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Realizing DNA's medical promise remains a costly challenge

Seventy years after DNA's structure was published, the prospects for gene therapies could be jeopardized by cost and complexity.

"We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.)," wrote James Watson and Francis Crick in this journal in 1953 (J. D. Watson and F. H. C. Crick *Nature* **171**, 737–738; 1953). "This structure has novel features which are of considerable biological interest."

In the 70 years since those famous words were published, researchers have poured huge effort into unravelling those features and harnessing them for medicine. The result is a flourishing understanding of the genetic causes of diseases — and a host of therapies designed to treat them.

Seventy years from now, the world might look back on 2023 as a landmark, as well. This year could see the first authorization of a therapy based on CRISPR–Cas9 gene editing, that involves tweaking the DNA in the body's non-reproductive (somatic) cells. Gene editing allows scientists — and could soon permit clinicians — to make changes to targeted regions in the genome, potentially 'correcting' genes that cause disease. Regulators in the United States, the European Union and the United Kingdom are evaluating a therapy that uses this approach to treat sickle-cell disease, and a decision could be made in the next few months.

But even as such advances accrue, researchers are worrying about the future role of gene editing — as well as other, more established forms of gene therapy — in treating disease. Gene therapies currently carry eye-watering price tags, putting them out of the reach of many who need them. High prices could diminish the willingness of government funders to pay for gene-therapy research. And that, in turn, would make it harder for research institutions to continue to attract top talent to the field. Researchers, especially health economists, must work urgently with industry and governments to find a more affordable funding model.

Million-dollar treatments

CRISPR–Cas9's speedy path to the clinic was paved by years of steady advances in forms of gene therapy that use a virus to shuttle genes into cells. Over the past decade, regulators have approved several such gene therapies, for example CAR-T-cell therapies, which engineer immune cells to treat cancer. Hundreds more are in clinical trials.

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These therapies typically cost something like US$1 million for a single treatment, and more once the costs of administering them, such as hospital stays and procedures required to isolate and manipulate cells, are factored in. Last year, the US Food and Drug Administration approved the first gene therapy to treat haemophilia B, a genetic disease that impairs blood clotting. The price is $3.5 million per treatment, making the therapy, called Hemgenix, the most expensive drug in the world.

Gene therapies are more costly to develop and produce than are more well-established treatments based on small-molecule drugs. But gene therapies can also carry the hope of a cure, freeing recipients from both long-term reliance on expensive medicines and the risk of hospitalizations. Some have argued that this justifies the high cost: if a therapy can save millions in downstream treatments, the initial outlay would still save money overall. Over time, after all, the costs of more-conventional treatments add up: one study, for example, found that in the United States, the cost of treating a person with sickle-cell anaemia until the age of 64 is $1.7 million (K. M. Johnson *et al. Blood Adv.* **7**, 365–374; 2023).

Even in wealthy countries, health-care systems are ill-equipped to shoulder the high initial costs associated with gene therapies. In 2021, therapeutics developer Bluebird Bio in Somerville, Massachusetts, withdrew plans to market a gene therapy for β-thalassaemia — another blood disorder — in Europe, after failing to reach an agreement with European authorities over the price. It said it would focus its sales efforts on the United States, where there has been comparatively little regulation of drug costs.

But even in the United States, costs matter. US health insurance is often subsidized by employers, and some are already saying that they will probably restrict their coverage of gene therapies in the next year, says Steven Pearson, president of the Institute for Clinical and Economic Review, a health-economics think tank in Boston, Massachusetts.

Low- and middle-income countries, meanwhile, are left entirely in the lurch. This is especially painful given that some of the diseases under consideration, such as β-thalassaemia and sickle-cell disease, are more common in poorer parts of the world than in wealthy nations. In some sub-Saharan regions, for example, it is estimated that about 2% of children are born with sickle-cell disease. This is likely to be an underestimate, given how little screening is taking place.

Improving access

It is too soon to know how much the CRISPR–Cas9 treatment for sickle-cell disease would cost; neither of its developers, Vertex Pharmaceuticals in Boston, Massachusetts, or CRISPR Therapeutics in Cambridge, Massachusetts, have disclosed what they will charge. But researchers are bracing themselves for the price tag to come.

At the Third International Summit on Human Genome Editing, held in London in March, much of the discussion centred on making gene-editing therapies accessible, particularly to low- and middle-income countries. The focus was on technological approaches to streamline the production and testing of such treatments. The sickle-cell

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treatment, for example, requires clinicians to isolate and edit blood-forming stem cells, destroy those that remain in the body, and then reinfuse the edited cells. Converting this to a genome-editing procedure that could be performed directly in the body rather than in isolated cells could make the treatment cheaper and more accessible.

