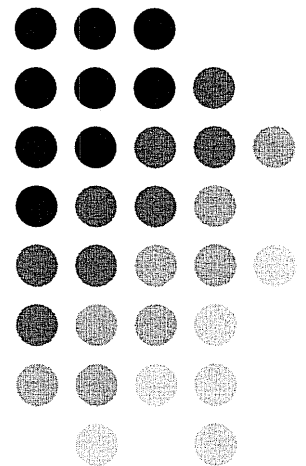
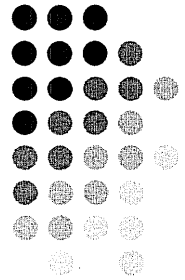


Technical Briefing ER/PR Database

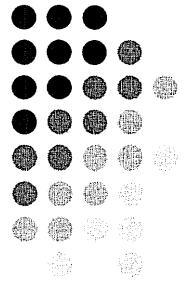
February 19, 2008
DRAFT





Background

- June 2007 – questions asked about patient contact. Was it complete?
- Department asked NLCHI to prepare database on communications and clinical information. Eastern Health endorses and provides full cooperation.
- Additional value for work of Commission.
- July 2007 – work commences (2 full time staff)



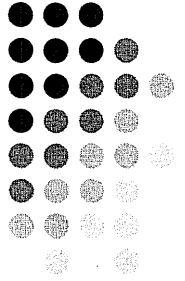
Content and Methodology

- Content

- Original scores/Mount Sinai scores
- Dates of testing
- Region/gender
- Type of contact/Date of Contact

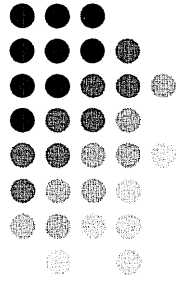
- Methodology

- All data backed up by source documents
- Multiple sources cross-checked to ensure accuracy and completeness
- All four RHAs involved
- Cooperation was excellent



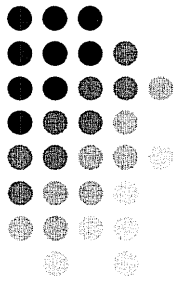
Database Limitations

- Due to multiple RHAs and multiple information systems, not certain that every patient captured (though much higher degree of certainty than before).
- Some retests were done on different samples, thus may affect comparability
- The Eastern Health retest process was not a research project – it was patient care.



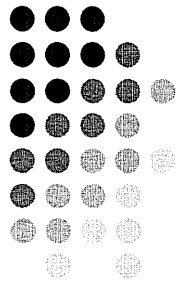
Number of Patients

- 06-11-23 – Easter Health reported 939 patients were retested.
- 07-11-02 – Minister announces actual number about 1000.
- Result – 1013 people had original ER/PR tests and were rested at Mount Sinai.



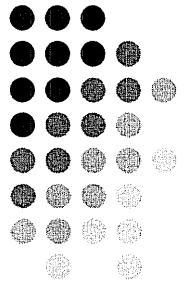
Number of Negative ER Patients

- 06-11-23 – Easter Health reports 12 people were confirmed positive, which means a total of 927 ER-negative patients were retested.
- Database confirms that 18 people were originally positive, which means the actual number of ER-negative patients retested at Mount Sinai was 995.



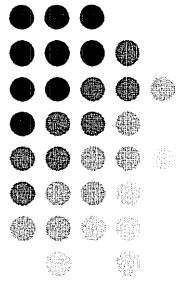
Number of Deceased ER-negative Patients

- 06-11-23 (and 07-05-17) Eastern Health reported 176 deceased out of the 939 patients sent to Mount Sinai.
- Did not use mortality database to identify deceased patients.
- Database includes 294 patients who were deceased on 06-11-23, and 323 one year later.
- This issue is one of data; not patient care or treatment.



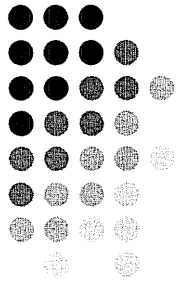
Contact with Families of Deceased

- Some families of deceased have already obtained results.
- In May 2007 Eastern committed to test all deceased and make results available.
- Will announce that data is now ready and provide contact information for families to identify themselves.
- This method is preferred over proactive contact given time elapsed and sensitivity of such information.



