

The spread of cancerous cells determined with new model developed at YSPH

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Cancer cell during cell division. Credit: National Institutes of Health

Researchers at the Yale School of Public Health have discovered a mathematical relationship that sheds new light on the rate at which cancer cells mutate and why some survive and rapidly multiply, yet



others do not.

The discovery by members of the laboratory of Jeffrey Townsend, Ph.D., the Elihu Professor of Biostatistics and of Ecology and Evolutionary Biology, will allow essential calculations to be performed that determine the likely scope of cancerous cells as they develop.

The finding has implications for decision-making for precision-medicine tumor boards, the selection and design of clinical trials, the development of pharmaceuticals and basic research prioritization.

The study is published in the Journal of the National Cancer Institute.

"For the past 10 years we've been able to calculate from tumor sequencing which mutated <u>genes</u> are winners and losers—which mutated genes help the cancer survive and reproduce, and which do nothing," Townsend said. "But we haven't been able to compute their cancer effect size—how important one mutation is compared to another. Now we can."

A major goal of cancer biology is to not just identify the important and unimportant genes to the development of cancer, but to determine the relative importance of each cellular mutation to the survival and spread of <u>cancer cells</u> and, ultimately, what it means for the patient, Townsend explained.

In the study, the researchers estimated the effect sizes of all recurrent single nucleotide variants in 22 major types of cancer, and quantified the relative importance of each.

Tumor sequencing studies have typically reported how frequent mutations are seen and a statistical measure (a P value) indicating whether the gene is overburdened with mutations beyond expectation,



both important measures. However, neither measure is an effect size for cancer. Neither measure communicates how important the gene is to tumorigenesis and cancer disease. To quantify cancer effect size, Townsend and colleagues broke down the frequency that a mutation is observed in tumors into two contributing factors: the baseline mutation rate, and the degree of selection for the mutation in the cancer lineage. Both mutation and selection contribute to the frequency of variants among cells. Townsend and colleagues were able to use diverse genomescale data to calculate the mutation rate. By essentially dividing out the contribution of mutation from the frequency that mutations were observed in tumors, they showed how to calculate the cancer effect size

Townsend credits the breakthrough to insights that come from having a background in <u>evolutionary biology</u>. "Whereas in the cancer world the focus has always been on mutation rates, the focus in evolutionary biology has been on the process of natural selection on those mutations. The quantification of cancer effect sizes is a great example of how interdisciplinary research is not only helpful, but essential to scientific progress," he said.

Why is the cancer effect size important? Townsend uses an example of a tumor, from which a DNA sequence shows that two genes known to be related to cancer have mutated. There are two highly effective drugs targeting these exact <u>mutations</u> but no clinical trial has been conducted to compare them.

"By looking at cancer through the lens of evolution we can harness the wealth of molecular data made available through <u>tumor</u> DNA sequencing to both better understand what is driving <u>cancer</u> and to also expand and refine evolutionary theory," said Vincent Cannataro, Ph.D., a postdoctoral associate and the study's first author.

More information: Vincent L Cannataro et al. Effect Sizes of Somatic



Mutations in Cancer, *JNCI: Journal of the National Cancer Institute* (2018). DOI: 10.1093/jnci/djy168

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