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Medicine Means More Than Molecules

The Doris Duke Foundation, where we work, has a long track record of supporting early-career fellowships that allow physicians to pursue research to improve patient care. For the past 25 years, we've invested $204 million in these clinician-scientists. An assessment we conducted in 2019 found that four or more years after their initial grant funding, 73% of our fellows had received subsequent National Institutes of Health (NIH) research grants, and the majority remained in research as their main professional activity.

We're also proud our fellows seem to be meaningfully changing health practices for the better. To gain insight into this difficult-to-measure outcome, we used an analysis that found only 25% of all biomedical research articles are cited in clinical trials or guidelines within two decades of publication. When we applied the same methodology to our fellows' publications, their citation rate for a comparable period was twice as high.

Recently, however, we have become concerned that we have been teaching to the wrong test, that our support is reinforcing an existing system of recognition and prestige tied to circumscribed paths of scientific inquiry. Specifically, our criteria for assessing fellowship applications are calibrated to a narrow set of markers for mainstream success and, in effect, exclude some research that may have incredible potential to improve human health.

Biased training paths

Here's what we've seen in our programs, which are explicitly intended to help people with MD or equivalent degrees carve out time from clinical duties to conduct research and thus to help physician-scientists launch research careers.

A decade ago, we noticed that our fellowships favored individuals with specific credentials who were from well-resourced research environments. For example, 44% of those awarded Doris Duke fellowships held joint MD-PhD degrees versus 30% of unsuccessful applicants. And 81% of successful applicants hailed from an institution in the ninety-fifth percentile of NIH funding, compared to 54% of unsuccessful ones.

More recently, we detected a potential unintended effect of our fellowship criteria. By supporting applicants and projects deemed most likely to draw future NIH funding, we also seemed to favor research questions that sought to tackle diseases through improved molecular understanding of underlying disease mechanisms rather than exploring interventions that might, say, prevent clinical encounters in the first place. Also apparently disfavored was research on practices that could make health care visits more effective or ways to treat disease that would result in more equitable outcomes.

When we analyzed our funding patterns for the last decade (2013–2023), we found that 40% of applicants proposed research to improve care, reduce disease, or boost the impact of proven interventions, but this group received fewer than 30% of our grants. Proposals in categories such as outcomes research, treatment, and prevention had success rates of 7%, while those focused on basic discovery or mechanisms of disease had a success rate of 11%—more than a third higher.

While applicants submitting etiologically focused proposals are doubtlessly pursuing profound and valuable science, our approach is likely sidelining other kinds

of vital innovation—particularly innovation in how to prevent disease, care for patients, and implement health services and disease treatments.

When we reached out to individuals who subscribe to Doris Duke Foundation's emails for anonymous input, their feedback affirmed our concerns: scientists reported that what they think will win funding and advance their careers shapes their research. One respondent said, "Much research activity is guided by available funding mechanisms rather than the most impactful ideas." Another said, "The funding climate shapes the scientific community as a whole; it is really beyond individual decisionmaking."

Resources and status always matter. But, for physician-scientists, they can play a decisive role. The median age of researchers' first NIH R01 grant—which signifies a researcher is able to lead independent projects—is around 42. Becoming a physician-scientist is an arduous path, requiring extraordinary talent, training, and dedication. In the face of these intrinsic difficulties, the vast majority of researchers will follow the material, psychic, and social rewards that are most readily available. If research on prevention, care, and implementation does not receive commensurate resources or provide the same professional traction as molecular research does, then those fields will struggle to garner the energy and attention necessary to deliver on their potential.

In some ways, the modern marvel that is the medical research enterprise seems to have succeeded too well. At a forum we convened last year, Christopher Austin, a pharmaceutical executive and former director of the NIH's National Center for Advancing Translational Sciences, encapsulated our worry. First he pointed out how enormous investments had brought technologies and understanding that opened incredible medical and scientific opportunities. Then he emphasized the need to apply that ingenuity and effort to later stages of translation: "I fear sometimes that we have gotten so enamored of our abilities, of the kinds of experiments that we do in model organisms. Models for what? Humans are the target species, and we now have the opportunity and the obligation to focus more on whole humans."

What falls to the side

Part of the problem with the molecular preoccupation of medical research funding is that its pursuit too often impedes or precludes the effective investigation of questions that could yield more immediate improvements in health and health care than are possible through the extended process required for drug development and approval. Questions like "What genes do cancer cells need to survive?" fit the current mold and might, eventually, lead to effective new drugs and diagnostic tests. But other important questions such as "What eating habits reduce weight loss and nausea during chemoradiation?" or "Can Zoom calls or in-person visits shorten hospital stays?" tend to receive less enthusiasm within the medical research community.

