tissue processors and they all pretty 4 much start at designated times and we have 5 those records. So that if someone wanted to 6 track down a specific case and say, okay, how 7 long was this in formalin, we will look at the 8 gross description to determine the time in 9 formalin and look at the tissue processor log 10 from which that was processed to find the time 11 out of formalin. Because in our tissue 12 processor, I think the first hour and 30 13 minutes is in formalin.</p> <p>14 Granted, there are going to be biopsies 15 that are done in doctors' offices and our 16 surrogate marker for the time in formalin with 17 those is currently the date of which the 18 biopsy is performed. We have a quality 19 initiative that we're going back to those 20 medical groups and asking that they place on 21 the requisitions that they send to us, the 22 time that the specimen goes into fixative. So 23 that'll tighten that up for us.</p> <p>24 We recognize that there are a lot of 25 players in acquiring tissue at various sites</p>
<p>1 degrees Celsius and the tissue should not be 2 kept in heated paraffin for extended periods 3 of time.</p> <p>4 COFFEY, Q.C.: 5 Q. I take it that's because the effect of doing 6 so is unknown?</p> <p>7 DR. DABBS: 8 A. Exactly, exactly. Documentation, 9 recommendation number ten. It is recommended 10 to include a designated field on the 11 requisition sheet for recording time into 12 formalin and time out. Time in formalin can 13 be dictated into a gross description, a 14 surrogate marker of time out of formalin is 15 when the tissue processor begins. Time of 16 collection recording is encouraged at clinic 17 sites where biopsies are performed. A 18 surrogate marker could be the date of 19 collection.</p> <p>20 So let me give you some examples here. 21 Our people who do the gross descriptions, 22 whenever they handle the specimens, they 23 dictate--this is the late item, the time in 24 formalin, and then that's placed. The time 25 out of formalin for us is the--our surrogate</p>	<p>1 all over and they're not necessarily 2 geographically close to us, and I'm sure you 3 have sites that aren't necessarily 4 geographically close to you. So communication 5 and coordination with surgical supplied 6 tissues and the rationale for doing this are 7 essential. I think if you tell people why 8 you're doing this, they'll understand and 9 they'll be cooperative.</p> <p>10 Standardizing the analytical variables, 11 as far as testing. We have to realize that 12 for any immunohistochemical reaction to take 13 place, all of the components, it should be 14 properly functioning, namely the primary 15 antibody, the detection system and the 16 chromogen. A drop of sensitivity of any of 17 these components will lead to an inadequate 18 assay with potentially false negative results.</p> <p>19 The original biochemical assay and 20 appropriately optimized immunohistochemical 21 assays will show a spectrum of ER or PR 22 content in individual cells, and we recognize 23 that for immunohistochemistry for ER or PR, 24 this means that some of the cells will be 25 negative, have no staining. Some of them will</p>

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1 be strongly positive, what we call three plus.  
 2 Some of them will be moderately positive, we  
 3 call two plus, and some of them will be weakly  
 4 positive, we call one plus.  
 5 So recommendation number 11. The  
 6 immunohistochemistry estrogen receptor assay  
 7 should be performed with one of three antibody  
 8 clones, 1D5, 6F11, SP1, and the reason for  
 9 this is because there have been published  
 10 outcome studies with each one of these  
 11 antibodies. Now with the 1D5 antibody, the  
 12 studies that initially came out in the mid 90s  
 13 were by Perchuck. I might have mentioned this  
 14 paper earlier, where they looked at five  
 15 percent and ten percent cut offs and both of  
 16 them were adequate in terms of outcome. What  
 17 has subsequently happened is that for 6F11,  
 18 there was a paper by Harvey in 1999 and Dr.  
 19 Craig Allred is also on that paper. That  
 20 outcome study used a one percent cut off, one  
 21 percent or greater, and those people had a  
 22 positive outcome with respect to therapy. So  
 23 as little as one percent staining cells was  
 24 considered to be a positive result.  
 25 And I will then make a comment about SP1.

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1 There was a study published in the Journal of  
 2 Clinical Oncology in December of 2006 in which  
 3 they used this antibody and compared it to the  
 4 1D5 using the one percent cut off. One  
 5 percent was a good number, in terms of  
 6 outcome, once again. What they did show is  
 7 that the SP1 antibody did have about eight  
 8 percent, eight to ten percent more positive  
 9 cases in terms of the presence of estrogen  
 10 receptor. However, those cases were generally  
 11 weakly positive with estrogen receptor for the  
 12 SP1.  
 13 So most institutions right now have these  
 14 validated studies with 1D5, 6F11, and SP1 as  
 15 one percent. There are many institutions that  
 16 use that as a cut off, one percent or more.  
 17 Some institutions still use ten percent.  
 18 Another issue here, ER assay should be  
 19 performed by standardized methods, preferably  
 20 using FDA approved test kits, and for your  
 21 information, I was the person who actually  
 22 pushed this at this consensus conference. I  
 23 felt that since we were making--taking great  
 24 pains to analyze or standardize all of the  
 25 pre-analytic variables, that we also needed to

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1 standardize the platform upon which testing  
 2 was taking place, and the ultimate  
 3 standardized test is one that has gone through  
 4 FDA approval. It is a recipe for doing a test  
 5 and deviation at all from that testing  
 6 procedure makes it invalid as an FDA test. So  
 7 this is one testing procedure that is  
 8 completely prescribed. It's a cookbook, if  
 9 you will, and everyone pretty much agreed with  
 10 this concept, that it was an attempt at  
 11 standardizing the actual testing platform.  
 12 Recommendation number 12, positive and  
 13 negative test controls should be included with  
 14 every estrogen receptor IHC batch run.  
 15 Internal positive controls. In this context,  
 16 an internal control consists of tissue or  
 17 cells in the same section or a separate  
 18 section from the same patient specimen as the  
 19 test section. External positive control and  
 20 normal tissue from the same patient or from a  
 21 different patient. Other external positive  
 22 controls that can be used for ER and PR  
 23 include benign gynecologic tissues such as  
 24 endometrium, endomyometrium, cervix,  
 25 endocervix and even ovarian tissue.

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1 Metrics. This is something that I also  
 2 pushed for. It is highly desirable to  
 3 maintain laboratory metrics for each  
 4 prognostic predictive test results in order to  
 5 monitor for potential analytic drift. For  
 6 example, published literature indicates that  
 7 70 to 80 percent of breast cancers are ER  
 8 positive. This should be a benchmark for each  
 9 laboratory to monitor.  
 10 Standardizing interpretation. The NIH  
 11 consensus statement that I mentioned before,  
 12 published in 2001, recommended any nuclear ER  
 13 as allowing a patient to be eligible for  
 14 endocrine therapy. Harvey, in 1999, these  
 15 investigators, using the 6F11 clone for ER IHC  
 16 recorded that proportionate positive cells and  
 17 the intensity of staining, known as the Allred  
 18 score, then correlated the results with  
 19 clinical outcomes in a large cohort of breast  
 20 cancer patients treated with adjuvant therapy,  
 21 almost 2,000 patients.  
 22 Cheang, this is the paper I referred to  
 23 from the Journal of Clinical Oncology,  
 24 December 2006, using SP1 clone and compared it  
 25 to 1D5. One percent positive cells was a cut

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1 off for a positive result, more than 4,000  
 2 patients.  
 3 So recommendation number 13, a commonly  
 4 employed threshold for positive results for ER  
 5 IHC assays, in terms of the potential benefit  
 6 from adjuvant endocrine therapy is one percent  
 7 positive tumour cells, with a one plus or  
 8 greater signal. So this differs from the NIH  
 9 consensus statement of the year 2000 by a very  
 10 small amount actually. It's between zero and  
 11 one percent. There are some institutions that  
 12 may still include this as a statement on the  
 13 report, and we are one of them. We do that  
 14 for two reasons. Number one, that statement  
 15 has been made. It has never been changed. It  
 16 has never been -  
 17 COFFEY, Q.C.:  
 18 Q. That's the NIH?  
 19 DR. DABBS:  
 20 A. That's the NIH consensus statement, that's  
 21 correct. And the other issue is that  
 22 patients, cancer patients in particular, are  
 23 very savvy when it comes to investigating  
 24 their own disease, especially on the internet,  
 25 and if one were to find that statement, one

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1 might question as to why a test is--their test  
 2 is called negative when they have 0.5 percent  
 3 cell staining with estrogen receptor. So we  
 4 certainly know, and I've pointed out before,  
 5 and the NIH consensus statement says itself  
 6 that there is a gradation of response,  
 7 depending on the amount of hormone receptor  
 8 present. So with someone with less than one  
 9 percent, the predicted response would be low,  
 10 but nevertheless, there could be a finite  
 11 response and so we report as--we report the  
 12 positive, percent of cells and this actually  
 13 would translate into an H Score, as I said  
 14 before, one percent, one plus the H Score  
 15 would be one, okay.  
 16 Recommendation No. 14, "The  
 17 interpretation of ER assay should include an  
 18 evaluation of both the percent of positive  
 19 tumour cell nuclei and the intensity of the  
 20 staining reaction." I think the intensity of  
 21 the staining reaction is important and I'll  
 22 show you how we report it. Actually, this  
 23 group adopted what we have been reporting at  
 24 Magee-Women's Hospital since the year 2002  
 25 where the percent of cell staining one plus,

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1 the percent of cell staining two plus and the  
 2 percent of cells staining three plus are  
 3 recorded. That's raw data. What we have  
 4 recently begun to do as of about six months  
 5 ago is we convert this into the H Score so  
 6 that there's a numerical value that comes out  
 7 of this. Again, if 100 percent of cells are  
 8 three plus, the H Score is 300. If ten  
 9 percent of cells are two plus, the H Score is  
 10 ten times two, it's 20, okay. If 40 percent  
 11 of cells are one plus, the H Score is 40 times  
 12 one or 40. And you add up all these. This  
 13 plus this, plus that equals the H Score, okay.  
 14 And lastly I show this slide. I think  
 15 that the intensity of staining is one of the  
 16 items that one needs to look at in their assay  
 17 as not just because it's there, but because it  
 18 tells you something about your assay. This,  
 19 the ER assay and no matter what paper you look  
 20 at, whether it's by dextran-coated charcoal  
 21 assay or by the early immunofluorescent  
 22 studies where they were looking at cells with  
 23 immunofluorescence or by immunoperoxidase.  
 24 All of the papers talk about a heterogeneity  
 25 of immunostaining of tumour cell nuclei. If

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1 you look here, these cells that are opaque  
 2 brown, that's a three plus result. You cannot  
 3 see any nuclear staining through it. This is  
 4 negative, okay, that's a negative result,  
 5 that's just pure counterstain, this blue, pale  
 6 blue. This is opaque. So, what's in between?  
 7 Well, we have some that are pale, which would  
 8 probably be considered to be one plus. Then  
 9 we have some that are kind of granular but you  
 10 can still see a little bit of blue through it.  
 11 That's a two plus. So we have zero, one plus,  
 12 two plus, three plus. And you should see that  
 13 in a certain proportion, probably 20 percent  
 14 of all ER cases that you do, you will see this  
 15 kind of heterogeneity. If you don't, it  
 16 suggests that the method you're using is too  
 17 sensitive and what has been described in that  
 18 situation, actually, is all the cells looking  
 19 like this right here or like this and nothing  
 20 in between. And that, in my opinion, is not  
 21 an optimized assay. If you're trying to  
 22 translate the results of one testing into  
 23 another and you're not getting the same  
 24 results, it's not an optimized test. So  
 25 that's what this committee is recommending,

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1 that the reason they're recommending this  
 2 reporting is because they recognize that this  
 3 is the way that tumour cell nuclei should  
 4 stain. And in words, the IHC assay for ER  
 5 should be optimized so that the staining can  
 6 capture this dynamic range in terms of the  
 7 distribution and intensity of staining and the  
 8 level of expression should therefore be a part  
 9 of the interpretative results of these tests.  
 10 And lastly, negative ER results on a  
 11 needle core biopsy should be repeated on the  
 12 surgical excision. At Magee-Women's Hospital,  
 13 and I think at probably most laboratories in  
 14 the States hormone receptors and HER2 are  
 15 performed initially on the core biopsy that  
 16 show cancer. These are specimens that are  
 17 small, they are readily fixed, there is no  
 18 cutting of them required, they still need a  
 19 minimum exposure time to formalin of eight  
 20 hours, the results are usually out the next  
 21 day and the oncologists want to know what  
 22 those results are so that they can begin  
 23 planning therapy even before definitive  
 24 surgery takes place. So if we have a negative  
 25 result for hormone receptors, completely

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1 negative for ER and PR on core biopsy, we want  
 2 to repeat that, even with adequate controls,  
 3 we want to repeat that on the excision  
 4 specimen to make sure that we're not dealing  
 5 with a sampling issue. Because in weakly  
 6 positive cases for hormone receptors you can  
 7 have significant variability from place to  
 8 place in the tumour so that you can have wide  
 9 areas that are completely negative and you can  
 10 have some areas that are weakly positive and  
 11 even some areas that are moderately positive.  
 12 So that's why we will repeat it on a  
 13 representative tumour block from the actual  
 14 surgical excision specimen or mastectomy or  
 15 whatever that would be to make it air tight  
 16 that we're not missing a positive case, okay.  
 17 COFFEY, Q.C.:  
 18 Q. So, Doctor, in relation to that, I take it  
 19 that on a needle core biopsy if it's positive,  
 20 the ER result is positive?  
 21 DR. DABBS:  
 22 A. Yes.  
 23 COFFEY, Q.C.:  
 24 Q. In your institution is it repeated then on the  
 25 surgical excision or is it just treated as

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1 positive?  
 2 DR. DABBS:  
 3 A. It's treated as positive.  
 4 COFFEY, Q.C.:  
 5 Q. Positive.  
 6 DR. DABBS:  
 7 A. We don't repeat it.  
 8 COFFEY, Q.C.:  
 9 Q. And why is that?  
 10 DR. DABBS:  
 11 A. Well, because there's a body of literature  
 12 that clearly shows that there's a very high  
 13 correlation, better than 95 percent, of  
 14 results with what you find on core biopsy  
 15 compared to excision specimens. The few  
 16 percent that don't correlate are usually the  
 17 ones that are negative on a core biopsy that  
 18 end up being focally positive on a resection  
 19 specimen. And so because of that difference,  
 20 that's why we repeat them on negative cores.  
 21 COFFEY, Q.C.:  
 22 Q. Doctor, if we could, please, Doctor, I'd like  
 23 to take you to the section of your  
 24 presentation dealing with "Best Practices,  
 25 IHC, Pre-Analytic Antibody Optimization."

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1 Perhaps you could just kind of look through  
 2 that. It's--and then--okay. Doctor, okay, if  
 3 we just--if you could, please, there's a slide  
 4 entitled "Best Practices, IHC, Pre-Analytic."  
 5 THE COMMISSIONER:  
 6 Q. That would be on page -  
 7 COFFEY, Q.C.:  
 8 Q. No, that's -  
 9 THE COMMISSIONER:  
 10 Q. Page 9 of the exhibit.  
 11 COFFEY, Q.C.:  
 12 Q. Page 9 of the exhibit. No, it's further along  
 13 in the slide presentation itself.  
 14 THE COMMISSIONER:  
 15 Q. Down--there we go.  
 16 COFFEY, Q.C.:  
 17 Q. There we are. Doctor, here if you just go on  
 18 to the next page then--I wanted to ask you,  
 19 and then one more. Wait now, back, I  
 20 apologize, right here. Doctor, looking at the  
 21 matter of "Best Practices, IHC, Pre-Analytic  
 22 Antibody Optimization."  
 23 DR. DABBS:  
 24 A. Yes.  
 25 COFFEY, Q.C.:

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1 Q. I have some questions for you about, you know,  
2 kind of what might happen or what are the  
3 potential effects of failing to optimize.  
4 And, for example, and you've referred to this  
5 already, the idea of diluting antibodies?  
6 DR. DABBS:  
7 A. Yes.  
8 COFFEY, Q.C.:  
9 Q. And so in this whole process antibodies, if  
10 they're not premixed, are diluted at some  
11 point?  
12 DR. DABBS:  
13 A. Yes.  
14 COFFEY, Q.C.:  
15 Q. And what else, what other types of materials  
16 are diluted in this whole process?  
17 DR. DABBS:  
18 A. Well the other items that could be diluted  
19 would be the secondary antibody that is put on  
20 the primary antibody. So it's critically  
21 important that the primary antibody be diluted  
22 properly and it's obviously critically  
23 important that the person who is doing those  
24 dilutions knows how to do them and to do them  
25 with consistent accuracy.

