Technical Brief on Statistical Tables from Estrogen Receptor/Progesterone Receptor (ER/PR) Database

DRAFT: February 29, 2008

Tumor = hormonal therapy

1. Introduction

This note provides a summary interpretation of the statistical tables from the NLCHI ER/PR Database. The tables address clinical issues only. Communications data will be forthcoming.

Throughout this report, references are made to original data from the Eastern Regional Health Authority. It is important to bear in mind that the data represents patients from all regions of the province and that not all of the steps in ER/PR testing take place in the Eastern Health laboratory. For example, tissue extraction and fixation occur at many sites throughout the province before transport to the laboratory, and post-laboratory interpretation and reporting by pathologists occur at many sites as well. Eastern Health collected and reported data on the retesting process for all patients starting in 2005, and therefore the data against which the NLCHI database can be compared was produced by Eastern Health.

Throughout this paper, the terms "case" and "patient" are used interchangeably and mean the same things. The term "tests" refers to ER/PR tests, with the distinction that some "cases" and "patients" had more than one "test" included in the database. The term "original test" refers to a test at the Health Sciences Centre laboratory between 1997 and 2005. A "Mount Sinai test" or "retest" refers to a new test conducted at Mount Sinai Hospital between 2005 and 2008 on a tissue sample that was the subject of an original test.

A statement about database methodology is contained in Appendix 3.

2. Total Cases

Eastern Health reported to the public on December 11, 2006 that there were 939 ER negative patients retested at Mount Sinai. This number was also reported to the Minister of Health and Community Services on November 23, 2006, to the court in affidavits, and to the media and public throughout the period in 2007 leading up to the appointment of the Commission of Inquiry.

The 939 total was explained by Eastern Health as containing all patients who had an ER negative test result performed at Eastern Health between 1997 and August 2005 and subsequently sent to Mount Sinai for retesting. The 939 total included 18 patients with original ER-positive results, meaning that they were ER positive before being sent to Mount Sinai. This is a small anomaly, attributable to specific requests from physicians to have these original ER positive results retested.

Using the same time period and inclusion criteria, NLCHI found 1013 patients, or 74 greater than the number reported by Eastern Health. It is not possible to explain completely the difference between the original 939 total and the new 1013 total because, as part of the tracking and data management process within Eastern Health, the spreadsheet which originally contained the 939 count was overwritten with updates. Therefore, it cannot be known with certainty how many cases, or which cases, were present or absent from the older Eastern Health spreadsheets. However, the general explanations for the new, higher total are:

- Some cases were identified by Eastern Health or self-identified by patients after the initial reporting of 939;
- Some cases of deceased individuals were not initially forwarded for testing because of a perception in some RHAs that only living patients need be identified;
- The challenges faced by Eastern Health (e.g., multiple information systems from which to identify original ER/PR tests and original test ~~scores~~ results; multiple channels for submitting retests to Mount Sinai; lack of an overarching information system to integrate records for all unique patients) made it difficult to identify every case.

Within the 1013 patients, or cases, there are 18 original ER positives that were sent to Mount Sinai for retesting. Removing these cases for analytical purposes, there were 995 ER-negative cases for which tissue samples were retested at Mount Sinai.

3. Comparison of Eastern Health's November 23, 2006 Briefing for the Minister with New Database Results.

The briefing by Eastern Health for the Minister of Health and Community Services on November 23, 2006 identified 939 cases of which 763 were living and 176 deceased. While some of the 176 deceased cases had been retested at Mount Sinai, they were not included in the detailed results as the focus was on the results and treatment recommendations for living patients.

If Eastern Health had captured all of the cases that are in the new database, and had it been linked to the Provincial Mortality Database (through NLCHI), 295 people would have been identified as deceased at that time instead of 176.[1]

In the briefing for the Minister, 104 patients were identified as requiring a treatment change. A matching number in the new database is not available for "treatment change". Such a comparator could be identified by examining additional records which identify treatment recommendations, a step that was not within the scope of this project.

[1] A year later, in November 2007, the number of deceased was 323 people.

4. Time frame for Retesting

The date that samples were sent to Mount Sinai can be determined for most of the cases. There are 52 cases where the date of testing cannot be determined from existing records. Out of the remaining xxx cases, 85% were sent in 2005, 4% were sent in 2006, 11% were sent in 2007 and xx% were sent in 2008. Not all results were back at the end of 2005. Majority of results back by ... ??

