**ISSUE: The word “were” and preceding comma in “This is a theoretical percentage, were there a fictional treatment that guaranteed that the women represented would not die of breast cancer” found to be difficult to interpret.**

ACTION: Change to “This is a theoretical percentage, if there were a fictional treatment that guaranteed that the women represented would not die of breast cancer”.

**ISSUE: Clinicians unsure what to enter for “size” in case of multiple tumours.**

ACTION: Change “size” infobox to read: “The size of the tumour in millimetres. If there was more than one tumour, enter the size of the largest tumour.”

**ISSUE: Ki-67 is not in fact part of what OncotypeDX reports, contrary to the information in the current infobox.**

ACTION: Remove “If you have an Oncotype DX test done on the cancer to estimate your recurrence risk, checking Ki-67 levels is included as part of the testing.” from Ki-67 infobox.

**ISSUE: Difficulties in understanding how to enter information about micrometastases (see ‘Micrometastases: The core issue and intended interpretation of inputs’ later in document)**

ACTION: After extensive discussion between ourselves, Paul Pharoah, and others with relevant expertise, the approach and wording described at the end of this document has been approved by Paul Pharoah, as well as the clinical advisory group, with these additional comments from the clinical advisory group:

*“Need to be absolutely clear what to do with 2mm – macro or micro?*

*And same for 0.2mm.*

*Also – will you spell out what to do for ITC?”*

Wording at the end of this document has therefore been clarified to read “larger than 0.2 mm but not larger than 2.0 mm in largest dimension” rather than “between 0.2 mm and 2 mm in diameter”, in line with the AJCC definition.

We are hesitant to spell out what to do for ITC due to differences of opinion among researchers as to whether they have prognostic value. In any case David Dodwell and Paul Pharoah have noted that majority opinion is that ITC have no prognostic value, and this is consistent with the instructions as they are currently written (which instruct users only to set “micrometastases” to a number greater than 0 when there are micrometastases).

**Micrometastases: The core issue and intended interpretation of inputs**

We have now discussed this at length with Paul Pharaoh and understand that the algorithm currently behaves as follows:

* If the input is for positive nodes is 1 or greater, then “micrometastases” is not offered as a choice. This is appropriate because the original data on which the model is based did not contain information on number or size of micrometastases, only the number of positive nodes.
* If the input for positive nodes is 0, then “micrometastases” is offered as a choice.   
  + Entering “Yes” for micrometastases effectively sets the value of the “positive nodes” variable in the model to 0.5 (see footnote[[1]](#footnote-1) for a summary of the rationale. We met with Paul last month and discussed approaches to publishing/validating such rationales before adding updates of this sort in the future… you can expect to see an update from Alex, David S, or myself on this topic relatively soon)
  + Entering “No” sets the value of the “positive nodes” variable to 0.

However, this has been confusing to some clinicians -- the note from the clinician who directly contacted us hits the nail on the head with respect to the core issue:

“*“Regarding nodal involvement, the TNM staging stages micro metastases as node positive, not negative. However the tick box for micro mets only becomes active when you select '0' for 'positive nodes'."*

That is to say: If we consider a patient with one node which contains micrometastasis only, and the rest of the nodes are clear, this constitutes 1 positive node. However, if a clinician enters “1” under positive nodes, they will not have the option to select “yes” for micrometastasis. This is likely the reason why some people have been saying that they cannot enter micrometastases at all.

Paul suggested the following approach to making the inputs clearer, which we think makes sense:

* If the input is for positive nodes is 2 or greater, then “micrometastases” will not be offered as a choice.
* If the input for positive nodes is 1, then “micrometastases” will be offered as a choice.   
  + Entering “Yes” for micrometastases indicates that the 1 positive node was a micrometastasis, and effectively sets the value of the “positive nodes” variable to 0.5. Entering “No” indicates that it was a normal macrometastasis and effectively leaves the value of the “positive nodes” variable as equal to 1.
* If the input for positive nodes is 0, then “micrometastases” will not be offered as a choice.  
    
  Because many clinicians & registrars may be accustomed to entering [0 + micro Yes] for cases in which there is micrometastasis only, a “Why can’t I enter micrometastases?” link will appear when “0” is entered for the number of positive nodes, which links to a revised micrometastases info box explaining the change (see proposal for new info box contents on last page).
* “Enabled when positive nodes is zero” should be changed to “Enabled when positive nodes is 1”.

With respect to requests that clinicians be able to enter more specifics about the number of nodes with and without micrometastasis, or that they be able to enter the size of the detected micrometastases, Paul has indicated that there is not enough data to make use of these kinds of inputs effectively.

**Proposal for revision of the “positive nodes” and “micrometastases” info box text**

If the above approach to making the inputs clearer is adopted, the info box text will need to be changed accordingly. We worked up the following text for the “Positive nodes” and “Micrometastases” info boxes which has now been approved by Paul, avoids any discussion of ITCs (which are treated by the existing model as having no prognostic impact), and avoids the need to make any changes to the mathematical model.

**Positive nodes**  
  
The number of **positive nodes** is the number of lymph nodes to which cancer has spread. Some of them will have been removed during surgery and examined. A pathology report may quote a pair of numbers such as 2/3, meaning 3 lymph nodes were examined and cancer cells were found in 2 of them. In this case you would select '2'.  
  
If you select '1' here, the **micrometastases** input will be enabled.  
  
  
  
**Micrometastases**  
  
**Micrometastases** are small groups of cancer cells found in the lymph glands.  
  
Modern AJCC staging criteria define micrometastases as groups of cancer cells larger than 0.2 mm but not larger than 2.0 mm in largest dimension. Research suggests that patients who only have micrometastases have a better prognosis than those who have groups of cells larger than 2 mm [1].  
  
If you enter 1 positive node and “Yes” for micrometastases, this indicates that only one lymph node was found to contain cancer cells and that they were only micrometastases. Predict will model this as equivalent to half a positive node.  
  
This input is only relevant if you have entered 1 for the number of positive nodes.  
  
Click on 'Unknown' if this information is not available.  
  
   
  
[1] Iqbal J, Ginsburg O, Giannakeas V, et al. The impact of nodal micrometastasis on mortality among women with early-stage breast cancer. Breast Cancer Res Treat 2017;161(1):103-115.

1. Paul has explained the rationale for this as follows: The HR for micrometastasis is 1.49 compared to 1.82 for macrometastasis.  So macro v micro is a HR of 1.82/1.49 = 1.22. In our model the HR for nodes = x1 v nodes  = x2 is exp((log((x1+1)/10) - log((x2+1)/10))\*.7), For x1= 1 then x2 = 0.5 to give a hazard ratio of x1 v x2 of 1.22.  Hence treating micrometastasis as half a positive node. [↑](#footnote-ref-1)