

# THIS WEEK

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## Tracking genetic shifts in cancer

*A promising clinical study of people with lung cancer shows how much-discussed liquid biopsies can improve treatment.*

One of the biggest obstacles to surviving cancer is the way the disease can shift its shape and form over time. Tumours are diverse and contain cells of many different types, with different genetic and epigenetic make-up. This allows cancer to adapt to changing environments, survive treatments and spread.

Researchers want to combat this fundamental lethal property to improve treatment. But to study tumour evolution in this way is to chase a fast-moving target. Investigators must track the genetic shifts in cancer cells in real time by setting up prospective assays that sample and analyse tumours during therapy. In theory, it should then be possible to tailor a growing arsenal of cancer drugs to fight emerging patterns of resistance and relapse. But finding a way to do this in the least invasive way represents a formidable challenge — and one that lies beyond the reach of existing tissue biopsies.

There is another way. Over the past few years, interest has grown in developing techniques to analyse cell-free DNA in the blood, such as prenatal genetic testing for fetal DNA in the mother's bloodstream. As cancer takes hold, the blood fills with free-floating DNA released from dying tumour cells. These genetic fragments could be used to check on the evolution of the tumours they came from. And in a promising clinical study published this week by *Nature* (C. Abbosh *et al.* *Nature* <http://dx.doi.org/10.1038/nature22364>; 2017), scientists report how they have done just that. What's more, their trial design — incorporating prospective observations of these circulating fragments of cancer DNA — is a step towards implementing tumour-evolution monitoring as a clinical tool that can dynamically inform treatment.

The clinical data reported online in *Nature*, and in a parallel paper in the *New England Journal of Medicine* (M. Jamal-Hanjani *et al.* *N. Engl. J. Med.* <http://dx.doi.org/10.1056/NEJMoa1616288>; 2017), describe the results from the first 100 patients enrolled in a trial called TRACERx, which aims to follow the tumour evolution of people with lung cancer who are undergoing therapy. The *Nature* paper describes a test to assess and compare genetic changes in tumours and in the blood. The dynamic tracking made possible by this “liquid biopsy” sequencing shows that early recurrence of the disease can be detected, and is associated with identifiable features in the circulating tumour DNA.

The results of the analysis support the idea that such liquid biopsies could provide clinical benefit by simplifying procedures and allowing for more-intensive real-time monitoring. Clinical implementation requires additional long-term studies, so that the performance of this type of monitoring can be tested alongside therapy. This is starting to happen: the design of clinical cancer trials is evolving rapidly to accommodate biomarker testing, and a growing number of registered trials are in progress to prospectively monitor tumour progression in the blood.

Still, some challenges remain, including the feasibility and cost of routinely applying liquid-biopsy techniques in clinical practice.

Besides helping to guide clinical decisions, the information derived from close monitoring of tumours with liquid biopsies can be readily

fed back to the cancer-research pipeline. Investigators can use this information to work out the mechanism behind the remarkable plasticity of tumours, and translational colleagues could then build on these insights to provide clinicians with improved cancer-killing drugs.

*Nature* is pleased to bring to our audience this type of clinical study. Such research should not only help convert research findings into medicines, but also provide a wealth of information for basic and clinical scientists. We hope such papers will continue to foster collaboration, and to bridge the gaps between basic and clinical points of view. As they align their sights to parse DNA fragments in the blood, researchers of all types can learn more from patients about how to help them more effectively. ■

## Dangerous cut

*The numbers of surgeons involved in research are falling — the trend must be reversed.*

In Steven Soderbergh's classy television show *The Knick*, set in a New York City hospital in the early 1900s, competitive and obsessively driven surgeon-scientists work on the burning medical issues of the day — identification of blood groups to allow blood transfusions, for example, and facial reconstruction surgery that returns dignity to those disfigured by syphilis.

Would-be healers have been testing surgical procedures since the Iron Age first delivered the necessary cutting tools. And the need for surgical advances remains. From the first heart transplant in 1967 to the emergence of deep brain stimulation and hopes for regenerative medicine, research is needed to transfer benchside discoveries to the bedside.

It is a problem, then, to find that surgeons are increasingly turning their backs on research. Evidence suggests that, compared with a decade or two ago, surgeons apply for and receive fewer grants, publish less, and — perhaps most perniciously — feel that research is not part of their role. Anecdotal reports suggest the trend is widespread, and not restricted to the United States — where it is best documented.

The latest report on the subject, published last September in *Annals of Surgery*, indicates that, according to two different measures, academic surgeons' interest in research in the United States is falling in linear fashion (S. G. Keswani *et al.* *Ann. Surg.* <http://doi.org/10.1097/SLA.000000000000052r>; 2016).

The report, compiled by the Society of University Surgeons (SUS), looked at grants awarded by the National Institutes of Health (NIH) to the 25 top-funded academic medical centres, and found that the proportion of funding to surgical departments dropped from 3% to

2.3% over the period 2006–14. Within individual medical faculties, the proportion of money going to surgical departments also fell. This is consistent with earlier studies showing that fewer surgeon-scientists apply for NIH grants and that those who do tend to be less successful than their medical colleagues in non-surgical disciplines (S. J. Rangel and R. L. Moss *Surgery* **136**, 232–239; 2004).