The reason why there was an increase in cases in 2007 over 2006 was the identification of some deceased that had been originally omitted due to uncertainty over "inclusion criteria", the inclusion of cases between January and May 1997 over which it was initially unclear whether they were supposed to be retested, and the identification of additional cases that should have been sent in 2005.

5. Number of Cases and Tests by Year of Original Test

Table A in Appendix 1 displays the number of original ER-negative cases by year which were subsequently retested at Mount Sinai Hospital. Out of the total 995 patients, the volume of testing was highest between 1998 and 2002. There were 202 patients tested in the peak year of 2000. The volume of negative cases declined substantially in 2004 after the automated Ventana testing system was utilized. Breast tissue samples from all surgical locations in the province were sent to Eastern Health throughout this period, with the exception of Clarenville which has been sending samples for testing outside the province since 1998.

Should identify all sites.

It was actually the # of people identified for retesting

Initial diagnosis between 98-02.

6. Positivity Rates and Change Rates

a. Data Issues

The following are some methodological points about the data used to calculate positivity rates and change rates:

1. The calculations (in the attached tables) refer to tests rather than patients because the positivity rate measures a characteristic of a group of tests, not a characteristic of a group of patients. The number of original negative tests (the numerator in the positivity rate) was gathered by NLCHI using criteria which ensured the exclusion of ER/PR tests performed for a reason other than breast cancer, duplicate records and data entry errors.
2. The total number of ER/PR tests performed by Eastern Health (which is used as the denominator in the positivity rate) was provided by Eastern Health. This number excludes the "non-breast" ER/PR tests in St. John's (about 4-5% of total tests), but data was not readily available to identify and exclude the non-breast cases from outside St. John's. This data could be requested from the regional health authorities, but such an effort was outside the scope of this project. It is estimated that this factor has a small upward impact on the overall positivity rate, and is likely

to be less than the 4-5% of samples in St. John's because sites outside St. John's have fewer non-breast tissue samples that require ER/PR testing.

3. Some of the retest samples were not the same paraffin blocks that were used to produce the original slides. The number of instances where this happened is believed to be about 5-10%, and it is uncertain whether the impact of this factor is to increase, decrease or cause no change in the positivity rate.
4. Between 1997 and 2005 there were 49 ER negative cases (57 tests) [Check] which were subsequently identified as DCIS. For purposes of calculating the original positivity rate, these tests have been retained even though DCIS patients are not normally sent for ER/PR testing.[2] They have been retained because these tests were part of the original set of tests that Eastern Health performed.
5. Depending on the cutoff point used in the statistical tables, some tests could not be interpreted as negative or positive (the number of such tests varies between cutoff points), and therefore have been excluded from the calculations.
6. The original purpose of the retesting process was patient care, not controlled research. Nonetheless, the retest group represents the complete set of ER-negative cases between 1997 and 2005 and therefore is unbiased for Newfoundland and Labrador. The characteristics of the Newfoundland and Labrador population could vary from the characteristics of study groups in the literature, but this issue has not been assessed.

b. Interpretation Issues

The interpretation of the ER/PR database is complex because of the changes over time in clinical cutoff points to define positivity, the uncertainty over whether all pathologists and oncologists were using the same cutoff points, and the distinction between "technical positivity" used in the laboratory environment and "clinical positivity" used in the treatment environment. The following discussion explains how these issues have been addressed in the presentation of data from the ER/PR database.

Changes in Clinical Cutoff Point

An single required standard for classifying positive and negative ER/PR tests is not used in Newfoundland and Labrador, and much disagreement exists throughout the world on the appropriate standards. While there are alternative methods for scoring ER and PR tests, most of the current literature suggests that positivity occurs at the 1% or 10% threshold. In Newfoundland and Labrador, since 2001, oncologists have generally regarded the 10% threshold as the appropriate threshold, and they used 30% between 1997 and 2000, though it is uncertain whether there was uniform compliance with these cutoffs. All practitioners agree that, while there is professional disagreement about the right cutoff points, the final determination on a case by case basis, taking into account other patient-related factors, is based on the oncologist's professional

[2] DCIS cases are not normally tested for hormone receptivity because they are not normally prescribed tamoxifen in Canada. An ER/PR test would only be done for the purpose of determining whether a person might be a candidate for taking tamoxifen.

opinion. Therefore, for presentation purposes, data from the ER/PR database is presented several ways: 1) a 30%/10% split before and after January 1, 2001 to reflect the clinical environment as practiced in this province; 2) a 10% cutoff for all years and a 1% cutoff for all years to allow for comparisons with the scientific literature and to allow for a consistent cutoff over the whole testing period. The 1% cutoff is comparable to a "technical" measure of positivity, and is discussed further below.

