VIEWPOINT

What Happens When Underperforming Big Ideas in Research Become Entrenched?

Michael J. Joyner, MD
Laboratory of Human Integrative Physiology and Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota.

Nigel Paneth, MD, MPH
Departments of Epidemiology and Biostatistics and Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing.

John P. A. Ioannidis, MD, DSc
Stanford Prevention Research Center, Department of Medicine and Meta-Research Innovation Center at Stanford, Stanford University, Stanford, California.

Corresponding Author: John P. A. Ioannidis, MD, DSc, Stanford Prevention Research Center, Department of Medicine and Meta-Research Innovation Center at Stanford, Stanford University, 1265 Welch Rd, Medical School Office Bldg, Room X306, Stanford, CA 94305 (jioannid@stanford.edu).

For several decades now the biomedical research community has pursued a narrative positing that a combination of ever-deeper knowledge of subcellular biology, especially genetics, coupled with information technology will lead to transformative improvements in health care and human health. In this Viewpoint, we provide evidence for the extraordinary dominance of this narrative in biomedical funding and journal publications; discuss several prominent themes embedded in the narrative to show that this approach has largely failed; and propose a wholesale reevaluation of the way forward in biomedical research.

Primacy of the Narrative

In 2016 approximately $15 billion of the $26 billion of extramural research funding sponsored by the National Institutes of Health (NIH) could be linked to some version of search terms that include gene, genome, stem cells, or regenerative medicine.[1] These topics have also increased geometrically in their representation among published articles. Between 1974 and 2014 the annual number of published articles indexed in PubMed increased by 410% (from 234 613 to 1 196 110), but those identified with genome increased by 2127% (2705 to 60 246). Between 1994 and 2014, the annual number of articles indexed in PubMed increased by 175% (from 435 376 to 1 196 110), but articles identified with gene therapy or stem cell increased by 874% (2635 to 25 662) and 752% (3452 to 29 196). Apparently a large number of scientists either believe in the potential of these topics or feel compelled to work on them, recognizing that these topics constitute a major locus of important science, financial support, recognition, and prospects for a successful career.

Exploring Some Key Examples

In 1999, Collins[2] envisioned a genetic revolution in medicine facilitated by the Human Genome Project and described 6 major themes: (1) common diseases will be explained largely by a few DNA variants with strong associations to disease, (2) this knowledge will lead to improved diagnosis; (3) such knowledge will also drive preventive medicine; (4) pharmacogenomics will improve therapeutic decision making; (5) gene therapy will treat multiple diseases; and (6) a substantial increase in novel targets for drug development and therapy will ensue. These 6 ideas have more recently been branded as personalized or precision medicine.[3] Similarly, there is the increasing interest in and expectation that stem cell therapy—a seventh theme—can treat common diseases.[3]

To avoid the misconception that big ideas are all related to biological sciences, an eighth theme is the emphasis in the narrative on the clinical and research value of converting medical records to electronic formats. As of April 2016, the Centers for Medicare & Medicaid Services had paid $34 billion in financial incentives to service providers for implementing electronic health record (EHR) systems.[4] EHRs are an important aspect of this narrative because they are thought to provide the structural underpinnings of precision medicine. It has been suggested by some that some combination of these 8 big ideas will yield substantial cost savings for health care.

Expectations that a few DNA variants explain most common diseases have faded as the genetic architecture of most diseases has proved to be formidably complex. Apparently, hundreds or even tens of thousands of genetic variants are involved in each common disease. The function of these variants is difficult to decipher. Very few genes have found undisputed roles in preventive efforts or pharmacogenetic testing.

Continued enthusiasm for gene therapy ignores what is known from classic single-gene disorders such as sickle cell anemia. The complex biological processes set in motion by a single amino acid substitution that leads to painful crises, stroke, and other complications are not predictable from the genomic defect, but only by appreciating the complexity of biological systems at the level of tissues and organs. Sixty years after the discovery of the genetic defect, no targeted therapy has emerged for sickle cell anemia.