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1 COFFEY, Q.C.:  
2 Q. Doctor, if something is--the primary antibody  
3 is over diluted, what can the effect be?  
4 DR. DABBS:  
5 A. The effect can be that there is a false  
6 negative result.  
7 COFFEY, Q.C.:  
8 Q. And if it's not diluted enough?  
9 DR. DABBS:  
10 A. If it's not diluted enough, the same result  
11 can occur, because there is usually a narrow  
12 window of opportunity for the antibodies to be  
13 properly diluted so that they bind with the  
14 antigen in the tissue properly so that there's  
15 enough antibody and it's distributed equally.  
16 If you don't have enough antibody, that could  
17 be an issue; if you have too much antibody,  
18 that also can be--lead to a false negative  
19 result.  
20 COFFEY, Q.C.:  
21 Q. And we've also heard reference, you've  
22 referred to it and we've heard reference from  
23 others to antigen retrieval times?  
24 DR. DABBS:  
25 A. Yes.

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1 COFFEY, Q.C.:  
2 Q. What can the effect be of leaving--I take it  
3 an optimized antigen retrieval time is a  
4 particular amount of time a particular lab  
5 adopts?  
6 DR. DABBS:  
7 A. It is, it's a particular pH buffer, it's a  
8 particular time of exposure in whatever  
9 heating apparatus. There are lots of heating  
10 apparatuses that are equivalent, so it really  
11 comes down to time, you know, the duration and  
12 intensity, duration and intensity.  
13 COFFEY, Q.C.:  
14 Q. And, Doctor, then I take it then that within  
15 that antigen retrieval process with these  
16 multiple factors involved, that if too much of  
17 something is there, it can create false  
18 negatives?  
19 DR. DABBS:  
20 A. Yes.  
21 COFFEY, Q.C.:  
22 Q. Like too much time?  
23 DR. DABBS:  
24 A. Yes, too much antigen retrieval certainly can  
25 cause a false negative.

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1 COFFEY, Q.C.:  
2 Q. And how about not enough?  
3 DR. DABBS:  
4 A. The same.  
5 COFFEY, Q.C.:  
6 Q. So there are numerous different ways of  
7 arriving at false negatives?  
8 DR. DABBS:  
9 A. Yes. And even with--there are instances where  
10 if you have too much antigen retrieval and  
11 there's a biotin reaction product as a result  
12 of the chromogen, that can actually yield  
13 false nuclear staining that may be interpreted  
14 by the unwary as a positive result for a  
15 nuclear antigen.  
16 COFFEY, Q.C.:  
17 Q. I'm sorry, could you just run that past us  
18 again, Doctor?  
19 DR. DABBS:  
20 A. Sure. If there's--by the ABC, the Abidin-  
21 Biotin Method, if the tissue is over antigen  
22 retrieved, that can give--that can result in  
23 the appearance of these biotin inclusions  
24 within the nucleus. And so if you're looking  
25 for a reaction product such as ER in the

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<p>1 nucleus, this will give a false positive</p> <p>2 result. It's not ER and it's not PR, it's</p> <p>3 biotin. That can be unleashed in the nuclei</p> <p>4 with over antigen retrieval.</p> <p>5 COFFEY, Q.C.:</p> <p>6 Q. But it can appear then through the microscope?</p> <p>7 DR. DABBS:</p> <p>8 A. Yes.</p> <p>9 COFFEY, Q.C.:</p> <p>10 Q. As if it's interpretable staining?</p> <p>11 DR. DABBS:</p> <p>12 A. It'll look just like it.</p> <p>13 COFFEY, Q.C.:</p> <p>14 Q. How do you guard against that, Doctor?</p> <p>15 DR. DABBS:</p> <p>16 A. Well, you have to be cognisant of the fact</p> <p>17 that if you're using an ABC protocol and</p> <p>18 making sure that the antigen retrieval</p> <p>19 duration and intensity falls within the realm</p> <p>20 of what's recommended by the manufacturer, and</p> <p>21 also during your optimization process that you</p> <p>22 obviously won't be seeing that kind of--that</p> <p>23 artifact as false positives in your tissues</p> <p>24 which should be negative, your negative</p> <p>25 controls.</p>	<p>1 DR. DABBS:</p> <p>2 A. I think that it's within the realm to accept</p> <p>3 what is stated on the bottle, but the way of</p> <p>4 testing for that is looking at the protocols</p> <p>5 which are suggested, because that's where you</p> <p>6 should be getting appropriate immuno</p> <p>7 reactivity, and if you're not, then that's</p> <p>8 when you need to take it up with the</p> <p>9 manufacturer. I'm not aware of any way that</p> <p>10 you can go into a pre-dilute and figure out</p> <p>11 what the actual titration concentration is.</p> <p>12 But rather, the proof in the pudding, so to</p> <p>13 speak, would be in the optimization process</p> <p>14 and making sure that what is positive is</p> <p>15 positive and what is negative is negative.</p> <p>16 THE COMMISSIONER:</p> <p>17 Q. Okay.</p> <p>18 COFFEY, Q.C.:</p> <p>19 Q. Doctor, in this matter I'm going to ask you</p> <p>20 about the idea of using in external controls</p> <p>21 for ER and PR testing.</p> <p>22 DR. DABBS:</p> <p>23 A. Um-hm.</p> <p>24 COFFEY, Q.C.:</p> <p>25 Q. I think you referred to already in the slide</p>
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<p>1 COFFEY, Q.C.:</p> <p>2 Q. Doctor, the issue of calibration of equipment</p> <p>3 in this whole process, how important is it?</p> <p>4 DR. DABBS:</p> <p>5 A. The calibration of equipment is critically</p> <p>6 important. It's just, you know, every</p> <p>7 component is critically important and</p> <p>8 especially if one is doing manual procedures</p> <p>9 in terms of making optimal dilutions.</p> <p>10 Calibration of the devices that you use, be</p> <p>11 they pipettes or whatever, has to be done on a</p> <p>12 periodic basis according to prescribed</p> <p>13 protocols and most manufacturers have ways of</p> <p>14 doing that.</p> <p>15 COFFEY, Q.C.:</p> <p>16 Q. Now, Doctor--just a moment, please,</p> <p>17 Commissioner.</p> <p>18 THE COMMISSIONER:</p> <p>19 Q. If you are purchasing premixed from a</p> <p>20 manufacturer, solutions, does--would the lab</p> <p>21 check on the manufacturer's stated solutions</p> <p>22 or do you accept, would it be acceptable in</p> <p>23 the--in your world to accept what is stated on</p> <p>24 the bottle which comes in from the</p> <p>25 manufacturer?</p>	<p>1 presentation that there can be various sources</p> <p>2 for external controls?</p> <p>3 DR. DABBS:</p> <p>4 A. Yes.</p> <p>5 COFFEY, Q.C.:</p> <p>6 Q. And could you just elaborate a bit on that,</p> <p>7 what's appropriate from your perspective in</p> <p>8 terms of deciding what sorts of external</p> <p>9 controls to use?</p> <p>10 DR. DABBS:</p> <p>11 A. I think from my perspective and what I strive</p> <p>12 to do is choose external controls that are</p> <p>13 going to show a dynamic range of reactivity</p> <p>14 with the antibody in question. And so there's</p> <p>15 a variety of tissues that are acceptable for</p> <p>16 that, there cervical, normal cervix,</p> <p>17 exocervix, endocervix, there are ovarian</p> <p>18 tumours, there are even breast tumours. And</p> <p>19 so what I like to use, actually, once I have</p> <p>20 the assay optimized, is I like to find a</p> <p>21 breast cancer that we have in abundance and</p> <p>22 one that shows a dynamic range. And as I--</p> <p>23 with reference to the one slide that I showed,</p> <p>24 I like to choose a tissue section that has</p> <p>25 strong positive, intermediate positive and</p>



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1 weakly positive and some negative, because  
 2 that way it tells me that each time that it's  
 3 placed on the patient's test control slide and  
 4 you look at that, it assures you that your  
 5 dynamic range is operating, that everything is  
 6 operating and hitting on all cylinders, that  
 7 what is strongly positive is decorated, what  
 8 is negative is not and everything in between  
 9 is, you know, variably expressed. That in my  
 10 opinion is the ultimate external control where  
 11 you have the luxury of putting that on every  
 12 slide. And you can find tissue -  
 13 COFFEY, Q.C.:  
 14 Q. Put on every slide, and that is on the same  
 15 slide as the patient tissue?  
 16 DR. DABBS:  
 17 A. Exactly.  
 18 COFFEY, Q.C.:  
 19 Q. Okay.  
 20 DR. DABBS:  
 21 A. Correct.  
 22 COFFEY, Q.C.:  
 23 Q. So it goes through the same process, I take  
 24 it?  
 25 DR. DABBS:

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1 A. Correct.  
 2 COFFEY, Q.C.:  
 3 Q. So it goes through the same process, I take  
 4 it, as -  
 5 DR. DABBS:  
 6 A. Goes through the same process, exactly. It  
 7 also acts as a dispense control, if you will.  
 8 No machine or device is 100 percent  
 9 infallible, so there may be an instance where  
 10 whenever the slide is in a certain position on  
 11 the machine and the antibody is supposed to be  
 12 squirted out, that for some reason it doesn't  
 13 squirt out. Well, you'll know that from your  
 14 external controls when it's negative as your  
 15 test control. And you'll look at that and  
 16 you'll say that's most likely a dispense  
 17 issue, let's repeat it, okay. So it acts in  
 18 that fashion, as well.  
 19 COFFEY, Q.C.:  
 20 Q. And, Doctor, in terms of then the phrase you  
 21 used is variable--sorry, variable--not  
 22 variable intensity, variable -  
 23 MR. SIMMONS:  
 24 Q. Expression.  
 25 COFFEY, Q.C.:

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1 Q. Expression, that's it, thank you, variable  
 2 expression, thank you. For the external  
 3 tissue, external control tissue, this sort of  
 4 variable expression in external control  
 5 tissue, Doctor, I take it, though, that the  
 6 people reading the controls have to understand  
 7 --would have to in order to understand what it  
 8 is they're supposed to be looking for, would  
 9 have to be familiar with the external control  
 10 tissues?  
 11 DR. DABBS:  
 12 A. Yes, most certainly.  
 13 COFFEY, Q.C.:  
 14 Q. In order to understand the sorts of variable  
 15 expression I should be looking for --  
 16 DR. DABBS:  
 17 A. Correct.  
 18 COFFEY, Q.C.:  
 19 Q. They have to be able to identify it in the  
 20 first place?  
 21 DR. DABBS:  
 22 A. Yes.  
 23 COFFEY, Q.C.:  
 24 Q. How do you--I take it as well, Doctor, though,  
 25 that external control tissue has a finite--

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1 there's only a finite amount of it, am I  
 2 correct on that?  
 3 DR. DABBS:  
 4 A. Well, to some degree. I think that every  
 5 pathology laboratory can go through the effort  
 6 of collecting tissues. There are always  
 7 different kinds of tumours available, and even  
 8 if you just look at breast cancers, you know,  
 9 routine processing of tissue, one almost never  
 10 puts the entire tumour through for diagnostic  
 11 purposes. It's just not necessary. So you  
 12 have, you know, a fair amount of left over  
 13 tissue that either go to disposal or you can  
 14 begin to create your own internal tissue bank  
 15 so that you have these paraffin blocks set  
 16 aside for use whenever, and it does take an  
 17 effort on the part of the laboratory, but, you  
 18 know, it's just like controlling for anything  
 19 else, it's like, you know, controls for  
 20 chemistry, for hematology, and what not. It's  
 21 just part of the usual operating procedure for  
 22 the laboratory. So my answer to that is that  
 23 it's really minimal effort, the tissue is  
 24 there, it's just a matter of setting it aside  
 25 and having it available for sectioning and

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1 made into controls.

2 COFFEY, Q.C.:

3 Q. Doctor, during the time frame that the  
4 Commissioner is dealing with, certainly during  
5 most of it, there's been evidence that she's  
6 heard to the effect that for much of it there  
7 were just external controls, one external  
8 control slide being used, certainly no more  
9 than one per ER test, and sometimes there was  
10 one external control slide for two or three  
11 patients ER slides, for example, and she's  
12 also heard that generally the external  
13 controls in that context, they weren't  
14 variable, didn't involve any variety  
15 generally, the approach was to adopt an  
16 external control that stained positive,  
17 strongly positive, in fact, okay.

18 DR. DABBS:

19 A. Uh-hm.

20 COFFEY, Q.C.:

21 Q. If an external control was expected to stain  
22 strongly positive, but it actually stained  
23 weakly, that was the way the pathologist  
24 interpreted it, what, if anything, would that  
25 suggest?

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1 DR. DABBS:

2 A. That would suggest to me that the actual  
3 staining process or pre-analytic phase for  
4 that tissue is probably not optimal because if  
5 you're not getting the proper strong staining  
6 of that, one has to look at the entire  
7 process, and if it's an external control that  
8 previously had been strongly staining, then  
9 you need to look at the actual technicalities  
10 of the staining process itself.

11 COFFEY, Q.C.:

12 Q. And technicalities in this context mean what?

13 DR. DABBS:

14 A. That would mean the antibody concentrations,  
15 the secondary antibody concentrations, the  
16 development process, and everything that we  
17 talked about before.

18 COFFEY, Q.C.:

19 Q. So it would be a signal to make further  
20 inquiries?

21 DR. DABBS:

22 A. Definitely.

23 COFFEY, Q.C.:

24 Q. In a technical sense?

25 DR. DABBS:

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1 A. Yes, it is.

2 COFFEY, Q.C.:

3 Q. Doctor, you've referred to in your  
4 presentation internal controls for ER and PR  
5 testing. Can you tell the Commissioner,  
6 please, about when you first were exposed to  
7 the idea of utilizing internal controls for ER  
8 and PR testing in IHC?

9 DR. DABBS:

10 A. Uh-hm.

11 COFFEY, Q.C.:

12 Q. When were you first exposed to that?

13 DR. DABBS:

14 A. Well, I think I was exposed to that early on,  
15 and by that, I mean probably as far as my  
16 residency goes, I think it was later in my  
17 residency whenever this started to come onto  
18 the scene for immunohistochemistry for ER. It  
19 would have been '84, 1984, 1983.

20 COFFEY, Q.C.:

21 Q. So sometime in the mid 80s?

22 DR. DABBS:

23 A. Mid 80s, yes, and further--and the issue there  
24 was that if there are normal breast elements  
25 present, they will stain to some degree, and

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1 we do know that normal breast elements will  
2 generally have a heterogeneous expression as  
3 well. There will be some that are weak and  
4 some that are very strong, and generally it's  
5 a minority of normal breast epithelium that is  
6 ER positive. So the issue there was if you--  
7 if it was entirely negative, that was  
8 generally a concern about the process and in  
9 the absence of appropriate external controls,  
10 would be a cause to look into why--basically  
11 query as to why these elements should be  
12 staining or not staining, so you have to look  
13 at the staining process.

14 COFFEY, Q.C.:

15 Q. And that was in the early days. As time went  
16 on, Doctor, within your profession where you  
17 practised, did the role of--did the importance  
18 or significance of internal controls to the  
19 whole process change over time or has it  
20 generally remained the same?