Consider research efforts such as those led by schools of nursing to improve care for people at risk of neglect, such as caregivers of patients with dementia, or people who experience health disparities across illnesses from heart disease to HIV. These clinicians' frontline experience brings keen insight into what really matters for improving patient outcomes, but funding mechanisms—especially when disparate schools and departments are involved—can be scarce. This is exactly the kind of research that we need more of, but our funding and training systems effectively serve to discourage it.

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This pattern of preference for molecular research extends beyond the Doris Duke Foundation. We are part of a subgroup of 33 nonprofit health research funders in the Health Research Alliance that have shared their 2012–2022 grant data to enable aggregate analyses. Overall, support for research on population and health services within this subgroup amounted to only 8% of the total over the 10-year span—compared to 77% for biomedical research and 15% for clinical research. A similar comparison of what NIH supports cannot be found in publicly available data. However, it is widely known that funding for biomedical research makes up a much larger share of NIH's portfolio than population and health services research.

Unquestionably, many distinguished scientists are working to advance implementation, care, and prevention. The NIH and a raft of (mostly young) agencies are helping them: the Agency for Healthcare Research and Quality (AHRQ, founded in 1989), the Patient-Centered Outcomes

Research Institute (PCORI, 2010), the National Center for Advancing Translational Sciences (NCATS, 2011), and even the Advanced Research Projects Agency for Health (ARPA-H, 2022). Still, in 2022, the research and development budgets for the Centers for Disease Control and Prevention, PCORI, and AHRQ were under $1.5 billion combined. (The fledgling ARPA-H, which had a $1.5 billion budget for 2023, is a welcome addition to the mix.)

In an editorial in *Science* this June, the NIH director recognized that biomedical research innovation alone is insufficient to improve population-level health. Director Monica Bertagnolli described two new initiatives explicitly intended to connect bench research to the clinic and to communities. She explained, "These initiatives will help translate scientific discoveries into effective health care," but acknowledged that, to succeed, they "will require not only support from NIH but commitment from the biomedical research community, other governmental agencies, health care systems, and private citizens who participate in research."

What could be done

While we have been reflecting on our own funding priorities in light of what we've discovered, broader soul-searching within the medical research establishment is necessary. After all, the Doris Duke Foundation's resources are less than 1% of federal research funding for health. Here are a few steps the research community might take to funnel more effort into research questions primed to boost health and well-being.

First, funders can rethink career awards by organizing funding around pressing health problems rather than career trajectories. Doing so would incentivize researchers to think less about which molecular questions they can "own" and instead direct their energies toward what afflicts human health—no matter whether knowledge falls into basic discovery or implementation of care. Such a shift would also encourage researchers to consider their work as part of a collective and collaborative endeavor across an array of disciplines. (Right now, researchers are overly incentivized to prioritize work that earns them individual recognition.)

Increased budgets for AHRQ, PCORI, and NCATS would certainly help advance this goal. But perhaps just as valuable would be greater coordination among these entities and the broader NIH in facilitating research that is at the intersections of agencies' missions.

Second, there should be more prizes, fellowships, major awards, and other honors attached to research for care, implementation, and prevention. A 2021 analysis spanning four decades of over 400 scientific prizes and thousands of awards found that topics associated with prizes showed "unexpected and significant" growth in new knowledge and entrants. In other words, prizes really do influence the kinds of questions that whole generations of researchers pursue.

The bad news, however, is that if prizes reflect a narrow understanding of what counts as valuable research, then they could further entrench that myopic worldview. And it's clear that in medicine the dominant paradigm is an overwhelming focus on molecular science. Physician-scientists have received Nobel Prizes in Medicine for discovering that nitric oxide acts as a signaling molecule in blood vessels (an incredible achievement), but not for showing how home health workers can ensure seniors take the right medicines.

Third, academic institutions should more actively facilitate innovations that improve health outcomes. One possible approach is promotion and assessment programs that credit broader social benefit in addition to career progression. Another approach is helping different parts of a university work together. During the height of the pandemic, for example, federal funding sparked overdue realignment in some academic medical centers to mobilize all-hands-on-deck problem-solving. In just one example, this process brought together separate New York University research centers, faculty in global public health, as well as social workers, nurses, and community health workers, to plan and organize visits to families in public housing to offer and administer COVID-19 testing and flu vaccinations. But these kinds of innovations have been the exception rather than the rule.

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Fourth, we need to valorize work to improve care and disease prevention. The innovative new drugs and diagnostics coming from biomedical research in the last few decades happened in part because established researchers celebrated new methods, materials, and technologies. They can bring similar advocacy to research on implementation and outcomes to accelerate our progress toward this next frontier in innovation.

Our faith in the power of high-tech scientific research has brought vaccines, medicines, and precise diagnoses; investments in such research have yielded huge dividends across society. Basic, molecular science should continue to receive our society's support. But it is also time to extend our belief in the power of science a little further—to the researchers who prioritize how to deliver care and improve health.

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