The SUS report also looked at the number of abstracts submitted to the annual Academic Surgical Congress between 2011 and 2015, and found that the proportion relating to basic science fell by 24%.

What is behind this dismaying trend? In a survey conducted among academic surgeons in 2000, the majority of respondents reported a belief in the value of basic scientific research, even if they were finding that growing clinical and administrative duties hindered their success. But by the time of the SUS report, there had been a mood shift. Some 1,000 academic surgeons responded to a survey that the authors carried out. More than half said that basic research was a priority in their departments — but just one-third said that it was realistic to expect surgeons to succeed in basic research. Most respondents said they had neither the time nor the motivation for research, and in any case lacked adequate departmental support and funding. Nearly two-thirds believed that basic research among trainees should be limited to a select few residents with the ambition and talent to be successful in future research activities.

Non-surgical medical departments are not affected in the same way. This is probably because the time pressures on surgeons are even greater than those on other physicians. Surgeons are faced with the

same increases in administrative duties as other medical-faculty members, but their clinical duties have grown faster. US hospitals depend increasingly on the income that surgeons generate — and have little motivation for encouraging them to spend time on research.

The flow of surgeons out of research is a problem that must be recognized and stopped. Translational medicine needs them too much.

**“Policymakers must stop seeing surgeons as easy sources of revenue.”**

Transplantation and transplant immunology have always been dominated by surgeons, and these areas are set to embrace a future that includes regenerative medicine and possibly xenotransplantation (transplantation of tissues and organs from other species). They are also much needed for crucial research into surgically treated diseases that only rarely hit the headlines — particularly in the correction of congenital birth defects, but also in adult disorders that rely on surgical skills, such as pancreatic cancers.

Involvement in research also allows surgeons to develop rigour in their everyday work, and to judge — and so maintain and improve — the quality of the work done by their peers.

Policymakers must create a health-care environment in which hospitals have incentives to think of patient care as inevitably linked to science, and to stop seeing surgeons as easy sources of revenue. But that's not going to happen any time soon. In the meantime, and at the very least, funding agencies should make it less burdensome for busy surgeons to apply for grants — and, in response, academic surgeons should apply more often, and thus increase their chances of success. ■

## ANNOUNCEMENT

## Nature Research signs DORA

Nature Research will this week formally sign up to the principles outlined in the San Francisco Declaration on Research Assessment, commonly known as DORA. Nature Research (the Nature-branded journals, *Scientific Reports*, *Scientific Data* and the Nature Partner Journals) has long been editorially aligned with the principles described in DORA, particularly the need to move away from the inappropriate use of the journal impact factor. (A collection of relevant editorials is available on our journal-metrics web page.)

As long ago as 2005, *Nature* was expressing concern about the problematic dependence on journal impact factors when individual scientists are assessed by their institutions and funders (see *Nature* **435**, 1003–1004; 2005). The skewed distribution of a journal's citation statistics (by a few very highly cited papers) undermines any fundamental usefulness of the impact factor, and the belief that a researcher's strengths can be measured by such a statistic is self-evidently absurd. So, too, is the misguided belief that numbers of citations are the only measure of a paper's scientific value.

Scientists have justifiably complained about the abuse of impact factors for years, and continue to do so (see page 411). That's not to deny that the factor has some value as an indicator of a journal's cumulative scientific impact. But so do other measurements, such as the immediacy index, the eigenfactor score and the article-influence score. Indeed, in assembling these and other indicators last year in the new Nature Research journal-metrics page, we created the 'two-year median citation score' as a less-skewed complement to the impact factor. We also provided definitions of each metric to help the reader to understand what they really mean, and to provide context for how our journals are performing.

We have examined researchers' opinions about metrics over recent months, and what matters to them when choosing where to submit their work. And in the second half of 2016, we carried out a survey of authors.

Some 985 authors from Nature Research and more than 2,500 from Springer Nature overall, who had published a research article during 2015–16, gave us their views, with the largest groups of respondents coming from Europe (47%), Asia and the Middle East (19%) and the United States (15%).

The survey showed a demand for publishers to provide more information about their journals: 85% of authors said that information on journal performance is important to them when deciding where to submit their work, but 48% thought that publishers did not provide enough. For junior researchers with less publishing experience, this information is particularly important.

The survey also revealed that authors were deeply interested in the quantitative and qualitative details of a journal's peer-review process. Journal choice was influenced by these and other experiences, including interactions with journal editors, an understanding of a journal's readership, and the overall reputation of a journal and its publisher. The survey did confirm that, despite knowledge of its limitations, the impact factor remains a key metric for researchers, although alternative metrics were considered by many to be as important for journal choice.

Since the survey, we have attempted to provide more-accessible information about what the different metrics mean, and about aspects of the peer-review process that researchers care about. The latter is particularly important, given that we employ some 300 professional editors dedicated to delivering efficient and robust peer review.

Accordingly, we have improved the Nature Research metrics page to provide extra information on median times for all the key stages of the submission-to-publication workflow. We've also created a new infographic with short, simple explanations of each of the metrics we now offer, which we've released under a CCBY licence so that anyone, anywhere, can use it. ■