21 DR. DABBS:

22 A. I think it's generally remained pretty much  
23 the same. No matter what antigen you're  
24 looking for, if you're looking for--you know,  
25 if you have a tumour and you do a keratin

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1 stain because you want to determine whether  
 2 it's a carcinoma, and there are normal  
 3 epithelial elements there, the normal  
 4 epithelial elements, depending on what keratin  
 5 you're using, should stain to some degree, and  
 6 if they're not, then that becomes an issue.  
 7 Then your internal controls are not working  
 8 properly which suggests that there's something  
 9 inherently wrong with either the pre-analytic  
 10 or analytic phases.  
 11 COFFEY, Q.C.:  
 12 Q. Now today, Doctor, in your laboratory at  
 13 Magee, how are then--how do you understand  
 14 then pathologists handle the issue of internal  
 15 controls for ER/PR, how is it handled now?  
 16 DR. DABBS:  
 17 A. Well, the ER/PR is performed on core biopsies,  
 18 and as I'm sure you're aware, sometimes core  
 19 biopsies of the breast may not contain normal  
 20 elements because the radiologist might hit the  
 21 tumour dead centre and get entirely tumour. We  
 22 do not reject the specimen because of that.  
 23 That's where our external controls become as  
 24 important as an internal control. Our policy  
 25 would be whether or not we had internal

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1 controls, if the tumour is negative, we repeat  
 2 it, and I mentioned that, but in the instance  
 3 where --  
 4 COFFEY, Q.C.:  
 5 Q. I'm sorry, just tell us that again.  
 6 DR. DABBS:  
 7 A. Sure. If we have a core biopsy that is  
 8 entirely negative for ER and PR, that we will  
 9 repeat that regardless of whether there's an  
 10 internal control present or not, positive, for  
 11 purposes of sampling, but for the internal  
 12 control itself, if we have a tissue, a core  
 13 biopsy that does not have an internal control  
 14 on it, we will not reject that specimen. We  
 15 will do the testing and if the result is  
 16 entirely negative, we will just default and  
 17 repeat that on the specimen. If it's  
 18 positive, and we have an adequate external  
 19 control, then we're good, we report that test  
 20 as a test result.  
 21 COFFEY, Q.C.:  
 22 Q. And, of course, in this context that you're  
 23 speaking about now in the present day, these  
 24 external control tissue is actually on the  
 25 patient slide?

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1 DR. DABBS:  
 2 A. Yes.  
 3 COFFEY, Q.C.:  
 4 Q. So it's gone through the same process --  
 5 DR. DABBS:  
 6 A. Right.  
 7 COFFEY, Q.C.:  
 8 Q. As the patient tissue has on the slide.  
 9 Doctor, you're the author of a text relating  
 10 to diagnostic immunohistochemistry. Can you  
 11 tell the Commissioner, please, from your  
 12 perspective--contributing author and editor,  
 13 to get it entirely correct. From your  
 14 perspective, what's your view as to the  
 15 reproducibility and reliability of  
 16 immunohistochemistry if done appropriately?  
 17 DR. DABBS:  
 18 A. Speaking of hormone receptors or in general?  
 19 COFFEY, Q.C.:  
 20 Q. In general first, and then hormone receptors.  
 21 DR. DABBS:  
 22 A. In general, I think that immunohistochemistry  
 23 is a robust test that when performed optimally  
 24 will give very consistent, accurate, and high  
 25 reproducible results. The nature of

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1 immunohistochemistry is that there is a  
 2 literature base upon which there are published  
 3 studies that talk about various clones of  
 4 antibodies and sometimes different techniques,  
 5 detection techniques, some of which are more  
 6 sensitive than others. So there will be some  
 7 variability, though small, if you're looking  
 8 at specific tests, and if you look, for  
 9 example, at estrogen receptor, generally  
 10 speaking those three antibodies that I  
 11 mentioned, the SF11, 1D5, and SP1, are very  
 12 robust antibodies and will give very  
 13 comparable results. Depending on what your  
 14 cutoffs are, that's where you will see your  
 15 variability in determining how much is a  
 16 positive result, but the way that most people  
 17 result them, there's really very little  
 18 variability. I would say, you know, just for  
 19 ER and maybe immunohistochemistry in general,  
 20 is somewhere between 1 in 5 percent if you  
 21 look at variation because of different clones  
 22 of antibody, different detection systems.  
 23 Everything else being equal, the results are  
 24 really small.  
 25 COFFEY, Q.C.:

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<p>1 Q. You mean the differences in results?</p> <p>2 DR. DABBS:</p> <p>3 A. The differences are small and probably no</p> <p>4 different than other very well controlled</p> <p>5 rigorous studies for testing in clinical</p> <p>6 pathology.</p> <p>7 COFFEY, Q.C.:</p> <p>8 Q. Doctor --</p> <p>9 THE COMMISSIONER:</p> <p>10 Q. Sorry, I just want to make sure I got that</p> <p>11 last point. When you're saying that, in</p> <p>12 effect, for IHC in general, and certainly for</p> <p>13 --and for ER, the variation in result which</p> <p>14 you would expect to be observed is really no</p> <p>15 different than the rest of the pathology lab?</p> <p>16 DR. DABBS:</p> <p>17 A. Generally speaking, any process where all of</p> <p>18 these variables that I'm talking about, the</p> <p>19 pre-analytic or highly controlled, yes.</p> <p>20 THE COMMISSIONER:</p> <p>21 Q. So done right?</p> <p>22 DR. DABBS:</p> <p>23 A. Done right, yes.</p> <p>24 THE COMMISSIONER:</p> <p>25 Q. Done right, you really wouldn't put IHC in a</p>	<p>1 moderately distributed, but nevertheless the</p> <p>2 concordance between what you call positive and</p> <p>3 a negative result is 100 percent. So I think</p> <p>4 that immunohistochemistry has come a long way,</p> <p>5 I think that the results are highly robust,</p> <p>6 reproducible and accurate and becoming more so</p> <p>7 for these really critically important</p> <p>8 predictive and prognostic factors, and the CAP</p> <p>9 ASCO guidelines addressed this a couple of</p> <p>10 years ago, and now we're trying to tighten it</p> <p>11 up on this end with the hormone receptor</p> <p>12 testing.</p> <p>13 COFFEY, Q.C.:</p> <p>14 Q. Doctor, from your perspective, is there what</p> <p>15 could be termed an acceptable error rate in</p> <p>16 ER/PR testing, you know, assuming that the</p> <p>17 testing procedure has been optimized? Is</p> <p>18 there any such thing as kind of an acceptable</p> <p>19 error rate, and I say error--one might not</p> <p>20 know which of two tests is the correct?</p> <p>21 DR. DABBS:</p> <p>22 A. I can look at that question in several ways, I</p> <p>23 would think. What threshold would I want in</p> <p>24 our laboratory if we had a repeat rate. I</p> <p>25 would want that to be less than 2 percent, and</p>
<p>Page 205</p> <p>1 class that was any different than the rest of</p> <p>2 the pathology lab?</p> <p>3 DR. DABBS:</p> <p>4 A. No, I would not. In fact, right now there are</p> <p>5 some commercial tests available in the States</p> <p>6 in which they're studied to look at a</p> <p>7 different testing method, RTPCR, Reverse</p> <p>8 Transcriptase PCR reactions for hormone</p> <p>9 receptor testing, and basically what they're</p> <p>10 doing is they're using immunohistochemistry as</p> <p>11 the benchmark, and they're finding very tight</p> <p>12 correlation with that, and these are very</p> <p>13 highly sensitive techniques that rely</p> <p>14 predominantly on messenger RNA, which is</p> <p>15 present in cell cytoplasm. So I think that's</p> <p>16 an attestation to tests that are well done</p> <p>17 will pretty much speak for themselves, and</p> <p>18 just recently we have some data where we</p> <p>19 looked at our results of ER/PR compared to</p> <p>20 external laboratory RTPCR and there's a 100</p> <p>21 percent concordance between test results for</p> <p>22 estrogen receptor. If you plot them out on a</p> <p>23 graphic form, I think the P value was</p> <p>24 something like .51, which means that you can</p> <p>25 draw a line through it. The data points are</p>	<p>Page 207</p> <p>1 we monitor that. WE have a monthly meeting</p> <p>2 where we look at all of those issues, and I</p> <p>3 know that that's what we monitor for</p> <p>4 immunohistochemistry in general. So if we</p> <p>5 starting bumping up to 2 percent or more, then</p> <p>6 we're going to go in and find out exactly</p> <p>7 where it is that the issues are, and it may</p> <p>8 not be IHC itself, it may be tissue lifting</p> <p>9 off a slide or something like that.</p> <p>10 COFFEY, Q.C.:</p> <p>11 Q. I'm sorry, so what is this up to 2 percent,</p> <p>12 what does this refer to, Doctor?</p> <p>13 DR. DABBS:</p> <p>14 A. Well, that's our threshold for looking at</p> <p>15 repeats for immunohistochemistry in our</p> <p>16 laboratory. So if we have--our expected</p> <p>17 repeat rate for immunohistochemistry, in</p> <p>18 general, is under 2 percent.</p> <p>19 COFFEY, Q.C.:</p> <p>20 Q. So the Commissioner understands this, of all</p> <p>21 the tests done in, say, any one month in your</p> <p>22 laboratory --</p> <p>23 DR. DABBS:</p> <p>24 A. Correct.</p> <p>25 COFFEY, Q.C.:</p>

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1 Q. I take it, it is not unknown to have to repeat  
 2 an IHC test?  
 3 DR. DABBS:  
 4 A. Correct.  
 5 COFFEY, Q.C.:  
 6 Q. That's not unusual.  
 7 DR. DABBS:  
 8 A. Right.  
 9 COFFEY, Q.C.:  
 10 Q. But you keep track of--your laboratory does,  
 11 how often that happens per month?  
 12 DR. DABBS:  
 13 A. Yes.  
 14 COFFEY, Q.C.:  
 15 Q. And if the rate of repeating hits 2 percent,  
 16 there are questions asked and inquiries made?  
 17 DR. DABBS:  
 18 A. Exactly.  
 19 COFFEY, Q.C.:  
 20 Q. Why is that, Doctor?  
 21 DR. DABBS:  
 22 A. Well, I think it's a reflection of good  
 23 practice and that you want to know what it is  
 24 that's being repeated and what it is that's  
 25 starting to bump up against that figure. It

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1 may be something that's actually unrelated to  
 2 the immunohistochemistry staining procedure  
 3 itself, it might be related to tissue lifting  
 4 off a slide for some reason. You know,  
 5 perhaps a new histo technician who is on board  
 6 who may not have followed procedure completely  
 7 and didn't bake the slides long enough. I'm  
 8 just making up an example.  
 9 COFFEY, Q.C.:  
 10 Q. Sure.  
 11 DR. DABBS:  
 12 A. So you're wondering why that is, and so that's  
 13 how we get to keep our finger on the pulse of  
 14 testing and issues related to it because we  
 15 want to be able to act proactively as soon as  
 16 we can if we see something like that  
 17 happening. I think it's good practice.  
 18 COFFEY, Q.C.:  
 19 Q. Doctor, the Commissioner has heard evidence,  
 20 of course, about--much evidence about what has  
 21 been phrased "conversions" here in this  
 22 matter. Doctor, several questions in this  
 23 regard. From your perspective, what could  
 24 account for or what might potentially account  
 25 for a patient who is originally--upon

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1 originally being tested, okay, for ER and PR,  
 2 in particular we'll use ER right now, a  
 3 patient who when originally tested for ER was  
 4 classified as a no expressor, zero percent,  
 5 and on retesting became what I'll refer to as  
 6 a high expressor, which as I say, I'll pick a  
 7 figure, 80 percent or 90 percent, using the  
 8 same block, albeit done in two different  
 9 laboratories, what could account for the  
 10 difference?  
 11 DR. DABBS:  
 12 A. I think it's probably safe to say that the one  
 13 thing that would not account for it would be  
 14 tissue fixation because if you're going from a  
 15 negative to--would be a strong positive  
 16 result, it's most certainly--almost certainly  
 17 not tissue fixation, but rather technique, and  
 18 by technique, I mean, this could be anywhere  
 19 from all the steps that I demonstrated.  
 20 Initial--the concentration, the tighter of  
 21 antibody, if that is not done correctly,  
 22 you're going to end up with a negative result.  
 23 COFFEY, Q.C.:  
 24 Q. In the original --  
 25 DR. DABBS:

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1 A. In the original lab, which when properly done  
 2 in another lab will show up as strongly  
 3 positive. It's not going to be related to  
 4 antibody clone because the clones that are out  
 5 there now are all fairly robust and very  
 6 comparable, so that's not going to be a cause  
 7 for it.  
 8 COFFEY, Q.C.:  
 9 Q. It wouldn't account for a low--no expressor to  
 10 a high expressor?  
 11 DR. DABBS:  
 12 A. Correct, no, it would not. So here we're  
 13 talking about technique. We're talking about  
 14 probably, you know, tighter of antibody would  
 15 be a crucial component, again a proper  
 16 dehydration and de-paraffinization, and, of  
 17 course, antigen retrieval is crucial there as  
 18 well. If antigen retrieval techniques are  
 19 comparable in this situation that you're  
 20 telling me, then we're really pointing all  
 21 fingers towards the initial antibody dilution  
 22 being improper and giving an original negative  
 23 result, which then when properly diluted, will  
 24 give you the appropriate result.  
 25 COFFEY, Q.C.:

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<p>1 Q. And that, of course, assumes that the antigen 2 retrieval methods --</p> <p>3 DR. DABBS:</p> <p>4 A. Are comparable.</p> <p>5 COFFEY, Q.C.:</p> <p>6 Q. And if they're not, if there are any one or 7 more deficiencies in that in the original 8 laboratory, it could account for a no 9 expressor to a high expressor in the retest 10 lab?</p> <p>11 DR. DABBS:</p> <p>12 A. Yes, correct, and, you know, it's not just 13 about heat and duration, but it's also about 14 buffers. So if the buffer calls for basic pH, 15 but it's being done in an acetic pH, that 16 would obviously be a huge defect that could 17 account for a false negative.</p> <p>18 THE COMMISSIONER:</p> <p>19 Q. Doctor, you said it's not going to be related 20 to antibody clone?</p> <p>21 DR. DABBS:</p> <p>22 A. Right.</p> <p>23 THE COMMISSIONER:</p> <p>24 Q. Because these things are quite standard, as I 25 understand?</p>	<p>1 percent, to what I'll refer to as a low 2 expressor, say, you know, somewhere in the low 3 1 to 10.</p> <p>4 DR. DABBS:</p> <p>5 A. Yes.</p> <p>6 COFFEY, Q.C.:</p> <p>7 Q. Or perhaps 1 to 15, and going from zero to a 8 relatively low number --</p> <p>9 DR. DABBS:</p> <p>10 A. Yes.</p> <p>11 COFFEY, Q.C.:</p> <p>12 Q. Zero in the original lab, St. John's in this 13 case, and Mount Sinai perhaps reports it at 5 14 or 10.</p> <p>15 DR. DABBS:</p> <p>16 A. Yes.</p> <p>17 COFFEY, Q.C.:</p> <p>18 Q. What could account for that?</p> <p>19 DR. DABBS:</p> <p>20 A. I think the exact same issues that I just 21 mentioned could account for it. There's 22 another--this particular scenario also raises 23 the possibility of primary poor fixation as 24 well that may not have been picked up with as 25 sensitive a technique locally, and--but when</p>
<p>Page 213</p> <p>1 DR. DABBS:</p> <p>2 A. They're fairly standard and fairly robust, and 3 typically what does not happen is you go from 4 a negative to a strong positive with any one 5 antibody.</p> <p>6 THE COMMISSIONER:</p> <p>7 Q. And would you say that same thing of the full 8 time period between 1997 and 2005?</p> <p>9 DR. DABBS:</p> <p>10 A. Yes.</p> <p>11 COFFEY, Q.C.:</p> <p>12 Q. And the clones you're talking about are 125 --</p> <p>13 DR. DABBS:</p> <p>14 A. 25 and 6F11 were the prevalent clones at that 15 time, yes.</p> <p>16 COFFEY, Q.C.:</p> <p>17 Q. And the Commissioner has heard evidence that 18 they are the two really in play here, I 19 understand.</p> <p>20 DR. DABBS:</p> <p>21 A. Right, the SP1 is a more recent addition 22 within the last two to three years.</p> <p>23 COFFEY, Q.C.:</p> <p>24 Q. Doctor, in effect, the same question, but in 25 relation to going from a no expressor, zero</p>	<p>Page 215</p> <p>1 properly performed assay comes out to a weakly 2 positive result elsewhere, so I could not 3 exclude primary tissue fixation as being 4 another variable. That might be an issue 5 there.</p> <p>6 COFFEY, Q.C.:</p> <p>7 Q. And this would be under or over fixation?</p> <p>8 DR. DABBS:</p> <p>9 A. Under.</p> <p>10 COFFEY, Q.C.:</p> <p>11 Q. Under fixation initially?</p> <p>12 DR. DABBS:</p> <p>13 A. Yes.</p> <p>14 COFFEY, Q.C.:</p> <p>15 Q. So what is a less than optimally fixed tissue, 16 an under fixed tissue, particularly if the 17 tissue inherently is a low expressor --</p> <p>18 DR. DABBS:</p> <p>19 A. Yes.</p> <p>20 COFFEY, Q.C.:</p> <p>21 Q. Then using less than optimized techniques in 22 the initial hospital, you might get zero --</p> <p>23 DR. DABBS:</p> <p>24 A. Yes.</p> <p>25 COFFEY, Q.C.:</p>

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1 Q. At least available to what the pathologist  
2 could see --

3 DR. DABBS:

4 A. Yes.

5 COFFEY, Q.C.:

6 Q. But run under optimal conditions using an  
7 optimal process on retest, the low expressor  
8 would properly low express despite the  
9 fixation problems?