The complex and adaptive nature of most tumors thwarts the optimistic projections for molecularly targeted therapy for cancer. A randomized trial of targeted therapy based on molecular profiling for advanced cancers from diverse anatomical locations showed no improvement in progression-free survival.[5] The NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) trial links patients with cancer to drugs targeted against their cancer DNA mutations. So far, just 2.5% of screened patients have been assigned to a trial intervention group. Even though this fraction should increase as the number of trial treatment groups is increased, even if effectiveness is demonstrated, the rarity of the targeted mutations means that this approach will help only a minority of patients with cancer.[6]

The prospects of effective treatment based on stem cells have been challenged in comprehensive reviews of the available trials. For instance, in congestive heart failure, improvements in cardiac function have been observed only in industry-sponsored studies, and a positive relationship has been noted between effect size and the number of experimental design flaws.[7] To its credit, the International Society for Stem Cell Research has issued "anti-hype" guidelines that "[h]ighlight the responsibility of all groups communicating stem cell science and medicine—scientists, clinicians, industry, science

communicators, and media—to present accurate, balanced reports of progress and setbacks."[8]

The financial and clinical benefits predicted from shifting to EHRs have also largely failed to materialize because of difficulties in interoperability, poor quality, and accuracy of the collected information; cost overruns associated with installation and operation of EHRs at many institutions; and ongoing privacy and security concerns that further increase operational costs. These features make the use of EHRs for research into the origins of disease, as proposed in the Precision Medicine Initiative, highly problematic. No clearly specified targets for either improved outcomes or reduced costs have been developed to assess the performance efficiency of EHRs. Although it is difficult to argue for a return to paper records, any claim of future transformation of the medical record should include well-defined accountability and review mechanisms. Otherwise, the health care system may become hostage, wasting increasing resources to continuously upgrade electronic technology without really helping patients.

None of these popular topics has had any measurable effect on population mortality, morbidity, or life expectancy in the United States. The improvements of the past decades in these outcomes, which have been substantial but are now stalling, have largely reflected improvement in nonmedical aspects of everyday life and the operation of broad-based public health and classic prevention efforts, such as curtailing smoking, that are undervalued as outmoded and old-fashioned by the narrative. The anticipation that improvements in medical care and outcomes derived from big ideas will reduce costs also seems unlikely given the high costs of applying targeted therapeutic interventions to small numbers of people based on complex and expensive technologies, as well as the inevitable overdiagnosis and overtreatment that follows from more intensive monitoring. Similarly, EHRs may increase health care costs due to their ability to enhance revenue capture and as a result of unanticipated security and upgrade expenses. What historical precedent is there that adoption of vast new oversophisticated technology reduces costs? Eventually, what is the definition of success and over what time frame?

A Need for Reevaluation

When claims about high-profile, dominant "big ideas" are viewed against their mediocre benefits, it seems that 2 basic courses of action are available. The first is to continue with calls for more funding, more complex measurements, and more sophisticated instrumentation. The second is to reevaluate and reset the current focus.

Public funders such as NIH should expand the funding for basic, "blue sky" science for which it is impossible to set, predict, and promise specific deliverables. In so doing, NIH should fund many more high-risk, unconventional ideas instead of supporting the same familiar highly funded research fronts. However, novel funding mechanisms like NIH Pioneer Awards are currently only a tiny fraction of the total budget.

When NIH funds translational or preclinical research with specific deliverables promised (as in the case of personalized medicine, and stem cell therapy), independent assessors should regularly appraise whether these deliverables were achieved and, if so, at what cost, and with what effect. Assessors must be objective, independent of the funding source, and have no professional stake in whether a particular line of research is deemphasized. The deliverable criterion should include public health benefit achieved by these initiatives (ie, measurable reductions in mortality and morbidity). Criteria such as number of publications, citations, prizes, and recognition are irrelevant as these are simply self-rewarding artifacts of the system. After several decades of substantial investment, the fundamental question is whether these big ideas have improved quality of life and life expectancy, by how much, for how many, and for whom. These are public dollars that should benefit the many, not the few.

Mechanisms should be in place to sunset underperforming initiatives. In the current environment, scientists are pigeonholed in a narrow discipline and are penalized by study sections if they exit their specific niche. There should be incentives for scientists to acknowledge that their research focus should be abandoned and help them switch to another potentially more fruitful research area.

Another key question is whether NIH is best suited to fund all kinds of research that have specific deliverables. In some cases, private entrepreneurs may be most suited to develop new drug targets, new drugs, new tests, and new technologies. Financial success in the market is a strong and sufficient incentive. Public funders may need to focus more on blue sky science and on late evaluation research, to evaluate without conflicts the drugs and other technologies developed by entrepreneurs.

NIH deinvestment in preclinical research promises that clearly do not deliver will allow more funding to be directed toward work of clear public health importance and for imaginative biomedical research that is truly innovative and not constrained by current narratives.

ARTICLE INFORMATION

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