Whole genome sequencing could enable personalised cancer treatment, study suggests
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Whole genome sequencing (WGS) is a technique that involves reading the entire genetic blueprint of a cancer cell and comparing it to a patient's healthy cells to see how the DNA has mutated. By studying all the mutations present in a whole cancer genome and seeking all the signatures in them, it is possible to identify the various factors that have acted upon the tumour.

To understand whether WGS might be useful in a clinical setting, Cambridge researchers teamed up with colleagues in Sweden running a population-wide project called SCAN-B, which has been recruiting all women diagnosed with breast cancer in the South of Sweden since 2010. This was critical as SCAN-B has a large amount of clinical outcome data.

This international collaboration of researchers used WGS to analyse tumours from patients who had been diagnosed as having triple negative breast cancers. These cancers are so-called because they lack three key molecules known as receptors. They account for around 9% of breast cancers and are associated with poorer outcomes. They are also more common amongst women with African and Asian ancestry.

"Whole genome sequencing gives us a complete view of the cancer genome. It reveals many things that we couldn't see previously, because we simply did not look for them," explains Dr. Serena Nik-Zainal from the Medical Research Council Cancer Unit at the University of Cambridge, who led the study.

"Having a complete cancer genome map for each patient helps us to understand what has caused each patient's tumour and treat each individual more effectively. Previously, it was like going on a voyage with only a limited map, but now, with whole...
genome sequencing we have a much better, more
detailed map and know the best route to reach our
destination."

The researchers then applied a machine learning
algorithm called HRDetect, which they had
previously developed to identify tumours with
signatures caused by mutations in the BRCA1 or
BRCA2 genes. Having a variant of either of these
two genes greatly increases an individual's risk of
developing breast cancer and a relatively new class
of anti-cancer drug called PARP-inhibitors have
been developed specifically for these tumours.
HRDetect scores had previously suggested that a
greater proportion of women in the general
population could have tumours that are very similar
to BRCA1/BRCA2-mutant cancers.

Taking the scores, the team categorised each
patient as either high, intermediate or low scoring.

Patients who scored highly were those that had the
best outcomes using current treatments for triple
negative breast cancers—they are also most likely
to respond to PARP inhibitors.

Surprisingly, those with intermediate scores had the
poorest outcomes. Current triple negative breast
cancer treatments had limited effectiveness
suggesting that new approaches would be
necessary to tackle these cancers. However, the
genetic changes and signatures revealed through
WGS gave clues to the mechanisms driving these
tumours, which in turn may help inform the
development of new drugs.

Those patients with low scores also have poor
outcomes, though not as badly as those in the
intermediate group. However, the WGS profile in
some of these tumours suggested biological
abnormalities that could potentially be targeted by
existing drugs or drugs currently going through
clinical trials, such as so-called checkpoint
inhibitors or AKT inhibitors.

"Using whole genome sequencing, we can truly
discriminate tumours that may or may not respond
to current drugs among triple negative breast
cancer patients, a type of breast cancer that we still
struggle to treat well," says first author Dr. Johan
Staaf from the Department of Clinical Sciences,
Lund University, Sweden.

"But importantly, this approach also gives us clues
to some of the mechanisms that are going wrong in
the poor-outcome tumours, and hence how we
might treat those tumours differently or how we
might develop new drugs."

The speed of sequencing technology has
progressed such that WGS can be carried out in 24
hours, with another 24-48 hours for analysis of the
data. In theory, therefore, it should be possible to
offer whole genome screening as a matter of
course to all patients, allowing a personal readout
of their tumour and potential treatment options.

"The potential for whole genome sequencing to
open up a personalised approach to treating cancer
is huge," says Dr. Nik-Zainal. "In the past, the cost
and issues with managing the huge volume of data
created barriers to its widespread application. But
we are moving closer to a time where it can be
routinely offered to all patients, with the potential to
transform the management of even difficult-to-treat
cancers."

More information: Whole-genome sequencing of
triple-negative breast cancers in a population-
based clinical study, Nature Medicine (2019). DOI:
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