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Rethinking evidence in medicine

We are launching a series on evidence in medicine, to discuss new approaches to assessing the safety and efficacy of cutting-edge health technologies and treatments.

Medicine is one of the oldest professions, with surgery dating back at least 31,000 years and medical treatises from ancient Egypt found from 1600 BC. Yet many medical beliefs from the ancient world are no longer held today — long gone are the theories of miasma, the four humors, or the heart being the seat of reason.

Medicine is today informed by evidence, but this is a relatively recent development. An early type of meta-analysis was conducted in 1904 to assess the efficacy of inoculation against typhoid fever, and the first randomized controlled trials were published in the 1940s, but the term 'evidence-based medicine' was coined as recently as 1992. In the decades since, randomized controlled trials, meta-analyses and systematic reviews have formed the foundation for the field.

Technological advances require fresh approaches, so we are today launching a new series on rethinking evidence in medicine, with a focus on demonstrating efficacy and safety for new therapeutics and health technologies, from gene editing to artificial intelligence (AI) health algorithms.

The COVID-19 pandemic has shown the best and worst of clinical trials, with the development of new vaccines and treatments in record time, together with innumerable underpowered trials with conflicting results, including those for ineffective treatments. More use should be made of master protocols (including basket, umbrella and platform trials), which are cost-effective and highly powered, as well as modern tools such as digitization, biomarkers, digital endpoints and real-world data, argues Vivek Subbiah in the inaugural Perspective of the series. Trialists should encourage reproducibility as a matter of course. This could include confidential sharing of individual patient data, or prospective meta-analyses of summary data during the trial itself.

Throughout the year, we will cover a range of challenges to the medical evidence status quo. Precision medicine presents many challenges to the traditional placebo-controlled trial. Treatments for rare diseases, including gene therapy, may be limited to a handful of potential patients, which would preclude a large trial. Long-term monitoring of treated patients will allow real-world safety and efficacy to be demonstrated. Despite its susceptibility to specific biases, real-world data has many uses: in rare diseases, for post-approval studies, for new indications for existing drugs, or as a synthetic control group.

Multi-model biomedical AI, machine learning and deep neural networks are beginning to enter healthcare, but with mixed results, in part because of a lack of racial and ethnic diversity in many training sets. The US Food and Drug Administration has recently announced that AI should be regulated as a medical device. Such algorithms become more accurate during their evolution, after testing on large amounts of real-world data outside of their training set, but a new algorithm requires fresh approval. Regulators should be nimbler and adapt to these new types of medical interventions, argues David Bates in a World View. Similarly, a platform for a gene-editing technology could be submitted for approval, with minor changes to the target sequence not requiring a lengthy approval process, as for variant-specific vaccines against COVID-19.

Not all new healthcare technologies provide benefits to health, and some may cause harm. A wearable monitor may show efficacy for weight loss, but wearables and apps (most of which are not regulated) may also lead to misdiagnosis, over-diagnosis or mental health concerns. Regulators should consider whether to widen their scope to include more apps, as well as develop a framework for assessing long-term harm alongside short-term benefits.

Crucially, more must be done to explain medical research to the public, patients, policymakers and politicians. Medical research is wasted if it does not lead to changes in public behavior or clinical practice. Visual tools for public health messaging could be more widely used, social media should be considered, and engagement with traditional media is critical.

From the patient's perspective, medical research should focus on their priorities. Patient advocates should be involved throughout the research cycle, ideally as co-investigators, and must be representative of the target population, particularly in low- and middle-income settings. Too few women and too few people of color are enrolled in clinical trials, especially phase 1 trials, which understandably reduces trust in their results. Tackling this is not only an ethical and moral imperative, but also helps build trust and combat disinformation and misinformation.

Collaborative relationships among health professionals, medical researchers and policymakers can be effective. The UK's Royal Society has a pairing scheme for politicians and scientists, while Science on the Hill, organized by *Scientific American* (which, like *Nature Medicine*, is part of Springer Nature), brings together policy leaders and scientists in the United States, to foster evidence-based policy. Such programs should be supported and replicated elsewhere.

Improvements to evidence-based medicine must include training a new generation of reproducibility scholars. Medical students should receive high-quality education in reproducibility, clinical trial design, critical appraisal of the literature (including the opportunities and challenges of pre-prints), and techniques to combat misinformation, which is a growing threat to health, especially that of under-served populations.

This series is intended as a starting point for discussions, so we encourage our readers to share their ideas for topics and priorities as we rethink evidence in medicine for the health benefit of all.

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