From: Ed Hunt
To: MHennessey@gov.nl.ca
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Subject: Info on ER/PR

Moira:

I have prepared a short note highlighting some of the issues related to breast cancer and the ER/PR issue. You may find it useful to better understand the science and feel free to share as necessary. I am in the process of drafting a request to CADTH but given the long weekend I don't expect to get through until Tuesday. We could ask for a list of the available articles and do the analysis ourselves (normally a 24 hour turn around for the articles) or ask CADTH to do nthe review for us (could be a few days). It will take us a bit of time to do the analysis.

Any sense of when we will need the research data? No doubt the reviewers will also get into this but it helps to ask the right question.

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Breast Cancer and ER/PR receptors

The prognosis for breast cancer depends on a number of variables. Some of these are listed as follows:

1. Classification of the tumor (benign to invasive)
2. Type of tumor (lobular or ductal)
3. Size of the tumor (< 2cm or > 2 cm)
4. Staging of the tumor (confined to a mass to metastasis outside the axillary lymph nodes)
5. Age of the woman
6. ER/PR receptivity
7. HER-2 receptors

When breast cancer is discovered the treatment varies from surgery, radiotherapy to chemotherapy or a combination of two or more treatment modalities. When treatment is planned further consideration is made with respect to additional adjunct therapy. If the tissue tests positive for ER/PR, tamoxifen or an aromatase inhibitor is offered as regular daily adjunct treatment. If the tissue is positive for HER-2, Herceptin may be offered.

The outcome for any patient obviously depends on any combination of the list of variables. ER/PR sensitivity is but one of the variables that influence outcomes. There is also evidence which suggests that the outcome is dependent on the ER/PR combination. In a 2004 study the following numbers were associated with respective tissue result.

EP +	and	PR +	5,704	71.4%
ER+	and	PR-	1,370	17.1%
ER-	and	PR+	220	2.8%
ER-	and	PR-	699	8.7%

What are EP/PR receptors and what is the relationship to drugs such as tamoxifen?

The receptor model suggests that each cell has a configuration that permits another molecule to attach to it. One such example is the red blood cell (RBC) which has receptor cites that bonds oxygen. This allows the RBC to transport oxygen from the lungs to the body's tissue cells. This is a weak bond thus allowing the oxygen to be dislodged from the RBC cell when it reaches the body's cells. These receptor sites are often not molecular specific and thus may accept other molecules that match certain molecular configuration. One such example is carbon monoxide. In fact carbon monoxide has a stronger bonding affinity to the RBC oxygen site than oxygen. Consequently in the presence of significant levels of carbon monoxide the RBC oxygen receptor sites are blocked with the carbon monoxide. This limits the body's ability to receive life giving oxygen and death often ensues.

In breast cancer cells the EP/PR receptor has the ability to bond hormones, in particular estrogen. Some tumors depend on estrogen to survive. Without estrogen the cells will "starve to death". Tamoxifen is a very weak sometimes considered an inert (or inactive) form of estrogen. However since it is an estrogen like molecule it can be bonded to the ER/PR receptor sites on the cells. If these receptor sites are saturated with tamoxifen it blocks the cell's ability to accept the more active estrogen molecules thus preventing the cells from multiplying and proliferating.

This is a simplified model to explain the role of the EP/PR receptors and tamoxifen. In reality the relationship is likely more complex. For example a tumor cell may be ER/PR positive but may also have high levels of a protein called AIB1. A 2003 study found that, in breast cancer patients receiving tamoxifen, high levels of AIB1 were associated with worst disease-free survival.

Given the foregoing discussion the proposed questions are valid. The suggested questions related to a clinical review are;

Clinical Review – Part One
(Note: it is recognized that the following questions will require the use of probabilistic estimates on existing medical research and standards.)

1. Given that certain people who would have required re-testing died before the errors were detected, can it be determined whether, and to what extent, accurate testing would have resulted in treatment that would have prolonged their lives?
2. Given that certain people required new treatment protocols after re-testing, can it be determined whether, and to what extent, the delay in appropriate treatment has had a negative effect on the quality of their lives and their life expectancy?

Clinical Review – Part Two
(Note: The following question will only be addressed by the Review only if the answers to questions 1 and 2 are affirmative with a reasonable degree of confidence.)

3. Given that certain people who would have required re-testing died before the errors were detected, determine whether, and to what extent, accurate testing would have resulted in treatment that would have prolonged their lives?
4. Given that certain people required new treatment protocols after re-testing, determine whether, and to what extent, the delay in appropriate treatment has had a negative effect on the quality of their lives and their life expectancy?

It is unlikely that there will be any certainty with respect to individual cases however there may be research available that may provide probabilistic estimates on each case based on the clinical information regarding each case. I have asked CADTH to search the literature to provide us with any research articles that may assist us in addressing these questions.