“Everything You Know About Survival Analysis in Cancer Is Wrong”

A new approach to prognosis looks to patients’ genomes for clues about how their cancer will behave.

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Cancer treatment decision-making depends on an accurate understanding of a patient’s prognosis. Mistaking a cancer’s aggressiveness can lead to either under- or overtreatment, both of which carry increased risk of fatality. Current methods of prognostication, which usually rely on examining cancerous tissue via X-ray or microscope, involve subjective judgments and sometimes fail to predict disease course. With the rise of DNA sequencing technologies, clinicians are increasingly looking to patients’ genomes for clues about how their cancer will behave.

It has been presumed that genomic features that drive cancer progression will be associated with worse outcomes, and vice versa—that is, if a particular mutation is associated with lower survival, then that gene must be a cancer driver. By this logic, genes that are associated with poor prognosis are also presumed to make the best drug targets, given their expected role as cancer drivers. This assumption makes intuitive sense, but until recently, it had not actually been tested.

A new paper by former Damon Runyon Innovator Jason Sheltzer, PhD, and Joan Smith, PhD, of Yale School of Medicine, upends this assumption. Analyzing genomic and survival data from over 10,000 patients across 33 cancer types, the pair found more than 100,000 genomic features (biomarkers) that can be used to predict patient outcome. These included genetic mutations, repeated or deleted genes, and over- or underexpressed genes. But crucially, the biomarkers most strongly associated with a poor prognosis involved “housekeeping” genes that perpetuate the cell life cycle, rather than cancer-causing genes. For example, the gene EGFR is a known driver of many cancers, but mutations in EGFR did not mean a lower chance of survival. Overexpression of PLK1, on the other hand—a protein that plays a key role in cell division—did correlate with a worse prognosis.

Dr. Sheltzer’s findings challenge the way we think about prognostication and targeted treatment of cancer. Because the genetic features associated with poor prognosis are not necessarily located in cancer-causing genes, therapies directed against these features tend not to be successful. This approach mistakes correlation for causation and fails to address the cancer’s root cause. The data shows that these “housekeeping” genes do have prognostic utility, however, lending support to Dr. Sheltzer’s and Dr. Smith’s principal claim: that the search for prognostic biomarkers should be

separated from the search for cancer drivers and potential drug targets.

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