10 DR. DABBS:

11 A. Correct, and even then the tissue may, in  
12 fact, be properly fixed, but it's a matter  
13 again of the technique. So it may just be a  
14 technique, it may be antibody dilution,  
15 antigen retrieval.

16 COFFEY, Q.C.:

17 Q. Doctor, what about a situation where the  
18 initial test showed the result was interpreted  
19 of what would fall into the category of being  
20 a low expressor, between 1 and 10, for  
21 example, becoming a high expressor on  
22 retesting, what could account for that, for  
23 example, something was originally reported as  
24 five and on repeat is--on retesting is  
25 reported as 95?

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1 DR. DABBS:

2 A. Again I think it's safe to say in that  
3 situation that the primary tissue fixation is  
4 probably all right, that it's about technique  
5 and once again falls back to antibody dilution  
6 or second antibody dilution antigen retrieval,  
7 the technique.

8 COFFEY, Q.C.:

9 Q. Doctor, I'll ask you this, and I point out,  
10 Commissioner, that just listening recently to  
11 Dr. Denic on the four retro converters, he  
12 attributed those to interpretation issues, but  
13 leaving that aside for the moment, Doctor, I'm  
14 going to ask you about particular  
15 potentiality, okay. What is in the original  
16 test reported as a low expressor, or fall into  
17 the low expressor category between 1 and 10,  
18 upon retesting going to zero, retesting in a  
19 second laboratory, the same block, is there  
20 anything that could account for that that you  
21 can think of, assuming that the second  
22 laboratory's technique is optimized, and  
23 perhaps the first laboratory may or may not be  
24 optimized?

25 DR. DABBS:

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1 A. Yes, yes.

2 COFFEY, Q.C.:

3 Q. Is there anything that could account for it?

4 DR. DABBS:

5 A. Well, I think that there are two issues that  
6 come to mind. One would be, of course,  
7 whenever you start cutting through a paraffin  
8 block, two things happen. One is you get  
9 somewhat of a different sample. So if you're  
10 going from something which is weak to begin  
11 with, you may cut into--cut a little deeper  
12 and get an area that's entirely negative,  
13 okay. Another would be if that tissue were  
14 not optimally fixed up front and, say,  
15 perceived far less than what is considered to  
16 be the best nowadays, the tissue up front gave  
17 a weak result, and with time with that tissue  
18 sitting in paraffin, it degenerated even  
19 further, okay. So when you cut it, you will  
20 get a negative result. So this is the two  
21 chief things that I can think of.

22 COFFEY, Q.C.:

23 Q. Just on that point, Doctor, because that's  
24 something that I stand to be corrected, I  
25 don't believe it's been raised here before,

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1 before the Commissioner, less than optimal  
2 fixing, under fixing --

3 DR. DABBS:

4 A. Uh-hm.

5 COFFEY, Q.C.:

6 Q. What happens after--what can potentially  
7 happen to that tissue after it goes into the  
8 paraffin block? What, if anything, is still  
9 going on or potentially could go on within the  
10 tissue itself in the paraffin block?

11 DR. DABBS:

12 A. Yes, I think that with--well, with something  
13 that's been less than optimally fixed,  
14 probably the initial sections that come off  
15 that block are probably going to be the best  
16 fixed of the lot, if you will, because  
17 generally formalin penetrates into tissue at  
18 the rate of 1 millimetre per hour. So if  
19 you're assuming that it got at least, you  
20 know, an hour or one to three hours, somewhere  
21 around two to three millimetres of that whole  
22 thickness will have seen some formalin, and be  
23 less than optimally fixed. So it wouldn't be  
24 surprising if you got a weak result there, but  
25 as you penetrate deeper into that, it's even

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<p>1 more poorly fixed or not fixed at all. So</p> <p>2 once you start slicing into that tissue</p> <p>3 further, you're going to be getting tissue</p> <p>4 that's even less well fixed, and material</p> <p>5 that's not fixed. So it's not going to be an</p> <p>6 easy--it's not going to be easy to obtain any</p> <p>7 result from that. What actually happens to</p> <p>8 it, it's in paraffin, it's likely to--it's not</p> <p>9 likely to degenerate any further, but if it's</p> <p>10 only been in formalin for a very short period</p> <p>11 of time, it's not raw tissue, but it's not</p> <p>12 fixed tissue either.</p> <p>13 COFFEY, Q.C.:</p> <p>14 Q. Doctor, can you tell the Commissioner, please</p> <p>15 --I'm going to ask you some things from your</p> <p>16 perspective kind of the practicalities of the</p> <p>17 ER/PR testing process as a pathologist.</p> <p>18 Doctor, if you are asked for a particular--I</p> <p>19 appreciate in your institution you're using</p> <p>20 generally needle core biopsies.</p> <p>21 DR. DABBS:</p> <p>22 A. Yes.</p> <p>23 COFFEY, Q.C.:</p> <p>24 Q. So--but as well I'll ask you to address your</p> <p>25 mind to the idea of using excisional biopsies</p>	<p>1 presence of tissue that could form an internal</p> <p>2 control have any relevance?</p> <p>3 DR. DABBS:</p> <p>4 A. Yes, it would. You would want to choose a</p> <p>5 block that has normal tissue on it, and--</p> <p>6 along with tumour. One of the new</p> <p>7 recommendations is that if you want to--it</p> <p>8 might be optimal to take a portion of normal</p> <p>9 breast and put it in the same block so that</p> <p>10 you're assured of having that somewhere, but</p> <p>11 in most cases where there's tumour, you can</p> <p>12 always take a section that has adjacent normal</p> <p>13 breast tissue.</p> <p>14 COFFEY, Q.C.:</p> <p>15 Q. Doctor, so you've chosen the most appropriate</p> <p>16 block in your approach and it's sent off to be</p> <p>17 processed and you get your slides back.</p> <p>18 Doctor, can you tell us, please, in what sorts</p> <p>19 of circumstances in relation to an ER and PR</p> <p>20 test would you cause them to be repeated--</p> <p>21 what would cause you -</p> <p>22 DR. DABBS:</p> <p>23 A. To be repeated?</p> <p>24 COFFEY, Q.C.:</p> <p>25 Q. Yes.</p>
<p>1 as well. When you go looking for which block</p> <p>2 to utilize for a patient, how do you go about</p> <p>3 it, what thought process do you bring to it?</p> <p>4 DR. DABBS:</p> <p>5 A. Sure. I think first of all you have to look</p> <p>6 at the entire case, so you will have looked at</p> <p>7 all of the slides, and then you will want to</p> <p>8 pull one that is representative of the tumour,</p> <p>9 and generally the morphology of breast cancer</p> <p>10 is they tend to have a reasonable fidelity</p> <p>11 from block to block, although on occasion you</p> <p>12 will find tumours that are mixed, that are in</p> <p>13 some areas better differentiated or less</p> <p>14 differentiated, so you want to try to choose a</p> <p>15 block that has something that representative</p> <p>16 of the entire tumour, especially areas that</p> <p>17 are of better differentiation, if you will,</p> <p>18 because we know by morphology the tumours that</p> <p>19 have better differentiation are more likely to</p> <p>20 be ER positive, and that's what it's really</p> <p>21 all about, trying to determine if the patient</p> <p>22 is ER positive. So that's the basis you would</p> <p>23 choose the block.</p> <p>24 COFFEY, Q.C.:</p> <p>25 Q. And, Doctor, in relation to that, is the</p>	<p>1 DR. DABBS:</p> <p>2 A. Well, given that there's normal control tissue</p> <p>3 on it, if the normal control tissue was not</p> <p>4 staining at all, if the tissue was somehow</p> <p>5 lost anywhere as a result of either poor</p> <p>6 dehydration or poor drying such that the</p> <p>7 tissue was lifted up or part of it was</p> <p>8 missing, if there was any aberrant staining</p> <p>9 that couldn't be explained, and by that, I</p> <p>10 mean, cytoplasm or other components of tissue</p> <p>11 staining that shouldn't be staining. In other</p> <p>12 words, tissues that should be negative that is</p> <p>13 staining positive, like fat and stroma,</p> <p>14 inflammatory cells, things like that. And of</p> <p>15 course, if the morphology is such that given</p> <p>16 everything else is working and the tumour</p> <p>17 which may be well differentiated, typical high</p> <p>18 expressor is negative, that would be cause for</p> <p>19 concern and for a repeat.</p> <p>20 COFFEY, Q.C.:</p> <p>21 Q. Now in this context then, a typical high</p> <p>22 expressor, what are you referring to there?</p> <p>23 DR. DABBS:</p> <p>24 A. Well, those are tumours that would be well</p> <p>25 differentiated adenocarcinomas. They</p>



<p style="text-align: right;">Page 224</p> <p>1 typically are Nottingham score, Nottingham 2 grade one. They would include things like 3 tubular cancers, classical papillary cancers, 4 and other tumours such as lobular carcinomas, 5 invasive lobular carcinomas. Also, looking at 6 the comparable in situ components of these 7 diseases, ductal carcinoma in situ of low 8 grade, lobular carcinoma in situ of classical 9 type. They're all high expressors uniformly, 10 and so if something like that came negative, 11 especially in the face of a negative control, 12 that would be a red alert to stop and have 13 this repeated and in fact, look at the entire 14 batch run for that day, and then go from there 15 and process that problem.</p> <p>16 COFFEY, Q.C.:</p> <p>17 Q. So bearing in mind the histology then, from 18 having--and by that point determined, from 19 your perspective, what the histology was 20 suggesting to you about the type of tumour it 21 was, you'd bear that in mind and compare that 22 to--and your expectations accordingly, with 23 what you were seeing on the slide?</p> <p>24 DR. DABBS:</p> <p>25 A. Yes, indeed.</p>	<p style="text-align: right;">Page 226</p> <p>1 well differentiated and in their classic form, 2 they're virtually all positive. Lobular 3 carcinomas, while not being classified as a 4 special type of ductal cancer, because it's 5 not a ductal cancer, is virtually always 6 positive for ER and that's--you know, that's 7 part of what I learned in my residency, and so 8 given the correlation of studies that 9 subsequently occurred with that, the histology 10 and whatnot, it all sort of made sense that 11 there's tumours that are well differentiated 12 or most like normal are in fact going to 13 express ER.</p> <p>14 COFFEY, Q.C.:</p> <p>15 Q. Doctor, I'd like to show you some documents. 16 Doctor, before I do that, there was another 17 exhibit that we'd entered today. It's Exhibit 18 P-2629. It's entitled "Comparison of 19 Evaluations for Hormone Receptors in Breast 20 Carcinoma using two manual and three automated 21 immunohistochemical assays." Go into this, 22 Doctor, I believe you had asked that this be 23 entered.</p> <p>24 DR. DABBS:</p> <p>25 A. Yes.</p>
<p style="text-align: right;">Page 225</p> <p>1 COFFEY, Q.C.:</p> <p>2 Q. And lobular invasive, invasive lobular should 3 be, more often than not, most often, positive?</p> <p>4 DR. DABBS:</p> <p>5 A. Yes.</p> <p>6 COFFEY, Q.C.:</p> <p>7 Q. And if it doesn't, the slide is not appearing 8 positive to you, the tissue, patient's tumour 9 tissue, you would cause questions to be asked 10 about that?</p> <p>11 DR. DABBS:</p> <p>12 A. That would be a deep concern, yes.</p> <p>13 COFFEY, Q.C.:</p> <p>14 Q. Doctor, in relation to that, I mean, these 15 various classes, what you've referred to as 16 typically high expressors, Doctor, when did 17 you first become aware of that, and adopt that 18 sort of approach? How far back in your career 19 does that go?</p> <p>20 DR. DABBS:</p> <p>21 A. Well, I think, as a resident, when we were 22 looking at these cases, it became clear that 23 there were subsets of tumours which we call 24 special types and these include tubular, 25 papillary, mucinous variance. These were all</p>	<p style="text-align: right;">Page 227</p> <p>1 COFFEY, Q.C.:</p> <p>2 Q. Can you tell us, please, about this?</p> <p>3 DR. DABBS:</p> <p>4 A. Yes, actually, I was a reviewer for this 5 paper. This paper came to me because I'm on 6 the editorial board of American Journal of 7 Clinical Pathology, and I was intrigued by it 8 because it was really the first paper that I 9 had run across that actually compared 10 different platforms, very different platforms, 11 including manual assays, and this paper 12 included products by Biogenics, by DAKO and by 13 Ventana, and you know, basically, if you 14 scroll down the paper to the point of the 15 tables that are illustrated here, I think 16 you'll get a feel for the general robustness 17 of the immunostaining platforms and, you know, 18 they have here, for example, over here, the 19 Biogenics, manual versus automated, and over 20 here, the codes for the DAKO manual, DAKO 21 automated and Ventana automated, and the 22 charts are really very comparable, if you look 23 at the incidents of positive cases, the 24 intensity of cases.</p> <p>25 So while they did demonstrate some</p>

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<p>1 variations in intensity and proportion of cell 2 staining, they really were not dramatically 3 different. These--I thought that one thing 4 that this paper showed and the reason why it 5 caught my eye, as a reviewer, is because it 6 does attest to the antibodies that are used 7 and their robustness. You can use different 8 platforms. When properly assayed, they turn 9 out to be very favourable and there really 10 aren't going to be any disastrous differences 11 in the way the test results are reported. So 12 the concordance between the different groups 13 were good and, you know, if you look at this 14 table here, the distribution of total scores, 15 you know, as you just sort of glance across 16 those, you'll see while there are differences 17 in scores, but they're not dramatically 18 different. There's nothing that's really 19 turning out to be negative where the other 20 methods are showing positive and whatnot. So 21 that an attestation in my view of the 22 robustness of this antibody group, and I think 23 the clones that they use in here for DAKO is 24 1D5, for the Ventana was 6F11, and the 25 Biogenics, I forget exactly what clone it is.</p>	<p>1 cursory way, and as well here, Doctor, there 2 is, on page four of this, there's--and into 3 page five and six, immunohistochemical 4 staining of steroid receptors. It reads 5 "correlation with biochemistry" and then five, 6 and then goes on down into page six, at that 7 time, and actually, I believe, 19 ER cases and 8 17 PR looked at. 9 Doctor, and again, just perhaps to try 10 and put this in perspective for the 11 Commissioner, your own practice as a 12 pathologist covers the bridge time between 13 biochemical assay being routinely used and IHC 14 ER/PR? 15 DR. DABBS: 16 A. Yes, it does. 17 COFFEY, Q.C.: 18 Q. Okay. Doctor, based upon your observations, 19 and I think most, if not all your professional 20 life, has been in the United States? 21 DR. DABBS: 22 A. Yes. 23 COFFEY, Q.C.: 24 Q. What, if anything, did you observe about what 25 would happen when institutions moved from</p>
<p>Page 229</p> <p>1 It's in here somewhere. But that was the key 2 point that I wanted to make, that it's 3 generally a robust assay and it's hard to-- 4 when properly performed, it's hard to steer it 5 wrong. 6 COFFEY, Q.C.: 7 Q. Doctor, if we could bring up, please, Exhibit 8 P-1850? Now Doctor, this is a memorandum that 9 was written back on February, dated February 10 16th, 1998, by Dr. Mahmoud Khalifa. The 11 reference is "reporting of estrogen and 12 progesterone receptor immunohistochemical 13 results" and the Commissioner has heard 14 evidence that, in fact, this was sent to all 15 pathologists throughout Newfoundland at the 16 time, and in effect, at the time, if you read 17 down through it, he says "it has been 18 suggested that assessment of ER/PR status, 19 invasive breast carcinoma, be performed IHC on 20 formalin fixed paraffin embedded tissues," and 21 before that, and in fact, up to that point in 22 time, there'd been a biochemical assay 23 approach utilized in Newfoundland, Doctor. 24 So Doctor, I believe you've had an 25 opportunity to at least review this in a</p>	<p>Page 231</p> <p>1 biochemical assays to ER/PR IHC testing? Was 2 there correlations done? How extensive, or 3 correlations not done, and just started up? 4 What were your observations? 5 DR. DABBS: 6 A. Yes. Well, I think some of the early papers, 7 in fact beginning with that very first paper 8 by Perchuck where they looked at 9 immunofluorescence, they made a comment. It 10 was almost--it wasn't quite an afterthought, 11 but they obviously did compare their results 12 with the DCC and said that cases that were 13 deemed to be positive by DCC were ten percent 14 or more positive cells by immunofluorescence, 15 and that was sort of like the shot across the 16 bow, the first time that that had ever been 17 reported as such. But as you look at the 18 papers throughout that were subsequently 19 reported, every one seemed to gravitate to ten 20 percent. Some of them clearly stated that 21 they used ten percent as an arbitrary cut off. 22 The other paper by Perchuck, in 1996, 23 where they looked at the 1D5, actually with 24 outcome, and they used a ten percent cut off 25 and said that this, you know, the patient</p>

