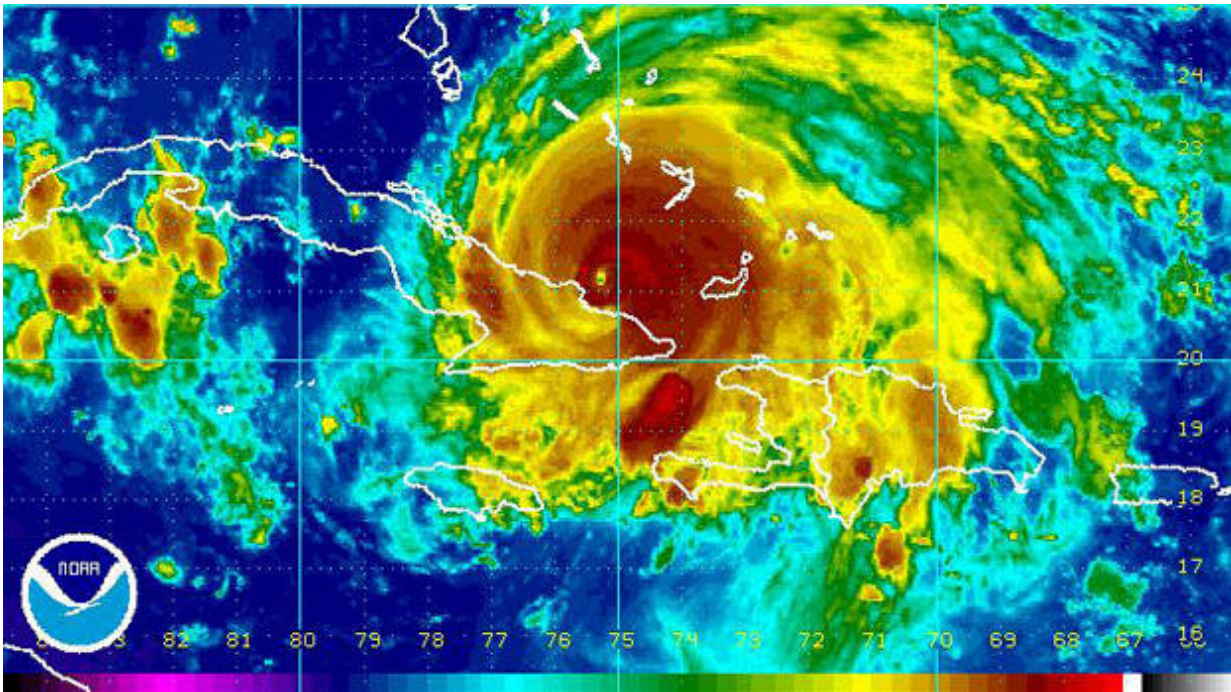# Learning from a cancer's past could predict its future

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Credit: NOAA/Wikimedia Commons

Complaining about the weather is a favourite pastime for many. And while we can't change it, the forecast gives us the opportunity to think ahead, plan and make sensible choices. Whether that's a change of outfit or using a different mode of transport, knowing what might lie ahead allows us to be prepared for what's predicted.

This is exactly where we want to be with cancer. Except that if we can predict how a cancer will behave over time, perhaps we can change its future, for the better.

A new study led by Cancer Research UK scientists takes us a step towards that goal. Published in *Nature Genetics*, they've used computers and genetic data to piece together a cancer's history, allowing them to develop a way to predict the next steps that the tumour will likely take as it progresses.

"We're revealing the secret history of a tumour, which we were never able to observe before," says lead researcher Professor Trevor Graham, from the Barts Cancer Institute in London.

"But the biggest thing about this work is that we're looking into the future, to know what a tumour will look like next week, month or even year."

That offers the chance that doctors could one day tailor treatment options in individual patients based on the predictions, keeping them one step ahead of the game. That's a distant goal, but this work helps carve a path to get there.

Past, present, and future

It's no surprise that this research has its roots in Charles Darwin's theory of evolution. Just like how a species changes as it adapts to its environment, so too does a growing tumour.

Scientists have been studying this process in species for many years. Thanks to sophisticated technology that reads an organism's DNA – alongside the computers and equations that quickly analyse the data – researchers can look back in time at a species' evolutionary history, and

its relationship with others.

And it's the same tools that make this possible for cancer too.

"We haven't invented new maths," says co-leading author Dr. Andrea Sottoriva, a Cancer Research UK Fellow from the Institute of Cancer Research, London. "We've taken what others have built over the past few decades to study various populations, and applied this maths to cancer."

By unravelling a tumour's past, the team hoped to understand more about what its future may hold. But as tumours are often studied at a single point in time, using a biopsy sample taken from a cancer that has already developed, the team needed to come up with a way to turn back the clock.

"The processes that took place before it was removed, how it grew, were previously invisible to us," says Graham.

So, the team turned their attention to existing data, making use of detailed genetic samples taken from tumours. They first began with DNA code read from just three patients – one with breast cancer, one with leukaemia, and one with lung cancer.

Cancer's secret diary

When a cancer grows its cells develop new genetic changes, meaning that one part of a tumour could have different genetic patterns to another. Studying this variety in the samples was key to this work.

"The question we wanted to answer was: 'how did that variety arise in the first place? Did it grow this way, or did it grow that way?'" Graham says.

Using maths that plots how a species evolves over time, the researchers built a computer simulation for the tumours. They then compared these different evolutionary scenarios to the genetic data from the patients, matching the scenarios that gave the same result.

From these matches, the researchers found the evolutionary path the cancers had likely taken, giving rise to the diversity that was found in each biopsy sample.

Next, they looked at 4 large groups of patient samples, spanning bowel, stomach and lung cancers, and also samples taken from cancer that had spread. These showed that genetic changes which give a cancer cell an advantage, such as being able to grow faster, emerge early in the tumour's development. But they also found that this process was still taking place in tumours that had spread, which could be caused by cells adapting to cancer treatment.

"A cancer's genetic information is a snapshot in time, telling you what the tumour looks like today," says Graham. "But it's also like a secret diary that records the dynamics that have happened over time.

"We're using this to learn something about the rules of cancer evolution."

Written in the rules

The team realised they could turn these rules into a way to predict how the cancers may evolve in the future. By running millions of simulations of tumour growth on computers, and seeing if their rules could forecast how these virtual cancers progressed, Graham is building confidence in their predictions.

"Once you know the rules, you can play the game," Sottoriva says.

"What we've done is enable predictions about cancer progression to hopefully be made in patients, so that treatment decisions could be made based on what the tumour will look like in the future, rather than today.

"But we haven't yet proven that's possible."

Next, they need to prove this technique's accuracy. And to do that, the researchers need to be able to track cancer evolution over time in the lab, and see if it matches their forecasts. And there's another key aspect that's so far missing from this work: how treatment might impact a cancer's evolutionary path. Finding that out is also next on their to-do list.

Research is like the weather. We don't know what the future holds. But in making predictions based on the evidence we have, an exciting and important journey of discovery awaits.

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More information: Marc J. Williams et al. Quantification of subclonal selection in cancer from bulk sequencing data, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0128-6

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