clarify what we mean by scientific

Uncertainty over Usage of Cutoff Points

The pathology reports show various descriptors used to report positivity and negativity. For example, some reports may say "0/0", which is a clear indication there is 0% staining and therefore a negative tissue sample. Other reports may include less precise descriptors such as "N", or "Neg/Neg", or "Weak Pos". The exact meanings of descriptors have not been determined with each reporting pathologist as part of the database exercise. Therefore, interpretation is necessary, and brings with it the possibility of a small amount of error. It is understood that the approach in interpreting the descriptors was consistent with the approach used by oncologists.

clarify

"Technical Positivity" and "Clinical Positivity"

In the laboratory environment the concept of technical positivity means that there is evidence of staining on an ER or PR slide. Even though the amount of staining may be less than 10%, and therefore in the region which oncologists may say the result is negative, the laboratory regards the test as positive because it has picked up the signal that some receptors exist in the cells.

ranging uncertainty

Clinical positivity is the concept used by oncologists to make treatment decisions. As noted above, the consensus cutoff currently in use, though not necessarily uniformly, is 10%. 0-1 neg 1-10% grayarea

The database presentation noted above using several cutoff points can address the distinction of technical versus clinical positivity. Clinical is best reflected in the 30%/10% presentation, while the technical positivity is best reflected in the 1% presentation.

Confusing

Analyzing PR

mo

In pathology and oncology, ER and PR are reported and considered together as they both provide information for treatment decisions. Interpretation is straightforward for three of the four possible ER/PR combinations: ER+/PR+ is clearly positive; ER-/PR- is clearly negative; and ER+/PR- can be deemed positive based on the clinical significance of the ER test. The approach to ER-/PR+ requires some discussion.

Oncologists at Eastern Health have advised that ER-/PR+ is a result they see periodically and a PR+ can be a determining factor in prescribing tamoxifen.

This opinion is confirmed by Rhodes (date), but he identifies a possible technical problem that may accompany a high number of ER-/PR+ results:

> In addition to ER, it is possible to demonstrate elevated progesterone receptor (PR) levels in a proportion of breast cancers, although PR alone is not a particularly strong independent indicator of tumour response to hormonal therapy. However, its presence does indicate a functioning hormone receptor pathway and is useful when unexpected results are obtained with the ER assay. For example, only approximately 3% of breast tumours are ER-negative and PR-positive. Therefore, the reporting of a relatively high number of ER-negative, PR-positive cases by a laboratory might indicate a technical problem resulting in false-negative results for ER.[3]

Another opinion by Moshin, et. al. (date):

> ...many clinicians depend on ER status alone to select patients for hormonal therapy.
> ...as compared to ER, PR adds only a limited amount of additional predictive information for response to hormonal therapy.

In assessing the degree of significance of PR in the database, it is also important to explain the use of PR in the retesting process by Eastern Health starting in 2005. One of the criteria used by Eastern Health to identify samples for retesting was ER negativity. The positivity or negativity of PR was not a factor. Therefore, samples that originally had ER-/PR+ results, and which may have been regarded as positive by oncologists at the time of a patient's initial treatment recommendation, were also gathered for retesting. Eastern Health has explained this approach as "casting a wider net" because it was not known whether ER-/PR+ patients were normally being prescribed Tamoxifen, and retesting might result in additional benefit for them.

A potentially confusing issue is Eastern Health's court affidavit in which it reports the number of clinically negative patients based on "ER/PR tests", yet in another affidavit the number of false negatives is reported as based on "ER test" cutoff points. The variance is explained by the fact that, in the latter, the court directed Eastern Health to identify all patients which converted from ER-negative to ER-positive, without consideration of PR.

[3] The use of scientific literature in assessing the ER/PR database results must be done with care to ensure that conclusions based on comparisons with the literature employ studies that were available before the date of the comparison.

To accommodate both perspectives, positivity rates and change rates (e.g., false negatives) are reported for ER-negative alone as well as ER/PR together, and both are presented at clinical cutoffs (30%/10%) and the technical cutoff (1%).