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1 correlation with outcome was better with the  
 2 1D5 antibody at ten percent than it was with  
 3 the dextran-coated charcoal method. One year  
 4 before that, Mascarelli, using the 1D5, did an  
 5 outcome study where they arbitrarily chose  
 6 five percent and ten percent, and both of the  
 7 outcomes of those patients was very good with  
 8 endocrine therapy, suggesting that you could  
 9 even go below ten percent with that. So if  
 10 you look throughout the history, you will find  
 11 that ten percent seemed to be a gravitational  
 12 number by which people gravitated to.  
 13 Now one of the things that pathologists  
 14 need to be aware of is whenever they see  
 15 results like this, they need to pay attention  
 16 to what is the paper exactly talking about?  
 17 What's the clone that they're using? What's  
 18 the method they're using? Because if you're  
 19 using their clone and their method, then you  
 20 have the right to use their cut off. But if  
 21 you're using a different clone and a different  
 22 method, you have no right to use that cut off,  
 23 because it hasn't been validated with an  
 24 outcome.  
 25 COFFEY, Q.C.:

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1 Q. So in terms of then the idea of, for example,  
 2 here, there's 30 percent. Dr. Khalifa does  
 3 not say he advocates 30 percent. There's no--  
 4 he's actually testified here and when you read  
 5 this carefully, he says it's only a  
 6 suggestion, suggestion in terms of even the  
 7 manner in which it was to be reported. But  
 8 here, on page three, there are examples.  
 9 Example two says comment, "evidence from the  
 10 available literature indicates that estrogen  
 11 receptor immuno-reactivity detected in less  
 12 than 30 percent of neoplastic cells would most  
 13 likely correspond to a negative result in a  
 14 biochemical assay of the same specimen.  
 15 American Journal of Surgical Pathology in  
 16 1990." Okay. Have you had a chance to look  
 17 at that, Doctor?  
 18 DR. DABBS:  
 19 A. I did look at that paper and, you know, the  
 20 issue--I don't believe that what is actually  
 21 stated here accurately reflects the content of  
 22 that paper. The paper actually looked at--it  
 23 looked at the dextran-coated charcoal method  
 24 and the immunohistochemistry assay of a  
 25 monoclonal antibody against 17 beta estradiol,

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1 which is not an estrogen receptor protein.  
 2 It's the hormone that's number one that they  
 3 were looking at. Number two, what they looked  
 4 at, this 30 percent number, was something that  
 5 they obtained by looking at what is called a  
 6 receiver operator curve and what that is, it's  
 7 an ordinate and abscissa, okay, an X and a Y  
 8 axis, and depending on how this curve looks,  
 9 it tells you about the sensitivity and  
 10 specificity. Simply put, the best test, a  
 11 best test theoretically, would be 100 percent  
 12 sensitive and 100 percent specific, okay, and  
 13 that curve, you wouldn't be able to see  
 14 because it would be the ordinate and the  
 15 abscissa, okay. For something that's less  
 16 than that, it's going to sort of be like a  
 17 parabolic arc, okay, and the worse the  
 18 sensitivity and specificity, the smaller that  
 19 curve will be. The better the sensitivity and  
 20 specificity, the highest area under that  
 21 curve, the higher area of that curve.  
 22 So what they looked at was they compared  
 23 the percent of cells that are positive by  
 24 immunohistochemistry with the ROC for the  
 25 assay. There was no outcome related in that

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1 study whatsoever. And they said whenever we  
 2 consider, if we consider the 30 percent  
 3 positive immunohistochemistry cells are, then  
 4 our test has this sensitivity and specificity.  
 5 That's all that said. It didn't recommend it  
 6 as a cutoff, there was no outcome associated  
 7 with it. So I have trouble with this  
 8 statement saying that "Immunoreactivity  
 9 detected in less than 30 percent of neoplastic  
 10 cells most like correspond to a negative  
 11 result." That's not what the paper said. The  
 12 paper said at 30 percent cutoff, that they had  
 13 optimal sensitivity and specificity for the  
 14 test is what it meant. And again, there was  
 15 no outcome associated with that.  
 16 COFFEY, Q.C.:  
 17 Q. Doctor, here Dr. Khalifa does--I'll just go  
 18 back up here, refer to, on the first page here  
 19 of the memo, the second paragraph, he said,  
 20 "The division of pathology of the Health Care  
 21 Corporation of St. John's has been applying  
 22 this technology" which would be the IHC  
 23 formalin fixed paraffin embedded tissue, "for  
 24 over a year. Recent audits correlating IHC  
 25 with biochemical results in selected specimens

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1 for both techniques have been running parallel  
 2 have shown high accuracy in the introduced IHC  
 3 detection. The results of these audits have  
 4 been discussed in several meetings and are  
 5 available for review." And we understand that  
 6 the fourth, fifth, and sixth pages of this  
 7 particular document reflect that review.  
 8 Doctor, in introducing something, like in  
 9 moving, for example, from a biochemical assay  
 10 to IHC on paraffin embedded tissue, comparing  
 11 the results, like, for example, 17 and 19  
 12 cases, I mean, what kind of--in your view  
 13 would that be enough, could you do with fewer  
 14 or should you use more?  
 15 DR. DABBS:  
 16 A. Between 17 and 19 case?  
 17 COFFEY, Q.C.:  
 18 Q. Well, yes, here is--because if you actually  
 19 look at them, you count them up.  
 20 DR. DABBS:  
 21 A. Yes.  
 22 COFFEY, Q.C.:  
 23 Q. Okay. He says these are ones with 100 percent  
 24 concordant cases, agreement on both receptors,  
 25 which has those there. And you can kind of

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1 look down through them, it's -  
 2 DR. DABBS:  
 3 A. Yes.  
 4 COFFEY, Q.C.:  
 5 Q. And on through them. And then on to the next  
 6 page, and 100 percent concordant cases agree  
 7 on both receptors and then 50 percent  
 8 concordant cases, agreement in only one  
 9 receptor. And then when you look at kind of--  
 10 this is a table.  
 11 DR. DABBS:  
 12 A. Right.  
 13 COFFEY, Q.C.:  
 14 Q. A spreadsheet, in effect. And what I wanted  
 15 to ask you about really is is the idea of  
 16 utilizing, for example, a sampling of by  
 17 comparison correlation of less than 20 in  
 18 introducing such a new technique, you know, in  
 19 comparison to one that you've been utilizing  
 20 and relying upon?  
 21 DR. DABBS:  
 22 A. Sure.  
 23 COFFEY, Q.C.:  
 24 Q. Would 20 be enough?  
 25 DR. DABBS:

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1 A. For something like this, no, I think that  
 2 you'd probably want to get at least something  
 3 like 50. And again, I don't know that there  
 4 really were any good guidelines back at that  
 5 time to, you know, say how many do I need to  
 6 do a correlational study. But this is a  
 7 pretty small sample. The other aspect, I  
 8 think, that as I recall from this, is that the  
 9 cutoffs for the Ligand Binding assay were a  
 10 little on the--were higher than what I was  
 11 used to seeing. I think it was this, that was  
 12 the immunohis--biochemical assay, yeah. The  
 13 biochemical reporting typically in the States  
 14 was reported at less than three was a negative  
 15 result, above that was a positive result. So  
 16 these are probably comparable here. But they  
 17 really weren't broken down as from three to 20  
 18 is equivocal, that was considered to be a  
 19 positive result, is positive.  
 20 COFFEY, Q.C.:  
 21 Q. Okay, just in your experience in the US?  
 22 DR. DABBS:  
 23 A. Yes. And all--yes. And in the early papers  
 24 and the papers on DCC following the paper by  
 25 McGuire where he used a three cutoff, everyone

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1 else pretty much adopted what he did, as well.  
 2 On occasional paper it might go up to ten, but  
 3 generally it was for most, probably the most  
 4 frequent number that I had seen was three for  
 5 the DCC.  
 6 THE COMMISSIONER:  
 7 Q. Mr. Coffey, wherever you can find a convenient  
 8 spot, we'll take the afternoon break.  
 9 COFFEY, Q.C.:  
 10 Q. Now would be convenient, actually,  
 11 Commissioner.  
 12 THE COMMISSIONER:  
 13 Q. All right, then.  
 14 COFFEY, Q.C.:  
 15 Q. Then we'll go on to something.  
 16 THE COMMISSIONER:  
 17 Q. We'll take a few moments.  
 18 (RECESS)  
 19 COFFEY, Q.C.:  
 20 Q. Doctor, before we leave Exhibit P-1850,  
 21 Doctor, now the paper reference by O'Keane, by  
 22 Doctor, I'm sorry, Khalifa, O'Keane's paper of  
 23 1990, Doctor, by 1998 in terms of the idea of  
 24 cutoffs for ER and PR results, percentage of  
 25 results, by 1998 what other papers existed in

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<p>1 terms of the percentages that they suggested,  2 you know, had appropriate relevance to, for  3 example, clinical outcomes in comparison to  4 other sorts of testing? Could you just tell  5 us, you referred to them, some of them  6 already, but I'd like you to kind of list them  7 for the Commissioner again?  8 DR. DABBS:  9 A. Sure. Well, the--sure. Two of the key papers  10 that came out in the mid '90s, one was by  11 Mascarelli in 1995 where they used the 1D5  12 clone and looked at arbitrary cutoffs of five  13 and ten percent. And then the other paper was  14 by Perchuck showing that the 1D5 was superior  15 to DCC in predicting outcome in patients  16 treated with endocrine therapy, again, using  17 the 1D5 and with a ten percent cutoff. And so  18 that became -  19 COFFEY, Q.C.:  20 Q. So do you recall what year Perchuck's paper  21 was?  22 DR. DABBS:  23 A. That was '96.  24 COFFEY, Q.C.:  25 Q. '96, okay.</p>	<p>1 comparing two different tests and nothing  2 more. There was no outcome associated with  3 that.  4 COFFEY, Q.C.:  5 Q. Doctor, by 1997 in your experience was IHC  6 being utilized in terms of using paraffin  7 embedded tissue, was it being widely utilized  8 in North America?  9 DR. DABBS:  10 A. Yes, it was being widely utilized.  11 COFFEY, Q.C.:  12 Q. And at that time would there have been a  13 number of tertiary care laboratories, at least  14 to your knowledge, utilizing it?  15 DR. DABBS:  16 A. Yes, indeed.  17 COFFEY, Q.C.:  18 Q. And would it have been possible, you know, at  19 the time, if a particular medical centre was  20 going to adopt ER/PR by IHC as a new approach,  21 replacing the biochemical assay approach, was  22 it possible at the time then to avail of or  23 utilize, compare your IHC results internally  24 with IHC results obtained elsewhere, could you  25 have done that kind of comparison?</p>
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<p>1 DR. DABBS:  2 A. Yes. And so, you know, even before that there  3 were several papers that weren't necessarily  4 tightly honed in to outcomes, but people were  5 using the ten percent number. And then once  6 these two papers came out I think that became  7 pretty much probably the most common cutoff  8 that people were using, at least in the States  9 at the time. And then subsequently, you know,  10 as I mentioned, three years later Harvey's  11 paper and things went down to one percent.  12 And but as I mentioned, the paper by O'Keane  13 is not really associated with an outcome, per  14 se, but what he is comparing is he's looking  15 at the sensitivity and specificity of the  16 dextran-coated charcoal test compared to IHC  17 and concludes that if you choose 30 percent of  18 positive cells by IHC as a positive result,  19 then you maximize your sensitivity and  20 specificity by the DCC test.  21 COFFEY, Q.C.:  22 Q. If you choose?  23 DR. DABBS:  24 A. If you choose. But there's no outcome  25 associated with it. I saw that paper as</p>	<p>1 DR. DABBS:  2 A. Well, if one is going to adopt IHC having used  3 DCC, then the best way to do this, and  4 Battifora actually wrote about this, that the  5 proper way to do that would be to look at your  6 outcomes with the DCC and then compare your  7 IHC with that. That way you're not just  8 comparing test to test, but you're comparing  9 the outcomes and that's what Perchuck and  10 Mascarelli had done. If one wants to do IHC  11 and adopt an external method, a method from  12 another laboratory that had been validated,  13 that would be an acceptable way. But as I  14 mentioned earlier, if you're going to do that,  15 you have to use precisely the same clone and  16 the same methodology to make sure that you're  17 recapitulating the exact conditions that the  18 other investigator or the other laboratory  19 used, and that would be an acceptable way. So  20 for example, nowadays when people use one  21 percent cutoffs or one percent or more, that  22 has been, those outcome studies have been done  23 for 6F11, 1D5 and SP1, the only--the devil is  24 in the details, you have to look at those and  25 see how those particular assays were performed</p>

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<p>1 and whether your metrics then are on par with 2 what those people reported. 3 COFFEY, Q.C.: 4 Q. I believe in the '96 paper by Perchuck? 5 DR. DABBS: 6 A. Yes. 7 COFFEY, Q.C.: 8 Q. You refer to--I'm sorry, would you just repeat 9 again, what was it he found? 10 DR. DABBS: 11 A. He found that the 1D5, using the 1D5 antibody 12 was better than the DCC method of predicting 13 response to endocrine therapy. 14 COFFEY, Q.C.: 15 Q. So the 1D5 IHC approach? 16 DR. DABBS: 17 A. Yes. 18 COFFEY, Q.C.: 19 Q. Was, in fact, better than? 20 DR. DABBS: 21 A. Better than. 22 COFFEY, Q.C.: 23 Q. From the old biochemical? 24 DR. DABBS: 25 A. Correct.</p>	<p>1 which gives you less than the optimal result? 2 DR. DABBS: 3 A. Um-hm. 4 THE COMMISSIONER: 5 Q. Am I reasoning that correctly or missing 6 something? 7 DR. DABBS: 8 A. Yes, I understand what you're thinking there. 9 And I guess the best way I would describe this 10 would be that based on the cutoffs that were 11 used in the study by Perchuck in looking at 12 the endocrine response of patients, they found 13 that the results that they used from ten 14 percent cells and greater was a better 15 predictor of outcome, they could better 16 predict the outcome of response to therapy 17 than using those cutoff values for the DCC 18 test. 19 THE COMMISSIONER: 20 Q. Okay. 21 DR. DABBS: 22 A. Now, what that suggested to me was that there 23 were more likely a number of false negatives 24 in that DCC test. And for the issues that I 25 described earlier in terms of sampling</p>
<p>Page 245</p> <p>1 COFFEY, Q.C.: 2 Q. Assay approach. 3 THE COMMISSIONER: 4 Q. Do I--I just make sure I understand this 5 correctly. But the way that is determined is 6 by looking at outcome for patients? 7 DR. DABBS: 8 A. Yes. 9 THE COMMISSIONER: 10 Q. And the method chosen to determine the use of 11 IHC for ER/PR in this province, as I 12 understood the evidence of Dr. Khalifa, was to 13 try to reproduce, using IHC, the result that 14 you would have gotten with the bioassay 15 method? 16 DR. DABBS: 17 A. Yes. 18 THE COMMISSIONER: 19 Q. Now, it just seemed to me then, I've said it 20 to another witness, that that's kind of like 21 putting--that's putting your foundation as 22 your foundation, a house of cards, because 23 unless you are confident that the bioassay 24 method was producing a great result, then you 25 might, in fact, be establishing an IHC method</p>	<p>Page 247</p> <p>1 predominantly - 2 THE COMMISSIONER: 3 Q. Um-hm. 4 DR. DABBS: 5 A. - I think that what Dr. Khalifa described in, 6 or actually referred to in the paper by 7 O'Keane is something very different. 8 O'Keane's paper said, here's our results on 9 DCC and here's what we have on IHC. If I want 10 to--what he, basically what he did was he 11 said, if I want to maximize my sensitivity and 12 specificity for the DCC test, that translates 13 into 30 percent positive cells by IHC, okay. 14 THE COMMISSIONER: 15 Q. Yeah. 16 DR. DABBS: 17 A. And to me that's comparing apples and oranges, 18 because you're trying to take the sensitivity 19 and specificity of one test and translate it 20 to a different test, which is impossible to do 21 in reality. So that's what that paper was 22 about. It was not about outcomes. It 23 basically said if you want to have the same 24 sensitivity and specificity of DCC, then you 25 have to call 30 percent positive IHC cells.</p>

