**No exceptionalism: Gene-editing needs rigorous evaluation before clinical application**

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Some of my colleagues and I take the old bingo-game approach to conferences: a point awarded for every mention of 'paradigm shift,' 'disruptive,' or 'game changer.' We can be rather smug about perceived naivety on the part of colleagues working in discovery-oriented research. We are also chronically irritated by the ongoing hype about genomics research, which is almost never lived up to. But I may have to shake off this jaded view of the world; it really does look like we have something genuinely exciting in the newest gene-editing techniques. *CRISPR-Cas9* is not the first, but it is easy; so much so that the Nuffield Council on Bioethics warns about 'garage scientists' paying less than $200 to add it to their DIY toolkit. So, we have a technology which seems to work, is easy to use, and may be very affordable. No problems?

Well, in many fields, including health and the environment, the possibilities opened up by gene editing beg extremely important questions about the ethical, legal, and social implications of its use, and the challenges it presents to national and international jurisdictions and regulatory authorities. Clearly, major stakeholders are actively on to these.

But, in the health field, even if we get to consensus about regulation and approval for use, there will always remain overriding questions of whether a treatment based on gene editing represents a good investment of public funds. I am unashamedly an advocate for evidence-informed policy and practice. Health-care resources are not infinite, and even fairy-tale increases in health-care spending cannot fulfil all potential needs or demands. The idea of opportunity cost – the benefits we forgo by not directing resources to the next best alternative use – underlines the simple fact that choices have consequences. This is why clear-headed evidence of benefits, harms, and costs for any new technology is not only desirable, but an ethical imperative. And this evidence should be comparative: if we compare a new treatment based on gene editing against nothing (or a placebo), then we can judge whether it 'works;' if we compare it against the best alternative existing treatment, then we can judge whether it is a better deal. Opportunity cost.

Comparative-effectiveness studies of treatment interventions based on gene editing will also need to be pragmatic – not done under ideal conditions, but under usual clinical conditions. The outcomes must be about people (death, survival, quality of life), not just biomarker responses. The cost data should reflect reality. Such studies need to be unbiased – which ideally means well-designed randomized, controlled trials – and the definition of 'effectiveness' must be pre-specified. This means deciding what is the most important outcome (length of survival? quality of life?) and how much more is enough (how much longer survival? how much better quality of life?). Is extending survival by, say, a few weeks a meaningful improvement in benefit? Would we feel that is a better use of scarce resources compared with the best alternative?

These are the kinds of decisions that researchers usually make when they design a comparative-effectiveness study, and they do so implicitly and even unconsciously on behalf of society. Is it time to extend these debates out to patients, families, and health-system stakeholders? Not sure how we do that, but perhaps we could start to think about this.

As a once-practising physician, and a researcher working on system implications of emerging health technologies, I am aware of how we desperately need progress for many devastating genetic disorders. Perhaps we may finally be on the brink of a game-changing breakthrough. I absolutely argue for an evidence-based approach. But objectivity does not mean lack of humanity, and scientific rigour must reflect societal values.

Here's to a hopeful future.

*Professor Brenda Wilson recently spoke at the ISSP / Genome Canada panel "Challenges of governing advances in gene editing advances"*