Understanding the Change Rate

Given that the results of the pathology reports are normally reported as a quantitative score between 0 and 100, it is possible to calculate the rate of change from negative to positive for the whole retest group. This approach is a mathematical approach, not a clinical one, and is not to be regarded as a substitute for the work of the tumour panel or other clinical judgments in the retesting process. In particular, the change rate in the test results is not an indicator of the proportion of patients who should have received alternate treatment. It is important to bear in mind that out of 317 patients who had "changed results" as reported by Eastern Health to the Minister on November 23, 2006, 117 needed a change in treatment.

c. Results:

The database results are presented below with respect to positivity rates, the ratio of ER/PR combinations to total tests, and change rates (i.e., false negatives). The 1997-2005 averages are presented, though the associated tables display considerable variability of annual results. In particular, the results begin to move much closer to the results expected in the literature starting in 2003, and strongly so in 2004-2005. The 1998 results are anomalous without apparent explanation.

Positivity (see Tables B to E)

Summary of Original ER/PR Test Data and Positivity Rates, 1997-2005, by Cutoff Point

Cutoff Point (%)	ER-	Total Tests (ER Adjusted)	ER-/PR-	ER- /PR+	Total Tests (HR Adjusted)	ER Positivity Rate	HR Positivity Rate	ER-/PR- % of Total Tests (HR Adjusted)	ER-/PR+ % of Total Tests (HR Adjusted)
30/10	1089	2533	871	207	2522	57.0	65.5	34.5	8.2
10	1030	2527	803	215	2514	59.2	68.1	31.9	8.6
1	815	2551	597	217	2550	68.1	76.6	23.4	8.5

Using a clinical cutoff of 30%/10%, there were 1089 original ER-negative tests between 1997 and 2005 which were retested at Mount Sinai Hospital. These original ER-negative tests comprised 43% of total tests, which means there was a

57% positivity rate for the whole period. Removing the ER-/PR+ tests from this group, and assigning them as ER/PR positive, the hormone receptor (HR) positivity rate is 66%.

Using a 10% cutoff point for the whole period, the number of ER-negative tests was 1030, the ER-positivity rate was 59% and the HR-positivity rate was 68%. Using a technical 1% cutoff, which is closely aligned with the way positivity is defined in the laboratory environment, the number of ER-negative tests was 815, the ER-positivity rate was 68% and the HR-positivity rate was 77%.

Table J presents a list of studies may be helpful in placing these results in context.

Ratio of ER/PR Results to Total Tests (see Tables B to I)

Original ERHA Tests: Using a clinical cutoff of 30%/10%, the ratio of ER-/PR- tests to total tests was 35% and the ratio of ER-/PR+ tests to total tests was 8%. Using a 10% cutoff point, the ratio of ER-/PR- tests to total tests was 32% and the ratio of ER-/PR+ tests to total tests was 9%. Using a 1% cutoff point, the ratio of ER-/PR- tests to total tests was 23% and the ratio of ER-/PR+ tests to total tests was 9%.

Mount Sinai Hospital Re-tests: Using a clinical cutoff of 30%/10%, the ratio of ER-/PR- tests to total tests was 24% and the ratio of ER-/PR+ tests to total tests was 2%. Using a 10% cutoff point, the ratio of ER-/PR- tests to total tests was 22% and the ratio of ER-/PR+ tests to total tests was 1%. Using a 1% cutoff point, the ratio of ER-/PR- tests to total tests was 19% and the ratio of ER-/PR+ tests to total tests was less than 1%.

Table J presents a list of studies may be helpful in placing these results in context.

Change Rates (False Negatives) - (see Tables F to I)

Summary of ER/PR Mount Sinai Retest Data and Change Rates, 1997-2005, by Cutoff Point									
Cutoff Points (%)	ER- Tests	ER-/PR- Tests	ER -	HR and DCIS Adjusted Total Tests	ER Negative Change Rate	ER-/PR- Change Rate	ER-/PR+ Change Rate	ER-/PR- % of HR- Adjusted Total tests	ER-/PR+ % of HR- Adjusted Total tests
30/10	623	584	39	2465	42.8	33.0	81.2	23.7	1.6
10	560	535	25	2457	45.6	33.4	88.4	21.8	1.0
1	491	480	11	2493	39.8	19.6	94.9	19.3	0.4

Using a clinical cutoff of 30%/10%, the number of original ER-negative tests between 1997 and 2005 dropped from 1089 to 623 after being retested at Mount Sinai Hospital. Thus, the change rate was 43% of total ER-negative tests for the whole period. Removing the ER-/PR+ tests from this group, and assigning them as ER/PR positive, the change rate was 33%. In other words, even though the proportion of false ER negatives was 43%, a more inclusive definition of positive, incorporating ER-/PR+ tests, means that the false negative rate from a clinical perspective was 33%.