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<p>1 Well, when I read that paper, I actually</p> <p>2 skipped over it and didn't even include it in</p> <p>3 the papers that I took seriously because I saw</p> <p>4 the flaw in that, that apparent attempted</p> <p>5 translation, because if you notice, no one</p> <p>6 before that or after that advocated those</p> <p>7 numbers.</p> <p>8 THE COMMISSIONER:</p> <p>9 Q. Um-hm.</p> <p>10 DR. DABBS:</p> <p>11 A. This paper, I think, was largely ignored in</p> <p>12 the literature, and for good reason. It</p> <p>13 compared--it tried to compare a sensitivity of</p> <p>14 the test with a totally different methodology</p> <p>15 with one that was in place.</p> <p>16 THE COMMISSIONER:</p> <p>17 Q. Okay. So if we come back to the lab in 1997</p> <p>18 or, you know, a little--in the mid '90s, put</p> <p>19 it that way, which was deciding to switch to,</p> <p>20 for what would seem to me to be valid reasons,</p> <p>21 IHC, less cost, perhaps potentially better</p> <p>22 reliability?</p> <p>23 DR. DABBS:</p> <p>24 A. Yes.</p> <p>25 THE COMMISSIONER:</p>	<p>1 pretty good, you know, lesser but still pretty</p> <p>2 good link to outcome response to therapy, so</p> <p>3 those were the steps that would have taken</p> <p>4 over time. But I think that still as I look</p> <p>5 at the paper by O'Keane, you know, they have--</p> <p>6 it's very different. I don't think that</p> <p>7 people in this area were using an anti-</p> <p>8 estradiol antibody. If you're going to adopt</p> <p>9 a procedure, you have to adopt the antibody,</p> <p>10 the procedure and everything. And anti-</p> <p>11 estradiol, that's an antibody to the hormone,</p> <p>12 not the hormone receptor. So that's why this</p> <p>13 paper, I don't think, really went anywhere.</p> <p>14 It was an interesting sort of study and the</p> <p>15 metrics that were done on it, comparing, you</p> <p>16 know, with the ROC curves and whatnot, were</p> <p>17 valid for this particular study, but there</p> <p>18 were not outcomes and no one uses an anti-</p> <p>19 estradiol antibody, okay.</p> <p>20 COFFEY, Q.C.:</p> <p>21 Q. Doctor, look, please, at Exhibit P-0113?</p> <p>22 Doctor, this is a series of, this exhibit is a</p> <p>23 series of memorandums by Dr. Gershon Ejeckam</p> <p>24 to pathologists. Well, the first two memos</p> <p>25 we're going to look at are to pathologists, in</p>
<p>Page 249</p> <p>1 Q. Then if one wanted to do that, what in your</p> <p>2 view would be the optimal way of determining</p> <p>3 what IHC was going to look like within your</p> <p>4 lab, the cutoffs, what solutions you would be</p> <p>5 using, that kind of thing?</p> <p>6 DR. DABBS:</p> <p>7 A. Right.</p> <p>8 THE COMMISSIONER:</p> <p>9 Q. How would you go about doing that?</p> <p>10 DR. DABBS:</p> <p>11 A. I think the way to go about that would have</p> <p>12 been to look at the papers by Perchuck and</p> <p>13 Mascarelli, in particular, because what they</p> <p>14 did was they showed that the methodology</p> <p>15 worked, that it correlated with the outcome</p> <p>16 response to therapy and that's really a</p> <p>17 clinical validation, and that's what needs to</p> <p>18 be done. And they did it with that particular</p> <p>19 clone, so by adopting that clone and that</p> <p>20 methodology, one would be on safe grounds,</p> <p>21 including the cutoffs, one would be on safe</p> <p>22 grounds in terms of making that step from the</p> <p>23 biochemical to the IHC assay, okay. Now, we</p> <p>24 know, you know, 20 years later that the cutoff</p> <p>25 can go down to one percent and it still has a</p>	<p>Page 251</p> <p>1 effect, the pathologists in Newfoundland and</p> <p>2 Labrador. And the subject is</p> <p>3 "Immunohistochemical Stains." The first one</p> <p>4 is dated April 4, 2003. And he writes,</p> <p>5 "Kindly note that immunohistochemical stains</p> <p>6 for the following antibodies, CK34, CD3, CD5,</p> <p>7 CD20, CD79A, CEA, ER and PR have remained</p> <p>8 unreliable, erratic and therefore unhelpful</p> <p>9 for diagnostic purposes. Consequent on the</p> <p>10 above, staining with these antibodies shall</p> <p>11 stop forthwith until we can solve the</p> <p>12 reliability, sensitivity and specificity</p> <p>13 problems. Efforts are under way and hopefully</p> <p>14 a solution will be found within the next four</p> <p>15 to six weeks. You will be duly informed when</p> <p>16 such stains can resume." And it's copied to</p> <p>17 Barry Dyer, who was the manager in the</p> <p>18 laboratory at the time, he's a technologist,</p> <p>19 and all other technical staff on</p> <p>20 immunohistochemistry. Now, Doctor, in</p> <p>21 relation to circumstances where you had, well,</p> <p>22 are listed here, eight antibodies, that one</p> <p>23 had to in the lab here locally, felt, or at</p> <p>24 least Dr. Ejeckam felt that he had to stop</p> <p>25 them being used, I'll just ask you first of</p>

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1 all, have you ever encountered any situation  
2 like that before in terms of being told about  
3 it?  
4 DR. DABBS:  
5 A. I personally have not encountered anything  
6 where anyone, you mean, suggested to me that  
7 they were having problems with antibodies and  
8 like that, no. I can make, you know, some  
9 general comments about 34 Beta E12. That  
10 antibody requires specific enzyme digestion.  
11 The other antibodies are pretty much, you  
12 know, what we would call meat and potatoes of  
13 immunohistochemistry laboratory. So when I  
14 see a memo like this, it suggests to me that  
15 there is something globally wrong with the  
16 laboratory, the IHC laboratory in general and  
17 probably is time for an SOS to obtain some  
18 expertise, technical, to come in and try to  
19 right things.  
20 COFFEY, Q.C.:  
21 Q. Doctor, and that was April 4th, 2003, dated.  
22 This is another memo of May 2nd, 2003. And  
23 again, it's in effect to all pathologists  
24 within the province from Dr. Ejeckam. The  
25 subject is "ER/PR Immunohistochemical Stains"

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1 here. And he is informing the pathologists  
2 that "We have rectified the difficulties  
3 related to the immunohistostain of ER/PR.  
4 Therefore, we can now resume regular requests  
5 for these antibody stains." And he goes on to  
6 provide a certain amount of information then  
7 about ER and PR. And this memo has been  
8 described as a, at the time, an educative  
9 memo. Have you had the opportunity to have a  
10 look at this?  
11 DR. DABBS:  
12 A. I have seen parts of this. There was a part  
13 that just went by, I think it was point No. 2.  
14 COFFEY, Q.C.:  
15 Q. Yes.  
16 DR. DABBS:  
17 A. ER/PR false negative results increased in core  
18 biopsies, therefore were possible"--yeah,  
19 that's actually, I think actually the reverse  
20 is true.  
21 COFFEY, Q.C.:  
22 Q. The reverse is true.  
23 DR. DABBS:  
24 A. It would be held by, I would say, the vast  
25 majority of people who do this, yes.

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1 COFFEY, Q.C.:  
2 Q. And why is that, Doctor?  
3 DR. DABBS:  
4 A. Well, you see, there for some time and without  
5 evidence, evidence based, I think that  
6 pathologists feel that smaller amounts of  
7 tissue fix quickly. And for a short period of  
8 time I think actually one of the CAP  
9 recommendations came out implying that you  
10 only needed one hour of fixation for core  
11 biopsies, which was, I think, rapidly  
12 retracted once they came out and people found  
13 out that there really wasn't any evidence  
14 based on that. Because I can see how if one  
15 is treating core biopsies as small portions of  
16 tissue that don't require much fixation, false  
17 negatives will be rampant, there's no question  
18 about that. In fact, in the States the vast  
19 majority of literature will say, you know  
20 what, core biopsies we find to be the best  
21 because larger specimens tend not to be fixed  
22 with attention to detail, okay, so they have  
23 chose core biopsies, in fact, to be the test  
24 method of choice. But that's actually  
25 clinician driven in our institution. But I

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1 can see how one can make a statement like  
2 that, because if core biopsies are not  
3 adequately fixed, false negatives will be  
4 rampant and there would be a tendency to under  
5 fix it thinking it's a small biopsy, it only  
6 needs two hours.  
7 COFFEY, Q.C.:  
8 Q. I take it, Doctor, that the fixation process  
9 not only involves penetration of the tissue by  
10 formalin, but as well, actual time in the  
11 formalin after the penetration has occurred?  
12 DR. DABBS:  
13 A. Exactly. And what it is is, you know,  
14 penetration of the tissue by formalin does not  
15 equal fixation. Fixation continues once the  
16 tissue is taken out of formalin and it's a  
17 chemical process that involves cross linking  
18 of a lot of proteins. And so some of it  
19 clearly still remains a mystery, but fixation  
20 does continue beyond exposure to formalin and  
21 that's why that minimum exposure time is so  
22 critical, to get enough formalin on board and  
23 enough fixation to occur for the proper  
24 immunohistochemistry to work.  
25 COFFEY, Q.C.:



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1 Q. And there's a reference in paragraph 5 to the  
 2 consensus statement?  
 3 DR. DABBS:  
 4 A. Yes.  
 5 COFFEY, Q.C.:  
 6 Q. Or at least there's a reference to it, I'm not  
 7 going to say that the actual--it's attributed  
 8 to be quote is in fact a quote, I'm not going  
 9 to suggest that.  
 10 DR. DABBS:  
 11 A. Right.  
 12 COFFEY, Q.C.:  
 13 Q. But that consensus statement of 2000 is  
 14 referred to in paragraph 5. And he says in  
 15 paragraph 6, "Higher staining intensity does  
 16 not reflect better results. This is a  
 17 function of staining procedure and may alter  
 18 all cytoplasmic staining in ER/PR immunostain  
 19 are to be considered as negative." I gather  
 20 that the last sentence, no one takes any issue  
 21 with that?  
 22 DR. DABBS:  
 23 A. Correct.  
 24 COFFEY, Q.C.:  
 25 Q. And the idea of "Higher staining intensity

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1 does not reflect better results." What does  
 2 staining intensity, from your perspective, how  
 3 is it properly considered here a factor, in  
 4 here?  
 5 DR. DABBS:  
 6 A. Well, I think that staining intensity is  
 7 important because if all of your results are  
 8 either strongly positive, you know, the three  
 9 plus nuclei and the rest are all negative,  
 10 your test is not really optimized properly.  
 11 So staining intensity is important with  
 12 respect to just an internal quality assurance  
 13 measure. And secondly, it does reflect the  
 14 amount of hormone receptor in a given nucleus,  
 15 because if you have something that's three  
 16 plus brown and opaque and something that's one  
 17 plus or two plus, you know, it is  
 18 quantitative. And you can get into fancy  
 19 machines, you can use your eyeball, you can  
 20 use an H Score, but that difference is there  
 21 and so that kind of difference in expression  
 22 is to be--is not to be taken lightly.  
 23 THE COMMISSIONER:  
 24 Q. While we're on the subject, we've heard over  
 25 the course of the past few months, I was going

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1 to say weeks, but it's been months, reference  
 2 to the Allred score.  
 3 DR. DABBS:  
 4 A. Yes.  
 5 THE COMMISSIONER:  
 6 Q. And how does that relate to your H Score?  
 7 DR. DABBS:  
 8 A. The Allred score is a different scoring method  
 9 that basically does the same thing. It takes  
 10 into account the proportion and intensity of  
 11 staining in any given tumour. And the  
 12 proportion basically there is a little cartoon  
 13 that comes with showing the proportion of  
 14 cells of something like greater than 75  
 15 percent and 50 to 74 percent and, you know, it  
 16 gets down to one percent, and then the  
 17 intensity is pretty much the same, zero, one,  
 18 two and three. So you have, on the intensity  
 19 side, zero, one, two and three, and on the  
 20 proportion side, one through five, so a top  
 21 Allred score would be eight, five plus three,  
 22 you add those together. And Dr. Allred used  
 23 that with Harvey in that paper from 1999 where  
 24 they looked at outcomes and used the one  
 25 percent, greater than one percent cutoff which

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1 corresponds to an Allred score of, I think, of  
 2 three. So it is a form of an H Score, if you  
 3 will, it's just dialled up differently, it's a  
 4 big different. And the, I think the H Score  
 5 has a broader dynamic range associated to it  
 6 as opposed to the Allred score and that's  
 7 probably the only benefit of using an H Score  
 8 over an Allred score. But there is nothing  
 9 wrong with using an Allred score. It does  
 10 adhere to the prescription that's suggested by  
 11 the committee in that proportion and intensity  
 12 should be scored. And Allreds method is  
 13 validated in that paper by Harvey from 1999.  
 14 THE COMMISSIONER:  
 15 Q. So then what is in common between the method  
 16 used in your institution and Allred is that  
 17 both intensity and the percentage -  
 18 DR. DABBS:  
 19 A. Yes.  
 20 THE COMMISSIONER:  
 21 Q. - are factored into the information which is  
 22 provided?  
 23 DR. DABBS:  
 24 A. Yes, they are. And, in fact, for cases where  
 25 we have DCIS only, ductal carcinoma in situ

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<p>1 only and we have a request for hormone 2 receptors, we score that according to Allred 3 because it's just easier matching up those 4 cartoons with that, so.</p> <p>5 THE COMMISSIONER: 6 Q. Thank you.</p> <p>7 COFFEY, Q.C.: 8 Q. I was going to ask you about that, Doctor, now 9 that you've raised it. The DCIS cases, what 10 approach does your institution take to, in a 11 case, a DCIS case or I suppose the same thing 12 would apply to a lobular carcinoma, too, they 13 can be in situ too, I gather? Am I correct or 14 incorrect?</p> <p>15 DR. DABBS: 16 A. That's an interesting question, but no one, to 17 my knowledge, has ever requested hormone 18 receptors on a lobular carcinoma in situ, and 19 I would dissuade them from it because I would 20 say you're wasting your money, it's 100 21 percent positive.</p> <p>22 COFFEY, Q.C.: 23 Q. And in terms then of DCIS cases, what is the 24 approach in Magee to whether or not ER and PR 25 tests are done on DCIS and could you explain</p>	<p>1 queried our docs in our interdisciplinary 2 tumour board asking what the rationale for 3 that was because that is assuming, you know, 4 the argument, my argument is that you're 5 assuming that that patient who has a negative 6 ER/PR in her DCIS will develop--or not require 7 hormone therapy. You're assuming that she 8 could never, ever develop an ER positive DCIS. 9 And while that sends a shudder through them, 10 they will point to at least one study, and 11 it's not that comprehensive a study, 12 suggesting that and it's only suggestive 13 evidence, that a patient who has a ER positive 14 DCIS develops an ER positive invasive tumour 15 and vice versa, those that are negative, okay. 16 But still, in my way of thinking of biology, 17 not everyone follows the rules and so my 18 suggestion to them was I didn't see where that 19 kind of testing really had a great deal of 20 science behind it, that what if a patient who 21 was ER negative, PR negative for DCIS 22 developed an ER positive invasive cancer and 23 were never on anti-hormonal therapy, then 24 what. And that's still a bone of contention, 25 if you will, hasn't been resolved. But that's</p>
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<p>1 why?</p> <p>2 DR. DABBS: 3 A. Sure. I think the rationale for doing hormone 4 receptor testing on DCIS is laudable and it 5 basically is, you know, DCIS, the presence of 6 DCIS is certainly a risk factor for subsequent 7 invasive breast cancer. And so oncologists, 8 if they're going to give therapy, at least a 9 group of them believe that it's important to 10 know whether it's receptor positive or 11 negative. And so the rationale for doing that 12 is if it's positive, then they're going to 13 treat the patient with therapy that causes a 14 reduction, and that means either Tamoxifen or 15 Arimidex or something along those lines if 16 it's ER positive. Our policy is if it's pure 17 DCIS, we will wait--from the core biopsy, if 18 we have a core biopsy of DCIS, we don't do the 19 hormone receptors, we wait for the resection. 20 If it's pure DCIS and then we get a 21 prescription from the doc that says do hormone 22 receptors, then we will do them, we don't 23 reflex them. So that's the situation where we 24 will do those hormone receptors. We report 25 them with the Allred score. And I have</p>	<p>1 their rationale for the testing in DCIS.</p> <p>2 COFFEY, Q.C.: 3 Q. And, Doctor, here at P-0113 is a reference to 4 ER positive tumours and the ones you'd 5 referred to earlier are there. And you've 6 indicated that--when you were speaking about 7 these, in fact, these are the ones you'd 8 named, tubular, mucinous, papillary?</p> <p>9 DR. DABBS: 10 A. Papillary.</p> <p>11 COFFEY, Q.C.: 12 Q. Papillary, I'm sorry, and you said though, 13 invasive wouldn't--I'm sorry, lobular wouldn't 14 fall into--it would tend to be ER positive, 15 but it wouldn't be classified in the same way 16 these were?</p> <p>17 DR. DABBS: 18 A. Correct. These are--this group here is 19 considered to be the so-called special type of 20 invasive ductal cancers.</p> <p>21 COFFEY, Q.C.: 22 Q. Ductal, okay.</p> <p>23 DR. DABBS: 24 A. And lobular, by definition, is not a ductal 25 cancer. So that's the only semantic different</p>