Another appealing approach is to develop gene-therapy platforms that have already been confirmed to be safe and effective. Gene-therapy developers could then just swap in a gene that targets the chosen disease, without the gamut of tests of safety and efficacy that are required when starting from scratch.

But technological solutions such as these will go only so far. US drug pricing has little to do with how much it costs to produce a therapy, says Pearson, because companies can charge as much as the market will bear. How much that price will drop in other countries could be limited by intellectual property rights and hindered by the complexities of making generic copies of biological drugs such as gene therapies. Some academic centres are trying to develop and deploy gene therapies without relying on pharmaceutical companies, but it is unclear how far such efforts can stretch without the financial resources and regulatory expertise found in industry.

In addition to pricing, gene-therapy technologies are mired in debates around regulation and intellectual property. How each of these plays out will determine how far researchers can go in capitalizing on Watson and Crick's initial discovery. It's important that scientists have an active role in these debates, and that they push such discussions to the fore sooner rather than later.

Rosalind Franklin was let down by a dysfunctional team

The story of how DNA's structure was found is one of a collaboration from which one member was unforgivably excluded.

Seventy years on from the discovery of the structure of DNA, controversy still surrounds two central points: how much credit Rosalind Franklin deserved, and the degree to which she was denied it. A lot of what we know about Franklin's contribution comes from other people. Initially these were Franklin's main collaborators: her colleague at King's College London, biophysicist Maurice Wilkins, and molecular biologists Francis Crick and James Watson at the University of Cambridge, UK. Each wrote autobiographical accounts and gave interviews to journalists and researchers. Franklin, a physical chemist, left no comparable account: she died from ovarian cancer in 1958 at the age of 37.

> "Franklin was excluded from networks of men who shared data and insights."

Franklin's perspective in her own published words has always been missing from the story that led to the inclusion of three papers[1–3] in *Nature* in 1953. In this issue, zoologist Matthew Cobb and medical historian Nathaniel Comfort (who are writing separate biographies of Crick and Watson) reconstruct the development of Franklin's ideas using her papers, archived at Churchill College, University of Cambridge (see page 657).

One clear conclusion is that the untangling pf DNA's structure was a team effort. Crick and Watson were the theoreticians and model builders — literally, using cardboard cut-outs to illustrate possible structures. But they could not have arrived at the right structure without experimental input: X-ray diffraction data from Franklin, Wilkins and Franklin's student Raymond Gosling.

Besides this confluence of theory and experiment — which Watson and Crick did not acknowledge in their original paper — management support was essential to the project's success. Senior academics at both universities were very involved, partly because they wanted to get to the structure before US chemist Linus Pauling did.

But if the discovery was a true joint effort, at least one member of the team, Franklin, was also very much on the outside. She was excluded from the networks of men who continuously shared data and insights. There were frequent clashes and the evidence of sexism is clear in Watson's 1968 account *The Double Helix* in which he wrote: "Clearly Rosy [sic] had to go or be put in her place."

Journalist Brenda Maddox, who drew on Franklin's personal correspondence for her 2003 biography *Rosalind Franklin*, makes a further important point. Franklin was Jewish and unhappy in a broader atmosphere of antisemitism at King's College London at the time: leaving was more important to her than completing the work on DNA. Crystallographer J. D. Bernal observed in his obituary of Franklin that she was an enthusiastic collaborator and mentor, and happier at Birkbeck College in London than King's, leading a team that worked on the tobacco mosaic virus.

Franklin eventually reconciled with Crick and Watson. And Cobb and Comfort point out that, in a 1954 paper, the two men acknowledge that their structure "would have been most unlikely, if not impossible", without Franklin's data[4]. Assigning due credit is an indication of collaboration, and it's an injustice when this happens only after the event.

The broader point is that Franklin's colleagues — and the scientific environment they moved in — refused to recognize her strengths, purely because of who she was. Sadly, that remains the case: the title of a paper published in *Nature* last year[5], "Women are credited less in science than men", says it all. Diversity, equity and inclusion are concepts that some still regard as fashionable impositions and anathema to 'good' science. The DNA story shows that they are the foundations of beneficial collaboration and scientific progress.

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3. Franklin, R. E. & Gosling, R. G. *Nature* **171**, 740–741 (1953).
4. Crick, F. H. C. & Watson, J. D. *Proc. R. Soc. Lond. A* **223**, 80–96 (1954).
5. Ross, M. B. *et al. Nature* **608**, 135–145 (2022).