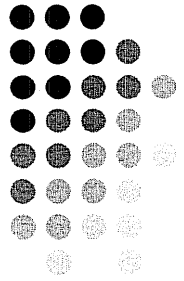
Total Tests at Eastern Health Positive and Negative

- As database focuses on ER-negative group, it was necessary to have the number of “total tests” in order to calculate positivity rates.
- This count was done by Eastern Health, monitored by NLCHI.
- Uncertainty about total for 1998.
- Small bias given inclusion of non-breast samples in total outside St. John’s.



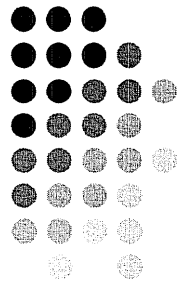
Usage of ER and PR

- Separate tests, but always performed and reported together.
- Both indicate pathways for receptivity, but not equally. ER stronger.
- Oncologists use both in making treatment decisions (even ER-/PR+)
- Even though all ER-negative samples were retested, some were PR+ and may have been treated with tamoxifen originally. Raises question why these were retested.



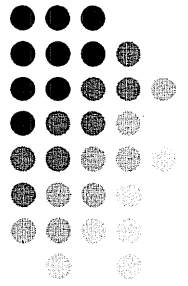
Cutoff Points

- Clinical context:
 - 1997-2000: less than 30% staining is negative; greater than 30% is positive.
 - 2001-2005: less than 10% staining is negative; greater than 10% is positive
- Technical Context:
 - Any staining is positive (e.g., 1% or greater)



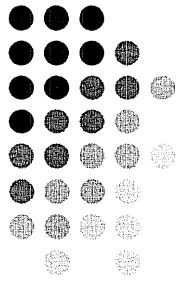
Expected Incidence of ER-/PR- and ER-/PR+

Year of Publication	ER-/PR- (%)	ER-/PR+ (%)
*Harvey et al (1999)	29.5%	
Rhodes et al (2000)	22.1	3.2
Anderson (2001)	18.6	3.4
Dako Manual **N.D.	15	4.0
Huang (2005)	17.3	1.6
Killeen (2006)	19.3	1.3
Francis et al (2006a)	17.4	2.5
Francis et al (2006b)	22.7	2.4
Collins et al (2008)	Any positivity 18.7 10% positivity 19.0	Any positivity 5.1 10% positivity 4.8



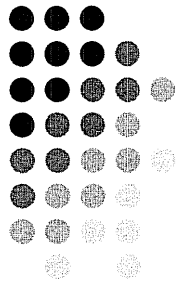
Incidence of ER-/PR- and ER-/PR+, 1997-2005 Average

Cutoff Point	Original		Retest	
	ER-/PR- % of Total Tests (HR Adjusted)	ER-/PR+ % of Total Tests (HR Adjusted)	ER-/PR- % of Total Tests (HR Adjusted)	ER-/PR+ % of Total Tests (HR Adjusted)
30/10	34.5	8.2	23.7	1.6
10	31.9	8.6	21.8	1.0
1	23.4	8.5	19.3	0.4



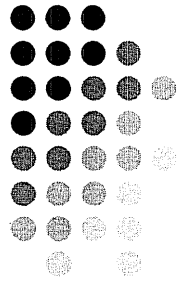
What is a Positivity Rate?

- Indicates the percentage of total tests which are hormone receptor positive, by cutoff point.
- If positivity is below a benchmark, or the expectations found in the literature, it may indicate the need for optimizing lab performance.



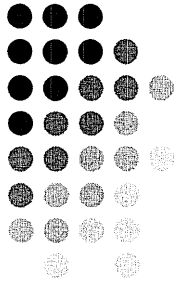
Expected Positivity Rate

Year of Publication	ER Positivity rate	HR Positivity rate (excludes ER-PR-)
*Harvey et al (1999)	70.5%	---
Rhodes et al (2000)	74.6%	77.8%
Anderson (2001)	78.5%	81.9%
Dako Manual **N.D.	81.0%	85.0%
Huang (2005)	81.1%	82.7%
Killeen (2006)	79.3%	80.6%
Francis et al (2006a)	80.1%	82.6%
Francis et al (2006b)	74.9%	77.3%
Collins et al (2008)	Any positivity 76.2% 10% positivity 76.2%	Any positivity 81.3% 10% positivity 81%



