Researchers demonstrate the promise of precision genomics in cancer treatment

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Researchers at NUI Galway have identified genomic signatures in women developing the most common type of breast cancer that can be associated with long-term survival. The NUI Galway team analyzed the genomes of breast cancer patients to look for associations with survival rates using advanced statistical techniques.

Carried out by Lydia King during her studies in NUI Galway's MSc in Biomedical Genomics program, the research has been published in the international journal *PLOS ONE*.

Early detection by national screening programs and timely treatment for patients diagnosed with 'luminal' types of breast cancer have resulted in excellent prognoses with survival rates of over 80% within five years of treatment. The challenge of long-term survival however is not as well understood and studies have shown that more than half of all recurrences for luminal breast cancers takes place after this time point. Identifying patients most likely to suffer relapses would therefore be invaluable to patient monitoring and choice of therapies.

Genomes are the collection of all DNA in the chromosomes of cells containing all of our inherited genetic information. Cancer is often described as a disease of the genome because it is a consequence of alterations in the instructions encoded within some of our cell's DNA that lead to them proliferating without restraint. These alterations are a hallmark of a tumor and can range from single base-pair errors in the DNA code to the duplication or deletion of entire chromosome arms. The level of alterations in the genome of a cancer cell is known as 'genome instability'.

The NUI Galway team focused on whether an overall measurement of genome instability in cancer cells from luminal breast cancer patients, observed at diagnosis and before treatment started, could provide additional information in predicting their long-term survival. To test this hypothesis, they analyzed data from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) led by Cambridge University.

METABRIC is one of the first multi-center studies aimed at uncovering links between the clinical and genomic properties of biopsies taken from

over 2000 patients suffering from primary breast carcinoma enrolled between 1977 and 2005. The richness of having both high quality genomic data and the up-to-date clinical data makes the METABRIC database a very powerful resource for researching breast cancer.

Lydia and her colleagues calculated the level of genome instability across all 2,000 patient genomes, then used multivariable statistical modeling to identify distinct long term survival outcomes for luminal subtype breast cancer patients. This enabled them to confirm the significantly worse prognoses for luminal A patients suffering from the most extreme levels of genome instability in their tumor biopsies.

Importantly, the NUI Galway researchers were able to stratify the patients into groups and link the genome instability score with clinical classifications. This provided clear evidence that patients diagnosed with Luminal A breast cancer that had high levels of genome instability exhibited similar patterns of reduced survival commonly seen in patients suffering from the more aggressive Luminal B subtype. Since patients identified as either Luminal A or B subtypes normally receive different treatments, the result suggests that incorporating genomic analysis into clinical care could improve diagnosis and allow oncologists to tailor treatments for individual patients. This approach of using genomic analysis is known as 'precision (or genomic) medicine' and is helping to define a new standard of care in many areas of clinical practice.

Senior author of the paper, Dr. Aaron Golden of NUI Galway's School of Mathematics, Statistics and Applied Mathematics, said: "This is an excellent example of how interdisciplinary research is supposed to work in the genomics data sciences. This started out as a speculative idea between myself, a physicist, and my colleague Dr. Andrew Flaus, who is a biochemist from the School of Natural Sciences, and was taken by Lydia for her MSc dissertation project. We then received the invaluable assistance of our statistician colleague Dr. Emma Holian and through

Lydia's phenomenally hard work we could demonstrate the promise of precision genomics in cancer treatment."

Commenting on this result, Dr. Pilib Ó Broin, Program Director of NUI Galway's MSc in Biomedical Genomics, added: "This is a fantastic result for Lydia and her supervisors and highlights the enormous benefits of training interdisciplinary scientists like Lydia who possess both the statistical and computational skills as well as the domain knowledge necessary to generate new biological insights from genomics data with the potential to improve patient care."

More information: Lydia King et al, Survival outcomes are associated with genomic instability in luminal breast cancers, *PLOS ONE* (2021). DOI: 10.1371/journal.pone.0245042

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