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<p>1 there.</p> <p>2 COFFEY, Q.C.:</p> <p>3 Q. And the reference to "low nuclear grade</p> <p>4 tumours are usually positive for ER/PR and</p> <p>5 negative for HER2/neu, while high grade</p> <p>6 tumours tend to be positive for HER2/neu and</p> <p>7 negative for ER/PR," do you agree with that?</p> <p>8 DR. DABBS:</p> <p>9 A. Correct, yes.</p> <p>10 COFFEY, Q.C.:</p> <p>11 Q. And now, Doctor, this happened, as you can see</p> <p>12 from the dates, in the main, in April of 2003,</p> <p>13 suspension of testing. If we could look,</p> <p>14 please, at Exhibit, just bring it up here, C-</p> <p>15 0228? Now Doctor, and go to, please--well,</p> <p>16 first of all, Doctor, that's just an</p> <p>17 immunoperoxidase request form that was in use</p> <p>18 here in St. John's or in Newfoundland, in</p> <p>19 fact, in 2003. This particular one is dated</p> <p>20 February 10th, 2003, and you see there,</p> <p>21 requesting ER/PR. Page two of the exhibit is</p> <p>22 the pathology report, or at least a portion of</p> <p>23 the pathology report, and then if you look at</p> <p>24 page four of the exhibit, you'll see there are</p> <p>25 two addendums there. One is March 17th, 2003,</p>	<p>1 Assuming for the moment it's the same block,</p> <p>2 would you expect to get, if the test were</p> <p>3 being carried out properly, going from an ER</p> <p>4 of less than one to 40 percent and a PR of 15</p> <p>5 percent to 73 percent, would you expect that</p> <p>6 kind of swing?</p> <p>7 DR. DABBS:</p> <p>8 A. No, that kind of swing, assuming that the</p> <p>9 slides have been properly interpreted, would</p> <p>10 be a red flag for an event that needed to have</p> <p>11 serious inquiry by lab administration.</p> <p>12 COFFEY, Q.C.:</p> <p>13 Q. Doctor, if we could look, please, at Exhibit</p> <p>14 C-0175? Now Doctor, this is again a pathology</p> <p>15 report. The surgical specimen number is a</p> <p>16 different surgical--different patient,</p> <p>17 different surgical specimen number, is</p> <p>18 03:SU4821, '03 being the year. The surgical</p> <p>19 specimen number being 4821. If we could go,</p> <p>20 please, to the second page, Doctor, you'll see</p> <p>21 here, addendum number one is dated May 6th,</p> <p>22 2003, and it reads here "when compared to</p> <p>23 controls, the specimen is negative for</p> <p>24 HER2/neu, ER and PR," the rest of it relates</p> <p>25 to the HER2/neu test below this, and then</p>
<p>Page 265</p> <p>1 addendum number one, "estrogen progesterone</p> <p>2 immunoperoxidase method, ER occasional</p> <p>3 positive cells less than one percent, PR 15</p> <p>4 percent positivity," and Doctor, it's noted</p> <p>5 "no controls available" and then addendum</p> <p>6 number two, which is May 28th, 2003. The</p> <p>7 first one was reported before the April 4th</p> <p>8 memo, the second one is entered after the May</p> <p>9 2nd memo advising of the test being</p> <p>10 reinstated. May 28th, 2003, and it says "as</p> <p>11 requested, repeat estrogen and progesterone</p> <p>12 receptors by immunoperoxidase staining.</p> <p>13 Estrogen receptors 40 percent positivity and</p> <p>14 progesterone receptors 73 percent positivity."</p> <p>15 DR. DABBS:</p> <p>16 A. Yes.</p> <p>17 COFFEY, Q.C.:</p> <p>18 Q. So Doctor, now we don't know, in particular,</p> <p>19 why this test was repeated, but if--let me</p> <p>20 see, March, April, May, well it's in effect</p> <p>21 just over two months. If an ER/PR test were</p> <p>22 conducted just over two months apart on the</p> <p>23 same surgical specimen--now again, we don't</p> <p>24 know even if it's the same block, because you</p> <p>25 can't tell the way they report these.</p>	<p>Page 267</p> <p>1 addendum number two, three days later, on May</p> <p>2 9th, 2003, the pathologist reports "the ER and</p> <p>3 PR were repeated due to quality assurance</p> <p>4 issues. The repeated stains show the</p> <p>5 following: ER positive in 80 percent of the</p> <p>6 cells. PR positive in ten percent of the</p> <p>7 cells" and the doctor notes "this replaces a</p> <p>8 previous report" and she has contacted the</p> <p>9 Cancer Clinic to advise them of that.</p> <p>10 Doctor, now here, this first entry of</p> <p>11 addendum number one indicates that it was</p> <p>12 entered May 6th. If that entry of May 6th</p> <p>13 reflects a test after the testing resumed, if</p> <p>14 it does, after it resumed on May 2nd or</p> <p>15 thereabouts, if after the testing was resumed,</p> <p>16 one got a negative ER and PR and then three</p> <p>17 days later had the test rerun because one had</p> <p>18 concerns about quality assurance issues and</p> <p>19 got 80 and 10, would that, do you think, cause</p> <p>20 or should it have caused some inquiry to be</p> <p>21 made further?</p> <p>22 DR. DABBS:</p> <p>23 A. Yes, definitely. Again, this is a sort of red</p> <p>24 flag or a sentinel event, whatever language</p> <p>25 you want to use, to suggest that the process</p>

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1 for immunohistochemistry is erratic and needs  
 2 to be really thoroughly investigated.  
 3 COFFEY, Q.C.:  
 4 Q. If we could look, please, at Exhibit C-0174?  
 5 Here, Doctor, again this is a pathology  
 6 report. It relates to specimen number  
 7 02:SS5231. You'll see that in the top left-  
 8 hand side there.  
 9 DR. DABBS:  
 10 A. Yes.  
 11 COFFEY, Q.C.:  
 12 Q. If we could go, please, to page four? Thank  
 13 you, Registrar. Doctor, there are three  
 14 addendums here. The first of them doesn't  
 15 relate to ER/PR, but the second addendum,  
 16 addendum number two, is dated August 29th,  
 17 2002, which is in effect eight or nine months  
 18 before the ER and PR testing were suspended in  
 19 April of 2003. On August 29th, 2002, the  
 20 pathologist reported, addendum number two,  
 21 "immunohistochemical staining for estrogen  
 22 receptors is positive in approximately 15  
 23 percent of lesional cells.  
 24 Immunohistochemical staining for estrogen  
 25 receptors is negative," and then addendum

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1 number three, see that at the top of the page  
 2 there, on June 11th, 2003, the same  
 3 pathologist reported the following: "at the  
 4 request of Dr. Zaidi," and I will tell you  
 5 that Dr. Zaidi is an oncologist, okay, used to  
 6 practice in St. John's, "immunohistochemical  
 7 staining for estrogen and progesterone  
 8 receptors has been repeated. Estrogen  
 9 receptors show faint positivity in  
 10 approximately 10 to 15 percent of lesional  
 11 cells. Progesterone receptors are  
 12 unequivocally positive in approximately 75  
 13 percent of lesional cells" and it's entered  
 14 the same day.  
 15 Now Doctor, I appreciate the tests were  
 16 done, in effect, ten months apart, or almost  
 17 ten months apart, but if an ER is reported as  
 18 negative, and I take it in this context,  
 19 negative probably meant zero and PR 15, and  
 20 then on repeat, ten months, or just over ten  
 21 months later, it goes 10 to 15 ER and 75  
 22 percent PR, would that cause any questions to  
 23 be raised about what was going on, for  
 24 example, back in August of 2002?  
 25 DR. DABBS:

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1 A. Yes, again, assuming that this is performed on  
 2 the same block, this would be a cause for  
 3 concern, and again, the methodology of IHC  
 4 would need to be looked at very closely.  
 5 THE COMMISSIONER:  
 6 Q. I'm sorry, Mr. Coffey, but these things are  
 7 just running through my head. The point you  
 8 make about being performed on the same block -  
 9 DR. DABBS:  
 10 A. Yes.  
 11 THE COMMISSIONER:  
 12 Q. - I'm assuming that sort of nature being what  
 13 it is, in fact, there might be a variation as  
 14 you move through the block, the result that  
 15 you would get, or in theory, in any event, and  
 16 that's what I'm wondering is whether or not  
 17 there are studies done as to the sort of  
 18 normal variation in results that one might  
 19 expect from the same block?  
 20 DR. DABBS:  
 21 A. Well, I think that there can be some  
 22 variation. What strikes me is an ER that goes  
 23 from completely negative to up to 15 percent  
 24 of cells, that would be more variation than I  
 25 would be accustomed to, and especially going

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1 from 15 percent PR to 75 percent. That's a  
 2 big difference, and I think those two taken  
 3 together are most indicative that there's  
 4 something wrong with the process, that  
 5 whatever was done the first time was probably  
 6 improper. There's too much variation there.  
 7 THE COMMISSIONER:  
 8 Q. I guess what I'm asking is what would be  
 9 acceptable or considered normal variation if  
 10 you were running a test again for some reason,  
 11 and you would say essentially that's the same  
 12 result?  
 13 DR. DABBS:  
 14 A. I think a well performed ER test that is  
 15 negative and re-performed and found to have  
 16 less than one percent of cells would be  
 17 acceptable.  
 18 THE COMMISSIONER:  
 19 Q. Okay.  
 20 DR. DABBS:  
 21 A. On a deeper level, for example.  
 22 COFFEY, Q.C.:  
 23 Q. Doctor, if we bring up, please--sorry, before  
 24 we do that, so Doctor, here, in the context,  
 25 if you were just handed this and kind of asked

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<p>1 to read it, and looking at the space in time, 2 first report August of 2002, second report 3 June of 2003, and you pointed out from your 4 perspective there's a difference in the 5 results of some significance, if you were 6 faced with that, for example, in your own 7 laboratory, say you were to be, would that 8 cause you to do anything, and it was now 2003, 9 the second result, would that cause, do you 10 think, would it cause someone to question what 11 had been going on in 2002?</p> <p>12 DR. DABBS: 13 A. Yes, very definitely.</p> <p>14 COFFEY, Q.C.: 15 Q. Yes, and assuming, for example, for the 16 moment, that the 2003 test is the correct 17 result?</p> <p>18 DR. DABBS: 19 A. Right.</p> <p>20 COFFEY, Q.C.: 21 Q. That you're satisfied that it has been 22 optimized, as it were.</p> <p>23 DR. DABBS: 24 A. Correct.</p> <p>25 COFFEY, Q.C.:</p>	<p>1 COFFEY, Q.C.: 2 Q. And Doctor, I'm just going to ask you, perhaps 3 I'll ask you, from your perspective, when you 4 read this, what caught your attention? What 5 was it, if anything?</p> <p>6 DR. DABBS: 7 A. Well, I think that what caught my attention 8 was the sort of multi-factorial items that led 9 to failure and resultant false negative 10 results, beginning with, you know, as Dr. 11 Banerjee says here in the review of cases, 12 poor fixation, negative internal controls and 13 absent internal controls and so forth, and you 14 know, I think he did a very thorough review. 15 I was impressed with the review, and 16 everything here, as best I can tell, makes 17 sense, based on evidence.</p> <p>18 COFFEY, Q.C.: 19 Q. And -</p> <p>20 DR. DABBS: 21 A. The one item that I am looking at right now, 22 at the bottom of the page, where he says 23 "fixation time in formalin does not affect ER 24 results as long as two millimetre thick slices 25 of tissue are placed in fixative within 15</p>
<p>Page 273</p> <p>1 Q. That nothing happened in your lab in the 2 meantime, you might want to then question, 3 well, this earlier result, what does that 4 mean?</p> <p>5 DR. DABBS: 6 A. Correct.</p> <p>7 COFFEY, Q.C.: 8 Q. What was going on back then.</p> <p>9 DR. DABBS: 10 A. Yes.</p> <p>11 COFFEY, Q.C.: 12 Q. Doctor, I'm going to ask you now to look at, 13 please, Exhibit P-0046. Now, Doctor, this is- 14 -well, it's the first page, it's the cover 15 letter. It's dated October 17th, 2005. 16 Second page is the report by Dr. Diponkar 17 Banerjee of the British Columbia Cancer 18 Agency, dated October 17th, 2005, entitled 19 "External Quality Review of the Health Care 20 Corporation of St. John's, Laboratory Medicine 21 Programs, Immunohistochemistry Service," and 22 Doctor, have you had an opportunity to read 23 this?</p> <p>24 DR. DABBS: 25 A. Yes.</p>	<p>Page 275</p> <p>1 minutes of surgical excision and adequate 2 heat-induced antigen retrieval is performed." 3 That's about the only thing that I disagree 4 with there. Section thickness, while desiring 5 to be two millimetres, fixation time in 6 formalin does affect results and no matter 7 what the section thickness is and this is the 8 only thing that sort of stood out that I took 9 issue with.</p> <p>10 COFFEY, Q.C.: 11 Q. And if I recall correctly, Commissioner, Dr. 12 Banerjee, when he testified, he -</p> <p>13 THE COMMISSIONER: 14 Q. He agreed with you.</p> <p>15 COFFEY, Q.C.: 16 Q. Pardon me? He actually agreed with you, yes.</p> <p>17 DR. DABBS: 18 A. Okay.</p> <p>19 COFFEY, Q.C.: 20 Q. It's just the way it was phrased at the time. 21 He certainly pointed it out, my memory of it, 22 if my memory is correct, when he came and 23 testified. Now Doctor, that's the kind of 24 summary of the review of cases that had 25 converted up to that point in time, and this</p>