Using a 10% cutoff point for the whole period, the total number of ER-negative tests dropped from 1030 to 560, for a change rate of 46%. Removing the ER-/PR+ tests from this group, and assigning them as ER/PR-positive, the change rate was 33%.

Using a 1% cutoff point for the whole period, the total number of ER-negative tests dropped from 815 to 491, for a change rate of 40%. Removing the ER-/PR+ tests from this group, and assigning them as ER/PR positive, the change rate was 20%.

Table K presents a list of studies may be helpful in placing these results in context.

Appendix I: Results Tables (based on NLCHI Database results)

Table A: Number and Percentage of Original Negative ER Tests and Cases by year.

Year	Number of Tests with Negative ER	Percentage	Number of Cases	Percentage
1997	66	5.9	61	6.1
1998	161	14.5	140	14.1
1999	168	15.1	149	15.0
2000	202	18.2	181	18.2
2001	152	13.7	141	14.2
2002	160	14.4	147	14.8
2003	111	10.0	98	9.8
2004	64	5.8	54	5.4
2005	28	2.5	24	2.4
Total	1112	100.0	995	100.0

1. Some patients had more than one ER/PR test. Some tests for a single patient may have occurred in different years, but the patient appears only in a single year.
2. Between 1997 and 2000 ER negative is $\leq$30% and between 2001 and 2005 ER negative is $\leq$10%. This definition is based on a clinical guideline and was used to determine which tests would be retested at Mount Sinai Hospital.

Table B: **Original ER/PR Test Results at ERHA and Positivity Rates, 1997-2005 (Cutoff: 1997-2000: 30%; 2001-2005: 10%)**

Year	ER- Tests	Total ER/PR Tests (ER Adjusted)	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR Adjusted)	ER Positivity Rate	HR Positivity Rate	ER-/PR- % of Total Tests (HR Adjusted)	ER-/PR+ % of Total Tests (HR Adjusted)
1997	64	135	49	12	132	52.6	62.9	37.1	9.1
1998	159	216	125	31	213	26.4	41.3	58.7	14.6
1999	165	358	132	32	357	53.9	63.0	37.0	9.0
2000	199	329	170	29	329	39.5	48.3	51.7	8.8
2001	148	338	113	34	337	56.2	66.5	33.5	10.1
2002	159	319	122	36	318	50.2	61.6	38.4	11.3
2003	108	316	89	17	314	65.8	71.7	28.3	5.4
2004	62	327	51	11	327	81.0	84.4	15.6	3.4
2005	25	195	20	5	195	87.2	89.7	10.3	2.6
Total	1089	2533	871	207	2522	57.0	65.5	34.5	8.2

1. All data are from the NLCHI database except Total ER/PR Tests which is based on Eastern Health's count of all ER/PR tests performed between 1997-2005.
2. ER Adjusted – means that results for which the ER score could not be interpreted for making a positive or negative classification have been removed. HR (hormone receptor) Adjusted – means that results for which the ER/PR score could not be interpreted for making a positive or negative classification have been removed.
3. Positivity Rate = ([Total Tests] – [ER or HR Tests]) / Total Tests

Table C: Original ER/PR Test Results at ERHA and Positivity Rates, 1997-2000 (Cutoff: 1997-2000: 30%)

Year	ER- Tests	Total ER/PR Tests (ER Adjusted)	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR Adjusted)	ER Positivity Rate	HR Positivity Rate	ER-/PR- % of Total Tests (HR Adjusted)	ER-/PR+ % of Total Tests (HR Adjusted)
1997	64	135	49	12	132	52.6	62.9	37.1	9.1
1998	159	216	125	31	213	26.4	41.3	58.7	14.6
1999	165	358	132	32	357	53.9	63.0	37.0	9.0
2000	199	329	170	29	329	39.5	48.3	51.7	8.8
Total	587	1038	476	104	1031	43.4	53.8	46.2	10.1

Notes: Same as above.