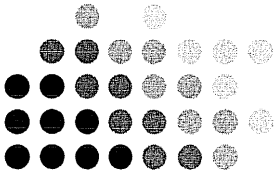
Database “Original Positivity Rate”, 1997-2005

Cutoff Point (%)	ER-	ER Positivity Rate	ER-/PR-	ER-/PR+	HR Positivity Rate
30/10	1089	57.0	871	207	65.5
10	1030	59.2	803	215	68.1
1	815	68.1	597	217	76.6

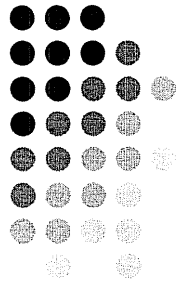


What is a Change Rate?

- The proportion of ER or HR negative tests that changed to positive after retesting
- E.g., false negatives

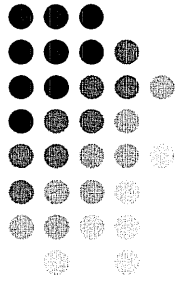


Expected Change Rate



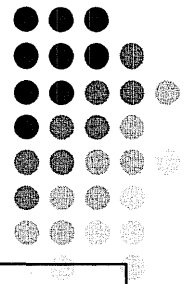
Database Change Rate

Cutoff Points (%)	ER Negative Change Rate	ER-/PR- Change Rate	ER-/PR+ Change Rate
30/10	42.8	33.0	81.2
10	45.6	33.4	88.4
1	39.8	19.6	94.9



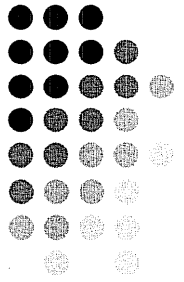
Contact with Patients

- Data was difficult to collect
- Actual contact process was dynamic, hectic, changing as results came in, and required coordination between four regions.



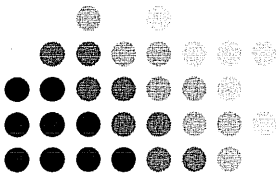
Method of Initial Contact with Patients

Method of communications	Total	
	No. of patients	%
Patient/Family initiated contact	46	4.5
Patient was contacted before results back	267	26
Patient was contacted after results were back	168	16.3
Patient was deceased before contact was made	233	22.7
Unable to contact	24	2.3
No Contact Made	53	5.2
Unsure if contact was made	9	0.9
Physician was informed by Health Authority of the results	10	1
Panel letter sent to the most responsible physicians*	145	14.1
Panel letter sent to the most responsible physicians also patient was contacted by physician*	26	2.5
Family of patient was contacted before results back	5	0.5
Family of patient was contacted after results back	2	0.2
Family of deceased was contacted	7	0.7
Direct consultation with Mount Sinai – Unable to confirm contact made	8	0.8
Other (outstanding information - require further clarifications)	4	0.4
Outstanding information	21	2
Total**	1028	100



Follow-up contact process

- Each RHA is being asked to verify non-contact. All non-contacts will be followed by with current contact to ensure completion.



Questions

DRAFT Press Release

Government Releases Data to Commission of Inquiry on Hormone Receptor Testing

.....announced today that the Newfoundland and Labrador Centre for Health Information (NLCHI) has substantially completed its work on a database on the Estrogen Receptor and Progesterone Receptor testing process at Eastern Health and the data is being provided to the Commission of Inquiry on Hormone Receptor Testing.

The database contains information on the original ER/PR results at Eastern Health, the retest results at Mount Sinai Hospital, and the how patients were contacted about the retesting process. This information should be useful to the Commission in the conduct of its investigations.

On November 2, 2007, Minister Wiseman informed the public that the total number of patients that were retested at Mount Sinai was higher than the 939 originally reported by Eastern Health on December 22, 2006. He said at the time that the number was about 10000. Today the Minister confirmed that the actual number is 1013. Although the retesting process focused on the patients who had original negative test results, there were 18 original positive cases that were also sent for retesting, which means that a total of 995 ER-negative patients were retested at Mount Sinai.

