Study reveals magnitude of variation in gene expression measurements within breast cancers

May 2 2013

An important new study has revealed the clearest picture yet of precisely how much measurement variation influences gene expression profiles of breast cancer.

The results show, for the first time, which gene expression measurements may benefit from pooling of biopsies from a single tumour, researchers said at the 5th IMPAKT Breast Cancer Conference in Brussels, Belgium.

These findings represent an important step toward allowing doctors to more precisely tailor an individual's treatment to a detailed analysis of their tumour's gene expression.

Over recent years, scientists have identified many genes, and groups of genes, that can provide crucial information about how an individual patient's cancer will respond to treatment with different drugs.

But a number of hurdles need to be cleared before tests to measure the expression of these genes can be used in clinical situations.

One important challenge is the fact that many different cell types can be present within a single tumour (known as intratumoural heterogeneity), each with different patterns of gene expression and potentially different sensitivity to drugs.

"Performing these tests with a single biopsy may or may not accurately represent that cancer, depending on intratumoural heterogeneity," explains lead author Dr Rosanna Lau from the University of Texas MD Anderson Cancer Center, US.

A further complication is that some of the variation between test results can arise from technical variations in the testing process, and not by real differences between samples (analytical variance).

To differentiate between these sources of variation in breast cancer, Dr Lau and colleagues performed DNA microarray analysis on three biopsies each from 51 breast cancers.

"Our results indicate that analytical variance, resulting from technical aspects of the assay, can be dramatically reduced by standard data processing methods such as normalizing and scaling," Dr Lau says. "Pre-analytical sources of variance, such as tissue preservation method and ischemia mostly did not affect gene measurements."

The dominant source of variance between biopsies from the same tumour was due to intratumoural heterogeneity, Dr Lau's group found. However, the extent of that variation depended on the particular gene or groups of genes being studied.

"Some genes, such as ESR1 and HER2, are very consistently expressed across the tissue, thus gene expression measurements display little variation between biopsies. However, other genes such as MKI67, which is known to be highly variable, is expressed less consistently, and therefore can produce vastly different results depending on the area of the tumour that is sampled," Dr Lau says.

For the first time, Dr Lau's group also showed how combining samples of two or three biopsies from a single breast tumour could effectively

overcome this variation for selected genes.

"Differences between tumours are much greater than variability within a tumour or a test. Our current study shows that we can get a comprehensive picture of the genes being expressed in the tumour by sampling multiple areas of the tumour and pooling the samples together. This increases the precision of the assay and allows us to make more reliable predictions related to the disease. The trade-off is that intratumoural heterogeneity is also averaged to a single, more consistent measurement."

This study is an excellent example of how researchers are rising to the challenges of tumour heterogeneity, comments Prof Charles Swanton, Chair in Personalised Cancer Medicine at the UCL Cancer Institute in London and from the Cancer Research UK London Research Institute, member of the ESMO Translational Research Working Group, who was not involved in the study.

"Developing accurate biomarkers that are not subject to real tumour sampling bias is of critical importance. This intricate study will likely be a gold standard by which other studies in this area are measured. Such in-depth analyses will ultimately be essential in the biomarker qualification process," he said.

"The study also emphasises the need to limit the potential for tissue processing or assay technologies to lead to spurious measurements through well-defined standardised operating procedures," Prof Swanton said.

Provided by European Society for Medical Oncology