Table D: Original ER/PR Test Results at ERHA and Positivity Rates, 1997-2005 (Cutoff: 1997-2005: 10%)									
Year	ER- Tests	Total ER/PR Tests (ER Adjusted)	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR Adjusted)	ER Positivity Rate	HR Positivity Rate	ER-/PR- % of Total Tests (HR Adjusted)	ER-/PR+ % of Total Tests (HR Adjusted)
1997	64	135	47	14	132	52.6	64.4	35.6	10.6
1998	143	215	101	39	211	33.5	52.1	47.9	18.5
1999	145	356	114	30	355	59.3	67.9	32.1	8.5
2000	176	326	146	29	325	46.0	55.1	44.9	8.9
2001	148	338	113	34	337	56.2	66.5	33.5	10.1
2002	159	319	122	36	318	50.2	61.6	38.4	11.3
2003	108	316	89	17	314	65.8	71.7	28.3	5.4
2004	62	327	51	11	327	81.0	84.4	15.6	3.4
2005	25	195	20	5	195	87.2	89.7	10.3	2.6
Total	1030	2527	803	215	2514	59.2	68.1	31.9	8.6

Notes: same as above.

Table E: Original ER/PR Test Results at ERHA and Positivity Rates, 1997-2005 (Cutoff: 1997-2005: 1%)									
Year	ER- Tests	Total ER/PR Tests (ER Adjusted)	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR Adjusted)	ER Positivity Rate	HR Positivity Rate	ER-/PR- % of Total Tests (HR Adjusted)	ER-/PR+ % of Total Tests (HR Adjusted)
1997	52	137	36	16	137	62.0	73.7	26.3	11.7
1998	118	218	77	41	218	45.9	64.7	35.3	18.8
1999	109	360	80	29	360	69.7	77.8	22.2	8.1
2000	136	332	110	25	331	59.0	66.8	33.2	7.6
2001	119	342	83	36	342	65.2	75.7	24.3	10.5
2002	128	320	87	41	320	60.0	72.8	27.2	12.8
2003	78	318	64	14	318	75.5	79.9	20.1	4.4
2004	54	328	42	12	328	83.5	87.2	12.8	3.7
2005	21	196	18	3	196	89.3	90.8	9.2	1.5
Total	815	2551	597	217	2550	68.1	76.6	23.4	8.5

Notes: same as above.

Table F: ER/PR Re-test Results at Mount Sinai Hospital and Change Rates, 1997-2005 (Cutoff: 1997-2000: 30%; 2001-2005: 10%)

Year	ER- Tests	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR and DCIS Adjusted)	ER Negative Change Rate	ER-/PR- Change Rate	ER-/PR+ Change Rate	ER-/PR- % of HR and DCIS Adjusted Total tests	ER-/PR+ % of HR and DCIS Adjusted Total tests
1997	42	40	2	129	34.4	18.4	83.3	31.0	1.6
1998	91	83	8	203	42.8	33.6	74.2	40.9	3.9
1999	93	80	13	349	43.6	39.4	59.4	22.9	3.7
2000	117	111	6	316	41.2	34.7	79.3	35.1	1.9
2001	67	64	3	329	54.7	43.4	91.2	19.5	0.9
2002	73	69	4	313	54.1	43.4	88.9	22.0	1.3
2003	64	63	1	307	40.7	29.2	94.1	20.5	0.3
2004	52	50	2	326	16.1	2.0	81.8	15.3	0.6
2005	24	24	0	193	4.0	-20.0	100.0	12.4	0.0
Total	623	584	39	2465	42.8	33.0	81.2	23.7	1.6

1. All data are from the NLCHI database except Total ER/PR Tests which is based on Eastern Health's count of all ER/PR tests performed from 1997-2005.
2. HR (hormone receptor) and DCIS Adjusted – means that tests classified as DCIS, and tests results for which the ER/PR score could not be interpreted for making a positive or negative classification, have been removed.
3. Change Rate = ([Original Tests] – [Mount Sinai Tests]) / Original Tests

Table G: ER/PR Re-test Results at Mount Sinai Hospital and Change Rates, 1997-2005 (Cutoff: 1997-2000: 30%)

Year	ER- Tests	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR and DCIS Adjusted)	ER Negative Change Rate	ER-/PR- Change Rate	ER-/PR+ Change Rate	ER-/PR- % of HR and DCIS Adjusted Total tests	ER-/PR+ % of HR and DCIS Adjusted Total tests
1997	42	40	2	129	34.4	18.4	83.3	31.0	1.6
1998	91	83	8	203	42.8	33.6	74.2	40.9	3.9
1999	93	80	13	349	43.6	39.4	59.4	22.9	3.7
2000	117	111	6	316	41.2	34.7	79.3	35.1	1.9
Total	343	314	29	997	41.6	34.0	72.1	31.5	2.9

Notes: same as above.

