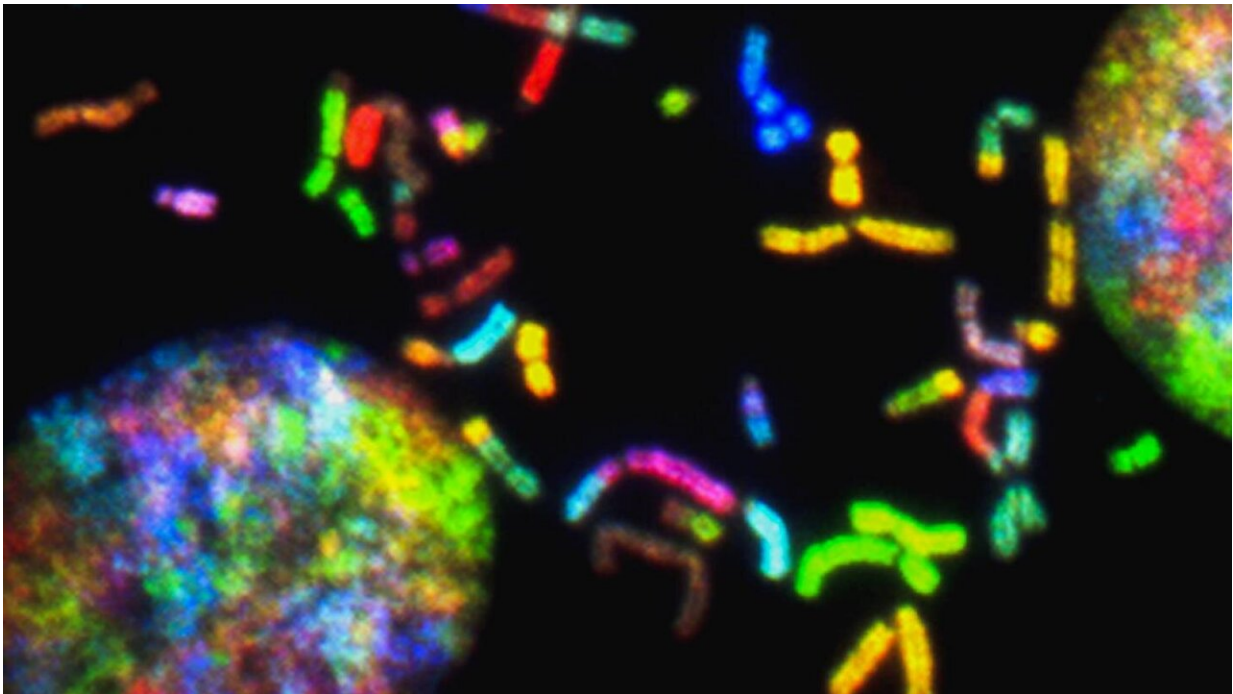


Algorithms uncover cancers' hidden genetic losses and gains

September 17 2020, by Molly Sharlach



Princeton computer scientists developed new methods that allow researchers to more accurately identify losses or duplications in chromosomes in cancerous tissue. Credit: Thomas Ried, NCI Center for Cancer Research, National Cancer Institute, National Institutes of Health

Understanding the specific mutations that contribute to different forms of cancer is critical to improving diagnosis and treatment. But limitations in DNA sequencing technology make it difficult to detect some major

mutations often linked to cancer, such as the loss or duplication of parts of chromosomes.

Now, methods developed by Princeton computer scientists will allow researchers to more accurately identify these mutations in cancerous tissue, yielding a clearer picture of the evolution and spread of tumors than was previously possible.

Losses or duplications in chromosomes are known to occur in most solid tumors, such as ovarian, pancreatic, breast and prostate tumors. As cells grow and divide, slip-ups in the processes of copying and separating DNA can also lead to the deletion or duplication of individual genes on chromosomes, or the duplication of a cell's entire genome—all 23 pairs of human chromosomes. These changes can activate [cancer](#)-promoting genes or inactivate genes that suppress cancerous growth.

"They're important driver events in cancer in their own right, and they interact with other types of mutations in cancer," said Ben Raphael, a professor of computer science who co-authored the studies with Simone Zaccaria, a former postdoctoral research associate at Princeton.

Although [medical science](#) has recognized the mutations as critical parts of cancer development, identifying these losses or duplications in chromosomes is difficult with current technology. That is because DNA sequencing technologies cannot read whole [chromosomes](#) from end to end. Instead, the technologies allow researchers to sequence snippets of the chromosome, from which they assemble a picture of the entire strand. The weakness of this method is that it cannot easily identify gaps in the DNA strand or areas of duplication.

To address this problem, Raphael and Zaccaria created new mathematical tools that allow scientists to search the vast collection of DNA snippets and uncover whether there are either missing pieces or

duplicates. The algorithms, dubbed HATCHet and CHISEL, are described in detail in separate publications on Sept. 2 in *Nature Communications* and *Nature Biotechnology*.

"All the cells you are sequencing come from the same evolutionary process, so you can put the sequences together in a way that leverages this shared information," said Zaccaria, who will soon begin positions as a principal research fellow at the University College London Cancer Institute and a visiting research scientist at London's Francis Crick Institute.

"The reality is that the technology for sequencing DNA in [individual cells](#) has limitations, and algorithms help researchers overcome these limitations," said Raphael. "Ideally, both the sequencing technologies and the algorithms will continue to improve in tandem."

Raphael's research group has multiple collaborations with cancer researchers who are beginning to apply the HATCHet and CHISEL algorithms to sequences from various types of patient samples and experimental models.

More information: Simone Zaccaria et al, Characterizing allele- and haplotype-specific copy numbers in single cells with CHISEL, *Nature Biotechnology* (2020). [DOI: 10.1038/s41587-020-0661-6](https://doi.org/10.1038/s41587-020-0661-6)

Simone Zaccaria et al. Accurate quantification of copy-number aberrations and whole-genome duplications in multi-sample tumor sequencing data, *Nature Communications* (2020). [DOI: 10.1038/s41467-020-17967-y](https://doi.org/10.1038/s41467-020-17967-y)

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