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<p>1 is in the summer and fall of--early fall of 2 2005. Then the conclusions about the reasons 3 for test failure is spelled out here, and in 4 effect, other than referring to the two 5 systems, DAKO and Ventana, he repeats the 6 reference to tissue fixation as concerns he 7 expressed earlier and refers to internal 8 controls, and his observations in relation to 9 them.</p> <p>10 Doctor, what I wanted to ask you, in 11 relation to this--but as well, before I do, I 12 also want to refer you to "other system flaws 13 observed." The idea of lack of dedicated 14 immunohistochemistry technologists, he points 15 out "a rotation system is used," was being 16 utilized at the time. Doctor, at your own 17 institution, are there dedicated 18 immunohistochemistry technologists?</p> <p>19 DR. DABBS: 20 A. There are some--there's a dedicated group of 21 histotechs, which are also well trained in 22 immunohistochemistry and we have, I think, 23 four or five of them, and they will rotate 24 onto that service, in addition to doing other 25 duties. But not all histotechs do</p>	<p>1 difficult and the techs can get mixed messages 2 and there's no one in control. There's no one 3 at the helm. There has to be that person so 4 that--and there should be, professionally, so 5 that they can share these ideas among 6 themselves and there's a lightning rod person 7 for issues that come up, so they can talk 8 about it among themselves professionally and 9 then take things to the technicians.</p> <p>10 COFFEY, Q.C.: 11 Q. Now, such a director of immunohistochemistry, 12 a pathologist, what sort of background do you 13 think is desirable anyway in such a 14 pathologist? Like how would one go about 15 choosing or recruiting such a pathologist 16 and/or training them?</p> <p>17 DR. DABBS: 18 A. I think that there probably are several ways 19 of doing that. First and foremost, one would 20 have to rely on the abilities that can be 21 documented from that person, either from past 22 experience, either in writing from references 23 or telephone calls or whatever. This person 24 is, you know, trying to forward themselves as 25 having the abilities. Of course, it's always</p>
<p>1 immunohistochemistry. It's a dedicated 2 subgroup who have the interest and skill and 3 desire and are also very critically appraised 4 in terms of their abilities and they sign off 5 on a checklist, you know, for duties that 6 they're competencies.</p> <p>7 COFFEY, Q.C.: 8 Q. Number two here, he refers to "a lack of an 9 officially designated pathologist as director 10 of immunohistochemistry service," and he 11 notes, in his view, "the technologists thus 12 get conflicting feedback from a large number 13 of pathologists." He notes "there's no 14 accountability for the quality of the 15 service." Doctor, at least at your 16 institution, is there a director of 17 immunohistochemistry service?</p> <p>18 DR. DABBS: 19 A. Yes.</p> <p>20 COFFEY, Q.C.: 21 Q. Is that a pathologist?</p> <p>22 DR. DABBS: 23 A. Yes, and that is very important, in my 24 opinion, because what can happen is if you 25 have a lot of people chatting up results, it's</p>	<p>1 desirable to have someone who is published in 2 the field as well, to show that competency, 3 ask them what sort of meetings that they've 4 attended, what sort of groups they've been 5 involved with and so forth. So there really 6 aren't immunohistochemistry fellowships per 7 se. That's a very rare breed, and so 8 fellowship training would not be an expected 9 route of getting someone like that. It's all 10 about experience, publishing, references to 11 date.</p> <p>12 COFFEY, Q.C.: 13 Q. He also refers to a lack of standard operating 14 procedures for grossing, fixation, tissue 15 processing, block selection, positive control 16 block selection, method optimization through 17 systematic titration, incubation time, and 18 antigen retrieval time for each analyte. 19 Doctor, first of all from your perspective, 20 should a pathology laboratory have standard 21 operating procedures for all of those things?</p> <p>22 DR. DABBS: 23 A. Very much so.</p> <p>24 COFFEY, Q.C.: 25 Q. And what are the risks associated or potential</p>

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<p>1 consequences associated with not having SOPs 2 from your perspective? 3 DR. DABBS: 4 A. Well, without having SOPs, I don't see how 5 actually a laboratory, at least in the States, 6 could survive a CAP inspection or whatever 7 governing body would be doing the inspection 8 because all of these things are expectations, 9 these things are no checklists, all of the 10 manuals that we're talking about with standard 11 operating procedures, they have to exist. 12 They were viewed by inspectors and so forth. 13 Without them, I think there's really no 14 accountability for assurance--for quality 15 being assured, yet alone quality control. So 16 it's a recipe for disaster. 17 COFFEY, Q.C.: 18 Q. Doctor, can you tell us, please, about how in 19 the United States, clinical laboratories--at 20 least the pathology end of the clinical 21 laboratory is accredited or inspected or 22 licensed? How does that work in the United 23 States? 24 DR. DABBS: 25 A. The governing bodies basically is the federal</p>	<p>1 just going to happen. I think we're moving in 2 that direction, but right now they're 3 unannounced inspections. 4 COFFEY, Q.C.: 5 Q. I'm sorry, right now they're -- 6 DR. DABBS: 7 A. They're unannounced inspections, but you know 8 what window--if they say you're going to be 9 between July and December of 2008, you'd have 10 some time -- 11 COFFEY, Q.C.: 12 Q. During that time frame. 13 DR. DABBS: 14 A. If someone is going to show up unannounced, 15 right, but I think the way it's evolving is 16 that at one point in time no one is going to 17 give you a window, they're going to say we're 18 going to inspect when we want to. 19 COFFEY, Q.C.: 20 Q. We just accredited or licensed you, we'll be 21 back in due course? 22 DR. DABBS: 23 A. Correct. 24 COFFEY, Q.C.: 25 Q. Doctor, can one, to your knowledge in the</p>
<p>1 government and there are multiple venues by 2 which one can choose to be inspected. There's 3 a joint commission accreditation of hospitals 4 is one, there's CMS, Centre for Medicare 5 Service, is another, and then there are other 6 agencies which have been permitted to inspect 7 under the aegis of the aforementioned 8 entities, and that includes the CAP, College 9 of American Pathologists. So those are the 10 entities which inspect. They do so on a two 11 year cycle. They have a checklist which 12 everyone is very familiar with, and, in fact, 13 every year one is supposed to do a self- 14 inspection, to do through these to look at any 15 potential deficiencies. There are quarterly 16 updates for the checklists in various areas 17 that should be gone over by people in the 18 quality assurance part of the laboratory, and 19 in essence, one should be ready for an 20 inspection at any time. Now in the States, the 21 laboratory inspections are unannounced. Even 22 though, you know when you're going to have a 23 window of opportunity. I suspect the future 24 is going to be it's going to happen whenever 25 it happens, they won't give you a window, it's</p>	<p>1 United States, run a tertiary care clinical 2 laboratory pathology division without being 3 accredited or licensed in some manner? 4 DR. DABBS: 5 A. Not at all. 6 COFFEY, Q.C.: 7 Q. Why is that? 8 DR. DABBS: 9 A. That's because the federal government has set 10 guidelines for accreditation of hospitals, and 11 this is also under the aegis of the old 12 Clinical Laboratory Improvement Act, which 13 sets guidelines for laboratories and this is 14 an evolving area as well. For hospitals to be 15 accredited, they have to have accreditation at 16 the laboratory as well. If the laboratory is 17 not accredited, the hospital would not have 18 the laboratory to function. 19 COFFEY, Q.C.: 20 Q. Doctor, he refers to a lack of 21 subspecialization amongst pathologists leading 22 to a lack of in-depth knowledge of IHC 23 technical and interpretation details and 24 pitfalls. Doctor, your career spans well over 25 two decades now. Doctor, in the area of</p>

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<p>1 pathology, and again I'll just ask you</p> <p>2 generally about your experience in the United</p> <p>3 States, subspecialization within pathologists,</p> <p>4 how far has that gone?</p> <p>5 DR. DABBS:</p> <p>6 A. That's--subspecialization in pathology is a -</p> <p>7 it's an evolving concept. There are more and</p> <p>8 more large medical centres that have moved to</p> <p>9 subspecialty sign out. For example, Mass.</p> <p>10 General Hospital, Cleveland Clinic, our</p> <p>11 institution--if you look at our institution,</p> <p>12 we have gone to basically a product line sign</p> <p>13 out where there is a bench for every</p> <p>14 subspecialty area. So there is a group of</p> <p>15 pathologists entirely dedicated to head and</p> <p>16 neck cancer, a group to GI cancer, thoracic</p> <p>17 pathology, cardiac pathology, neuropathology,</p> <p>18 renal medical biopsy, genital urinary</p> <p>19 pathology, GYN and breast, and at Magee, Magee</p> <p>20 is actually a separate hospital, it's been a</p> <p>21 women's hospital for many decades and there</p> <p>22 was at one time--Magee used to be a general</p> <p>23 hospital, but what's happened over time is</p> <p>24 that all of the general surgery that is</p> <p>25 performed there, those specimens are shipped</p>	<p>1 do a more accurate job?</p> <p>2 DR. DABBS:</p> <p>3 A. More efficient, more accurate, yes, and even</p> <p>4 some commercial laboratories in the States are</p> <p>5 now picking up on this concept as well. So</p> <p>6 it's--with the amount of knowledge and</p> <p>7 complexity of specimens and expectations,</p> <p>8 subspecialty sign out is increasing.</p> <p>9 THE COMMISSIONER:</p> <p>10 Q. Do I take it then there are no generalists in</p> <p>11 your institution?</p> <p>12 DR. DABBS:</p> <p>13 A. At the UPMC core hospitals, that includes</p> <p>14 Presbyterian Shadyside Hospital and Magee, if</p> <p>15 you want to look at general pathologists, I</p> <p>16 would say that they're sprinkled throughout on</p> <p>17 one of them. I did a lot of general pathology</p> <p>18 that still sticks with me, but I do a lot of</p> <p>19 specialty sign out now. So what's happening</p> <p>20 in terms of recruiting for pathologists who</p> <p>21 come out of training and go directly into a</p> <p>22 subspecialty area, they probably--their</p> <p>23 general capabilities will probably atrophy</p> <p>24 over time, but part of the UPMC system there</p> <p>25 are, I think, ten other community hospitals</p>
<p>1 to our centres of excellence where those</p> <p>2 pathologists sit. So, for example, if someone</p> <p>3 does GU surgery or GI surgery, we package up</p> <p>4 those specimens, fix them appropriately and</p> <p>5 ship them to the hospitals. They're not very</p> <p>6 far away. They're within a half an hour</p> <p>7 drive. Subsequently if there's breast or GYN</p> <p>8 surgery done at the other UPMC hospitals in</p> <p>9 our vicinity, they ship those specimens to us.</p> <p>10 So that's how the subspecialty works.</p> <p>11 COFFEY, Q.C.:</p> <p>12 Q. And why is that?</p> <p>13 DR. DABBS:</p> <p>14 A. Well, it works that way because there's a</p> <p>15 limited number of pathologists with</p> <p>16 subspecialty expertise, and rather than</p> <p>17 having, you know, six centres with breast</p> <p>18 pathologists which is going to be difficult to</p> <p>19 come by, you put them all in one place and</p> <p>20 have them do all that work. So it's worked</p> <p>21 out pretty well.</p> <p>22 COFFEY, Q.C.:</p> <p>23 Q. I take it, that's all with a view to the</p> <p>24 principle that all things being equal,</p> <p>25 subspecialists will do or can be expected to</p>	<p>1 where there are general pathologists, and the</p> <p>2 funnel complex cases to the centres of</p> <p>3 excellence. So that's our workload sort of</p> <p>4 flows.</p> <p>5 COFFEY, Q.C.:</p> <p>6 Q. Doctor, I'm still on the topic in paragraph</p> <p>7 five and the idea of subspecialization. We've</p> <p>8 heard, Doctor, that immunohistochemistry as a</p> <p>9 subject matter has grown considerably over the</p> <p>10 past 20/25 years.</p> <p>11 DR. DABBS:</p> <p>12 A. Yes, very much so.</p> <p>13 COFFEY, Q.C.:</p> <p>14 Q. And I gather that it's expected to grow again</p> <p>15 or at least to continue to grow?</p> <p>16 DR. DABBS:</p> <p>17 A. Yes.</p> <p>18 COFFEY, Q.C.:</p> <p>19 Q. Doctor, from your perspective, how practical</p> <p>20 is it for a general pathologist to be able to</p> <p>21 expect today--for example, coming out of</p> <p>22 school today, coming out of a residency today,</p> <p>23 to be able to perform all the different types</p> <p>24 of analysis that might be required or might be</p> <p>25 done, for example, in your institution by a</p>



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1 number of different types of subspecialists,  
 2 how practical is that in today's world?  
 3 DR. DABBS:  
 4 A. I think for a community pathologist, that they  
 5 do a good job, and I think that the  
 6 expectations are there. I think that a good  
 7 deal of it depends on the residency training  
 8 that they have undergone. There are a number  
 9 of good, very good and excellent resources for  
 10 whatever area that we're talking about, and,  
 11 you know, immunohistochemistry is sort of a  
 12 meat and potatoes part of general surgical  
 13 pathology. So a good trainee is going to make  
 14 the effort to learn as much as they can from  
 15 their everyday practice, specimens that  
 16 they're exposed to, textbooks, and online  
 17 resources that they have, meetings that they  
 18 go to, and it's the expectation that they will  
 19 do that as well as they can because that's the  
 20 kind of thing that they will be dealing with  
 21 in their general practice. Many community  
 22 hospitals will rely actually on  
 23 immunohistochemistry, they'll send tests out  
 24 to commercial laboratories in the States, and  
 25 sometimes they'll get results back on line

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1 where they have a screen just like this, and  
 2 they can look at the images there. The tests  
 3 are all done by an outside laboratory. Of  
 4 course, the burden on them is knowing what  
 5 they're looking at, and the burden on the  
 6 laboratory is making sure that they have all  
 7 the adequate quality assurance methods in  
 8 place so that the product that they're giving  
 9 to their clients, the pathologists, is a good  
 10 quality.  
 11 COFFEY, Q.C.:  
 12 Q. Is there, for example, in relation to ER and  
 13 PR tests, is there any such thing to your  
 14 knowledge as sort of a minimum number, for  
 15 example, that a laboratory should be involved  
 16 in producing over--I'll just pick an arbitrary  
 17 period like a year.  
 18 DR. DABBS:  
 19 A. Uh-hm.  
 20 COFFEY, Q.C.:  
 21 Q. In order to kind of keep the technologist or  
 22 technician's skills sharp, where there be any  
 23 minimum number--are there any studies done on  
 24 that, do you know, first of all?  
 25 DR. DABBS:

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1 A. I'm not aware of --  
 2 THE COMMISSIONER:  
 3 Q. Are you talking about technologists?  
 4 COFFEY, Q.C.:  
 5 Q. Technologists first of all, technologists  
 6 first, yeah, in the laboratory.  
 7 DR. DABBS:  
 8 A. As far as technologists, I'm not aware of any  
 9 number in that regard, but what I can tell you  
 10 now is that with the move to automation that  
 11 adding another stain on the stainer is not a  
 12 feat that is difficult for a technologist who  
 13 is used to doing immunohistochemistry in the  
 14 first place. They certainly would have to be  
 15 accredited or signed off as being competent in  
 16 dealing with the appropriate controls and  
 17 handling those results appropriately. As I  
 18 think about this, I mean, what I see is  
 19 arbitrary and just my feeling, that if you're  
 20 seeing somewhere around one of these a day,  
 21 that would seem to be a reasonable number to  
 22 keep up competence of pathologists who's  
 23 looking at it, as well as the technologist.  
 24 So you know--even if they did a batch run,  
 25 say, once a week, if, you know--that might be

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1 doable as well. Our oncologists are pretty  
 2 demanding. They always want results  
 3 yesterday, so we run them as soon as we get  
 4 them and we usually have enough to do that  
 5 because we have, I think, about between 1500  
 6 and 1800 new cancers per year, so we have--we  
 7 always have multiple numbers per week of  
 8 ER/PR, but I would say roughly one a day would  
 9 seem to be reasonable.  
 10 THE COMMISSIONER:  
 11 Q. Mr. Coffey, whenever you can find a convenient  
 12 spot, we'll break for the day.  
 13 COFFEY, Q.C.:  
 14 Q. Perhaps I'll come back then tomorrow and pick  
 15 up at paragraph five, Doctor.  
 16 DR. DABBS:  
 17 A. Okay. Just before we do go, Commissioner,  
 18 there is another exhibit. I'll refer to this,  
 19 and I expect it'll be referred to tomorrow.  
 20 It's P-2630.  
 21 THE COMMISSIONER:  
 22 Q. Entered.  
 23 COFFEY, Q.C.:  
 24 Q. Thank you, Commissioner.  
 25 EXHIBIT ENTERED AND MARKED AS P-2630.

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1 THE COMMISSIONER:

2 Q. 9:30 in the morning. Thank you.

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1 CERTIFICATE

2 I, Judy Moss, hereby certify that the foregoing is  
3 a true and correct transcript in the matter of the  
4 Commission of Inquiry on Hormone Receptor Testing,  
5 heard on the 15th day of September, A.D., 2008  
6 before the Honourable Justice Margaret A. Cameron,  
7 Commissioner, at the Commission of Inquiry, St.  
8 John's, Newfoundland and Labrador and was  
9 transcribed by me to the best of my ability by  
10 means of a sound apparatus.

11 Dated at St. John's, Newfoundland and Labrador  
12 this 15th day of September, A.D., 2008

13 Judy Moss

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Inquiry on Hormone Receptor Testing

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