Table H: ER/PR Re-test Results at Mount Sinai Hospital and Change Rates, 1997-2005 (Cutoff: 1997-2005: 10%)

Year	ER- Tests	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR and DCIS Adjusted)	ER Negative Change Rate	ER-/PR- Change Rate	ER-/PR+ Change Rate	ER-/PR- % of HR and DCIS Adjusted Total tests	ER-/PR+ % of HR and DCIS Adjusted Total tests
1997	38	37	1	129	40.6	21.3	92.9	28.7	0.8
1998	77	72	5	201	46.2	28.7	87.2	35.8	2.5
1999	66	63	3	347	54.5	44.7	90.0	18.2	0.9
2000	99	93	6	312	43.8	36.3	79.3	29.8	1.9
2001	67	64	3	329	54.7	43.4	91.2	19.5	0.9
2002	73	69	4	313	54.1	43.4	88.9	22.0	1.3
2003	64	63	1	307	40.7	29.2	94.1	20.5	0.3
2004	52	50	2	326	16.1	2.0	81.8	15.3	0.6
2005	24	24	0	193	4.0	-20.0	100.0	12.4	0.0
Total	560	535	25	2457	45.6	33.4	88.4	21.8	1.0

Notes: same as above.

Table I: ER/PR Re-test Results at Mount Sinai Hospital and Change Rates, 1997-2005 (Cutoff: 1997-2005: 1%)

Year	ER- Tests	ER-/PR- Tests	ER-/PR+ Tests	Total Tests (HR and DCIS Adjusted)	ER Negative Change Rate	ER-/PR- Change Rate	ER-/PR+ Change Rate	ER-/PR- % of HR and DCIS Adjusted Total tests	ER-/PR+ % of HR and DCIS Adjusted Total tests
1997	36	36	0	134	30.8	0.0	100.0	26.9	0.0
1998	67	66	1	208	43.2	14.3	97.6	31.7	0.5
1999	57	56	1	352	47.7	30.0	96.6	15.9	0.3
2000	86	82	4	318	36.8	25.5	84.0	25.8	1.3
2001	61	57	4	334	48.7	31.3	88.9	17.1	1.2
2002	59	59	0	315	53.9	32.2	100.0	18.7	0.0
2003	55	54	1	311	29.5	15.6	92.9	17.4	0.3
2004	49	49	0	327	9.3	-16.7	100.0	15.0	0.0
2005	21	21	0	194	0.0	-16.7	100.0	10.8	0.0
Total	491	480	11	2493	39.8	19.6	94.9	19.3	0.4

Notes: same as above.

Table J: List of studies which identify positivity rates in samples of ER/PR test, and the cutoff points used

Year of Publication	Cutoff point	Number of cases	ER+/PR+ (%)	ER+/PR- (%)	ER-/PR+ (%)	ER-/PR- (%)	ER Positivity rate	HR Positivity rate (excludes ER-PR-)
*Harvey et al (1999)	IHC score of > 2 (corresponding to as few as 1% to 10% weakly positive cells) was used to define ER positivity)	1,982	70.5%		29.5%		70.5%	---
Rhodes et al (2000)	10% receptor positive threshold	2,222	54.8	19.8	3.2	22.1	74.6%	77.85
Anderson (2001)	National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) has no standard definition or centralized laboratory to determine HR expression. Depending on the assay used, each SEER site codes ER and pr expression as presence – positive or absence-negative	19,541	66	12.5	3.4	18.6	78.5%	81.9%
Dako Manual **N.D.	Allred score which incorporates not only the proportion of cells staining but also the intensity of those cells.		58	23	4	15	81%	85%
Huang (2005)	H score for ER and PR, a negative result was defined as a score of < 50, weakly positive as 51-100, moderately positive as 101-200, and strongly positive as > 200.	1,362	62.6	18.5	1.6	17.3	81.1%	82.7%
Killeen (2006)	Tumors considered positive if nuclear staining was detected by Image Analysis in ≥ 5% of tumor cells.	667	62.4	16.9	1.3	19.3	79.3%	80.6%
Francis et al (2006a)	Scoring system used a modified quickscore system, which utilized a combination of percentage of cells and intensity of staining.	591	69.4	10.7	2.5	17.4	80.1%	82.6%
Francis et al (2006b)	Participating labs used their own cutoffs 1-5%, 5-9%, 10% 22% of the labs did not provide an answer to the cutoff level used	8,128	59	15.9	2.4	22.7	74.9%	77.3%
Collins et al (2008)	Any positivity (nuclear positivity in > 1% of tumor cell nuclei) on Tissue Microarrray 10% positivity (nuclear positivity in > 10% of tumor cell nuclei) on Tissue Microarrray	336	Any positivity 73.5 10% positivity 66.4	Any positivity 2.7 10% positivity 9.8	Any positivity 5.1 10% positivity 4.8	Any positivity 18.7 10% positivity 19.0	Any positivity 76.2% 10% positivity 76.2%	Any positivity 81.3% 10% positivity 81%

