Australian researchers have identified epigenetic 'signatures' that could help clinicians tell the difference between highly aggressive and more benign forms of triple-negative breast cancer.

The new study, published in *Nature Communications*, compares the breast cancer DNA 'methylome' with that of healthy individuals. The methylome provides a new picture of the genome and shows how it is epigenetically 'decorated' with methyl groups, a process known as DNA 'methylation'.

The study reveals "distinct methylation patterns" in the primary biopsy breast cancer cells indicating better or worse prognosis.

Triple-negative breast cancers, which make up 15-20% of all breast cancers, lack any of the three receptors (oestrogen, progesterone or HER2) that would make them responsive to targeted drugs. Overall, patients have a higher risk of disease recurrence and shorter survival than those with other breast cancers.

Triple-negative breast cancer patients tend to fall into two categories: those that succumb to their disease within 3-5 years, regardless of treatment; and those that remain disease free for longer than the average non-triple-negative breast cancer patient (at least 8 years post-diagnosis).

At present, there is no reliable way to 'stratify' triple-negative cancers into these two sub-groups. Clinicians use tumour size, degree of spread, and infiltration of lymph nodes to determine whether a patient falls into a high-risk or low-risk category. Ironically, the outcome of triple-negative breast cancers is far less associated with cancer stage than other breast cancers.

"This is the first study to investigate the methylome of triple negative breast cancer - and its association with disease outcome," said project leader Professor Susan Clark.

"There is a clear need for better informed disease management. In the absence of robust prognostic tools, too many women are being over-treated.

Pathologist Dr Glenn Francis, who analysed the tissue samples for the study, agreed. "The information we have at the moment is based on statistics and probability, and we are forced to treat triple negative breast cancer patients as a group, even though we know that they are not a uniform population," he said.

"By stratifying tumours epigenetically, this study should enable us to track selected groups of
patients over time, monitoring how they respond to
different treatments."

"From a purely practical standpoint, it's useful that
reliable results were obtained from formalin-fixed,
paraffin embedded tissue - as this is the material
routinely used for diagnosis."

Dr Clare Stirzaker and Professor Susan Clark
developed the methodology to sequence the
methylome using DNA extracted from the archived
tissue blocks.

"We were very pleased to find a way to interrogate
this archival DNA - a valuable resource because
methylation patterns can be correlated with patient
outcomes," said Dr Stirzaker.

"Developing the methylation sequencing
methodology allowed us to answer a new
question."

Professor Clark acknowledges that the findings
now warrant further investigation in much larger
breast cancer cohorts. "We are very encouraged to
have found that epigenetics provides a promising
new prognostic tool - and look forward to the results
from the next phase of validation," she said.