The database also updates the number of deceased in the retest group. Eastern Health had identified 176 people as deceased on May 17, 2006, using data collected in the previous year. Unfortunately Eastern Health did not utilize the mortality database (of the Provincial Government) when making its calculation. The actual number of deceased in the previous year was 294 patients. By November 2007 the number of deceased was 323. These numbers reflect inaccurate data management. Eastern Health did not know the true extent of deceased patients within the retest group.

The database also allows for the calculation of positivity rates and change rates (i.e., false negative rates). Such rates can be calculated in many different ways, depending if the purposes is to measure the technical performance of the test in a laboratory environment, or the clinical value of the test when treating a patient. Furthermore, the definition of “positivity” changed within the 1997-2005 period, and there is no universal agreement among physicians regarding the most appropriate definitions. Therefore, the database has been used to calculate a variety of rates using different definitions. The data has been supplied to the Commission (see a summary in the backgrounder) so it can interpret the data as part of its investigation.

The Minister noted that, as these results now include all the retest results for people who were deceased, the regional health authorities are now in a position to provide these results to next of kin, should those next of kin make a request. (See backgrounder on how next of kin may obtain retest results.)

NLCHI also collected data on the manner in which patients were contacted by the regional health authorities to advise them that their tissue samples were being sent for testing, and to advise them of their new results. The key question is whether everyone was advised. The database shows that xx people were not contacted..... The Minister has requested the regional health authorities to make new efforts to contact these people immediately and to have this phase of activity completed next week.

The Minister also endorsed the message from the Canadian Cancer Society that if there is any person who has not received their results, or who is unsure whether or not their results were communicated to them, they should call.....

The Minister thanked NLCHI for its diligent efforts, and thanked all the staff in regional health authorities who cooperated so fully in this process. The Minister believes the exercise was valuable and will assist the commission of inquiry in its work.

DRAFT - Backgrounder

Purpose of ER/PR Database

The purpose of the database is to provide an objective foundation for describing the 2005-2007 ER/PR (Estrogen Receptor and Progesterone Receptor) testing and retesting process, from both clinical and communications perspectives.

Context

- ER/PR testing is the primary determinant of whether a breast cancer patient is offered Tamoxifen or aromatase inhibitor as part of their post-surgical breast cancer treatment. A “positive” ER/PR test result indicates that Tamoxifen should be considered; a negative result indicates that Tamoxifen may not have a clinical benefit for the patient.
- On May 17, 2006 Eastern Health reported publicly that the tissue samples of 939 patients were retested at Mount Sinai Hospital for ER/PR hormone receptivity. The original tissue samples were tested between 1997 and 2005. Of the group of 939 patients, 12 patients were known to have original positive results, leaving a balance of 927 with known negative results. As well, of the 939 patients, 763 were reported as living and 176 deceased.
- Detailed retest results were reported by Eastern Health for the 763 living patients. Eastern Health said that 381 patients had their original results confirmed at Mount Sinai; 317 patients had changed results, mainly from negative to positive, but also some who went from positive to negative; 13 did not have changed results but did require treatment change due to a change in professional opinion as to what constituted a positive result; and 52 had “ductal carcinoma in situ” (DCIS) for which no form of treatment would have been recommended.

Database Approach

- The focus of Eastern Health’s retesting effort was to retest every ER/PR negative patient that had an original test at the General Hospital site between January 1, 1997 and August 1, 2005. The Department asked the Newfoundland and Labrador Centre for Health Information (NLCHI) to construct a database on all patients that fell within the same parameters. Eastern Health endorsed the NLCHI project and cooperated fully in the data collection process.
- Given that Eastern Health is the only site for ER/PR testing in the province, it received tissue samples from many surgical sites in the province between 1997

and 2005, and after the establishment of the testing process in 1997 and 1998 it returned the prepared slides for interpretation by pathologists at these other sites. Therefore, the database reflects test and retest results for patients from all regions.

- Data were gathered by NLCHI on such topics as: date of original test, original test result, data of retest, retest result, date of contact with patient, and related patient information.