*Harvey et al. study only refers to ER positivity. PR is not addressed.
**2004 - last cited reference in the Dako Manual

Table K: List of Studies/Expert Opinion Addressing False Negative/False Positive Rates, Intra- and Interlaboratory Variation in IHC Assessment of Hormone Receptors.

Authors	Cutoff	Findings
Rüdiger et al (2002)	Unknown	11% false negative rate
Layfield et al (2003)	Variable cutoffs	Arbitrary cut point - 26% disagreement between labs Uniform cut points used – 28% disagreement between labs
Allred (2005)	1%	Approximately 20% for Estrogen Receptor
Rhodes et al (2001)	10%	Reliable assays found in only 36% of labs (24/66).
Regitnig et al (2002)	10%	**Unstained slides** False positive rate was 0% and the false negative rate was 1%. **Stained slides** False positive was 3% and the false negative rate was 2%.
Viale et al (2007)	10%	False negative rate as a percentage of negatives was 70% (73/105 tumors locally ER negative were positive i.e., > 10%); 7.6% or 8/105 had 1% to 9% positive cells.
Mann et al (2005)	0, <10% and ≥ 10%	False negative rate for core biopsies. **ER** (14%, 95% CI , 7.9% to 23.4%) **PR** (15%, 95% CI , 7.6% to 24.7%) **HR** (10%, 95% CI , 4.7% to 18.1%)
Rhodes et al (2000)	1% and 10%	Only 37% scored adequately on low expressing tumors
Collins et al (2008)	1% and 10%	**1% cutoff** 21.3% false negative rate as a % of negatives and 5.1% false negative rate as a percentage of total tests. 3.5% false positive rate as a % of positives and 2.7% false positive rate as a percentage of total tests. **10% cutoff** 20.0% false negative rate as a % of negatives and 4.7% false negative rate as a percentage of total tests. 12.9% false positive rate as a % of positives and 9.8% false positive rate as a percentage of total tests
Expert Opinion		
Allred (2004)		Community data - 30% false negative rate Repeat ER testing in difficult cases - conversion rate from negative to positive is 20-30%
Moshin (2004)		30% false negative rate
Magliocco (2005)		20% false negative rate

Appendix 2: NLCHI Database additional tables

Table 1: Database Contents	
Total Cases	1209
Total Patient Cases	1044
Less: Cases with original results before January 1997	---
Less: Cases with original results that were positive, and not known/included in Eastern Health spreadsheet August 1, 2006 (e.g., were retested after December 2006)	15
Less: Cases without original tests at Eastern Health.	16
Other???	---
Total A – Retested Cases consistent with December 2006 EH Report	1013
Less Original Positives up to December 2006***	18
Total B – Retested Cases with Original Negatives	995

Note: Total A includes:

-Any original positives that were identified in the August 1 Excel file

-Only those with original scores

-Cases with an original test done between January 1997 and August 2005

Total B includes

-Only those with original ***negative*** scores

-Cases with an original test done between January 1997 and August 2005

Table 3: Deceased (Using Total A)	
EH Reported as Deceased November 23, 2006	176
EH Reported as Deceased August 1, 2007	195
NLCHI Confirmed Deceased as of October 2005	238
NLCHI Confirmed Deceased as of November 23, 2006	294
NLCHI Confirmed Deceased August 1, 2007	315
NLCHI Confirmed Deceased November 26, 2007	322

Note: The vital status of any individuals from St. Pierre, or have since moved from the province are not captured.

Time Period of Original Test	Table 5: Number of Cases and Tests by Time Period of Original Test	
	Database (Total B)	Database (Total Original negative tests)
	# Cases sent for Retests*	# Tests sent for Retests*
1997	61	66
1998	140	161
1999	149	168
2000	181	202
2001	141	152
2002	147	160
2003	98	111
2004	54	64
2005 (August)	24	28
Total	995	1112

*Note: Excludes positives; negative defined as: ≤ 30 from 1997-2000, and ≤ 10 from 2001-2005. Includes tests with unclear original scores (i.e. weak positive, equivocal, etc.)