Challenges

- The key challenge which NLCHI faced in preparing the database was the lack of a single information system in Eastern Health which contained all the relevant data. Further, the spreadsheets and records used by Eastern Health to coordinate the retesting process did not contain results on all the patients who had been retested. Therefore, the methodology used by NLCHI was to draw data from a variety of information systems, and to cross-check between those systems to make sure all patients were included.
- Between 2005 and 2007, Eastern Health used spreadsheet software to track the retesting process. The main spreadsheet was regularly updated without maintaining old versions when a new version was created. Consequently, the specific version containing the 939 cases noted above no longer exists and there is no way of recreating it in the absence of knowledge as to which cases were included at that time and which ones were not. This limitation prevented NLCHI from verifying the exact count which was reported by Eastern Health on May 17, 2007, and on previous dates when reports had been provided.
- Despite this limitation, NLCHI was able to construct a database which reflects the totality of all original ER/PR negative patients, plus their retesting results and other related information. The Eastern Health total of 939 belongs to a period of time between August 2006 and May 2007, and is not directly comparable to the higher number of cases which has been identified by NLCHI.

Results and Interpretation

Database Results	Interpretation
Patients	
Total Number of 1997-2005 ER/PR cases (or patients) that were sent to/retested at Mount Sinai -1013.	Instead of 939 total patients reported by Eastern Health, there were 1013 patients whose tissue samples were sent to Mount Sinai for retesting. Most of the extra 74 patients were retested alongside other patients in late 2005 and early 2006, but some were omitted until 2007 due to limitations in the tracking and monitoring process.
Total number of 1997-2005	Instead of the 927 ER/PR negative patients reported by Eastern

ER/PR “negative” cases (or patients) that were sent to/retested at Mount Sinai – 995.	Health, there were 997 patients whose results sent to Mount Sinai for retesting. The explanation for the difference is the same as above.																								
Total deceased as of November 2006 – 294. Total deceased as of November 2007 – 323.	The under-reporting of the number of deceased reflects the fact that Eastern Health did not utilize an authoritative source for mortality data when reporting its results. The actual number of deceased was higher. Such data could have been obtained through NLCHI and the provincial mortality database.																								
Tests																									
Total number of original ER/PR negative tests that were retested at Mount Sinai – 1112.	Some patients had more than one original test between 1997 and 2005, so samples for each test were also sent to Mount Sinai.																								
Positivity Rate (ratio of original positive results to total ER/PR tests)	<p>The positivity rate is an important indicator for monitoring the quality of the ER/PR test in an immunohistochemistry laboratory. Many studies report positivity rates between 75 and 80 percent.¹</p> <table><tr><th>Cutoff Point (%)</th><th>ER-</th><th>ER Positivity Rate</th><th>ER-/PR-</th><th>ER-/PR+</th><th>HR Positivity Rate</th></tr><tr><td>30/10</td><td>1089</td><td>57.0</td><td>871</td><td>207</td><td>65.5</td></tr><tr><td>10</td><td>1030</td><td>59.2</td><td>803</td><td>215</td><td>68.1</td></tr><tr><td>1</td><td>815</td><td>68.1</td><td>597</td><td>217</td><td>76.6</td></tr></table>	Cutoff Point (%)	ER-	ER Positivity Rate	ER-/PR-	ER-/PR+	HR Positivity Rate	30/10	1089	57.0	871	207	65.5	10	1030	59.2	803	215	68.1	1	815	68.1	597	217	76.6
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1	815	68.1	597	217	76.6																				
Treatment Change																									
Number of patients requiring a treatment change.	When the retest results were reviewed by a panel of physicians in 2005/06, 117 out of the 939 patients were recommended by the panel for a change in treatment. After the original panel was disbanded, Eastern Health continued to refer patients with changed results to physicians for review. Data was not available on the number of additional patients which required a change in treatment.																								

¹ Cite studies.

Questions and Answers

If there is an expected false negative rate, is there also an expected false positive rate?

Why is this test performed if there is such a high rate of false results?

Is the false negative rate an “error” rate?

Why did the problem occur?

Did Eastern Health conceal the real number of deceased?

When did the Department know that the number of deceased was not 176 but much higher?

Is the mortality rate for breast cancer higher in this province than elsewhere? If so, would the false negative results be a contributor to this problem?

If the positivity rate was so low, why wasn't it identified and corrected before 2005? Or before Dr. Ejeckam intervened in 2003?

Will the 2000 positive ER/PR tests be retested? If not, why not?

Why is the Department releasing these results now?

Was Eastern Health involved in this database project?