Circulation: Cardiovascular Quality and Outcomes

SPECIAL REPORT

Inflection Point

Ideas for Accelerating Breakthroughs and Improving Cardiovascular Health

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Thank you to the American Heart Association and my community of Distinguished Scientists for the honor of giving this year's lecture. I am in this position, in part, because of the American Heart Association, an organization that inspired me, encouraged me, supported me, and taught me. The American Heart Association promotes science, health, and society's progress toward equity, and I am a proud member and a grateful beneficiary of its good works.

I am also in this position because of family, friends, patients, mentors, colleagues, teammates, and students, all to whom I owe so much. And to my academic home at Yale University and the Yale New Haven Hospital Center for Outcomes Research and Evaluation, where I am fortunate to be among so many who have enriched my personal and professional life and to whom I owe so much. Without them, I would not be here today.

Finally, I would like to acknowledge my parents. My dad was a practicing pulmonary doctor who worked from morning till night in the service of his patients. From an early age, I would accompany him on weekend hospital rounds, an experience that set me on my career course. And to my mom, whose belief in me, beyond all reasonable expectations, has always been a sustaining force. She taught me much about the power of encouragement. I dedicate this lecture to them.

I am proud to be the first outcomes researcher to give this lecture. The day has special significance for me as I am part of a wonderful community of people who established the Quality of Care and Outcomes Research Council, and the Quality of Care and Outcomes Research journal, and the Quality of Care and Outcomes Research Annual Scientific Sessions.

What is outcomes research?[1–3] Outcomes research strives to investigate, learn, and optimize health care results for the benefit of patients and society. The goal is to create knowledge and apply it in the service of producing better health outcomes—knowledge that ultimately, if not proximally, leads to tangible improvements in people's lives. Outcomes research focuses on what matters to people—whether they live and how they live.

Outcomes research is about promoting action and accountability, providing transparency about the results of health care, and illuminating what we have accomplished and what we have yet to achieve. We measure our progress by improving health, reducing suffering, compressing morbidity, and elevating patient self-determination. We do not measure our success by papers published, grants obtained, promotions achieved, or even distinguished lectures given. Outcomes research is scholarship with the purpose of improving health and health care from the patient's and society's perspective.

Setting the Stage

A Distinguished Scientist Lecture will often focus on achievements. Ordinarily, the lecture can be a victory lap, a chance to celebrate accomplishments and to

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regale the audience with tales of overcoming challenges to deliver remarkable breakthroughs. However, the time of a pandemic is not a moment to celebrate past achievements.

People are suffering, and we thirst for more evidence to guide decisions and improve outcomes. Almost a year into the pandemic, our ignorance remains immense and our tools are limited.

The pandemic has revealed the vulnerabilities in the scientific enterprise's form and function and has pressured us to think about new and better approaches. We showed our lack of agility, speed, coordination, and inability to deliver practice-changing insights rapidly.

In the United States, we have had over 12 million cases by mid-November and there have been an estimated 260K deaths, equivalent to about 78 deaths per 100000.[4]

However, I remain optimistic. We are not without accomplishments and may be positioned for important advances.

Many scientists in our community dropped their ongoing research agendas and leaped into action with the pandemic. I have seen remarkable collaboration among colleagues and institutions. The pandemic has galvanized research—and while we have yet fully to realize the benefits, knowledge is increasing with our new approaches to prevention, detection, and treatment. The pandemic has created an openness to change. We have an impetus to improve what our scientific enterprise can deliver.

There is a famous graduation speech by the late David Foster Wallace.[5] He starts by saying: "There are these two young fish swimming along and they happen to meet an older fish swimming the other way, who nods at them and says, 'Morning, boys. How's the water?' And the two young fish swim on for a bit, and then eventually one of them looks over at the other and goes, 'What the hell is water?'" Wallace goes on to say, "The point of the fish story is merely that the most obvious, important realities are often the ones that are hardest to see and talk about."

I believe that is true of our day to day existence in clinical research. We too often accept the assumptions of what is expected, how research gets done, and how change occurs. We become complacent with the pace. Perhaps the pandemic has, even transiently, awakened us from this trance.

Should we be thinking about our research into noncommunicable diseases, like heart attack and stroke, in a new way, with stronger resolve, more determination, greater accountability, and with bigger aspirations for what is possible because of our experience with the pandemic? These cardiovascular and cerebrovascular conditions are mostly preventable, cause substantial morbidity, disability, and death, cost society hundreds of billions of dollars annually, and impose losses on families and friends.

Imagine if another global threat appeared on the horizon. Suppose we suddenly recognized a condition that affected >100 million Americans and was a primary or contributing cause of death for 500000 a year just in this country, with an age-adjusted death rate of about 300 per 100000 and estimated annual costs exceeding $130 billion a year. How much urgency would we feel to address this threat? By the way, this condition is hypertension.[6,7]

This lecture is an opportunity to reflect on where we are, what we have done, and what we need to do in the battle against cardiovascular and cerebrovascular disease and health. By giving this lecture titled "The Inflection Point," you may see that I have foreshadowed my conclusion. The times call on us to focus on what we have yet to do and the opportunities ahead. Can the pandemic be an inflection point?

We fashion ourselves as sitting in a golden age of medicine. We have seen remarkable progress in the life sciences. Within the lifetime of our more senior colleagues, scientists described deoxyribose nucleic acid's structure. The basic scientists are propelling our understanding of the life sciences at a furious pace.

Research budgets are large and growing. The National Institutes of Health's budget increased from $11 billion in 1995 ($18 billion in 2020 dollars) to $42 billion in 2020.[8] The National Heart, Lung, and Blood Institute's budget increased from $1.3 billion in 1995 ($2.2 billion in 2020 dollars) to $3.6 billion in 2020. The National Institute of Neurological Disorders and Stroke had a budget of about $2 billion in 2020. The American Heart Association devotes about $200 million a year to research on cardiovascular and cerebrovascular health.[9]

The medical literature is large and growing. The publication of articles is growing at about 4% per year. In 2017, the National Science Foundation estimated that journals published over 500000 articles in the medical sciences and over 350000 in the biological sciences.[10] Medical device patents are increasing rapidly, with a >50% increase between 2007 and 2018.[11] Drug approvals are steadily growing.[12]

And the amount we invest in health care is large and growing. Also, as a society, we are investing ever more resources in health. Over the past 20 years, health care costs have increased from $1.3 trillion to $3.6 trillion or $11172 a person and 18% of the Gross Domestic Product.[13,14]

But what about our results? Yes, mortality from diseases of the heart and cerebrovascular disease have dropped, but Black Americans still have a much higher rate than others.[15–17] Also, the decline that was so prominent previously has stalled.

Moreover, progress is being overturned in places. There is evidence that age-adjusted mortality from

ischemic stroke is now rising. Death rates from hypertension, separate from the heart diseases, rose over the past 2 decades, with rural areas bearing a more significant burden. Again, there are also marked disparities by race. A recent article showed that hypertension control is getting worse, not better.[18] The rates of diabetes, along with obesity, are rising rapidly, starting almost 25 years ago. Deaths from atrial fibrillation are also increasing.[16]

A realistic assessment is that we are stalled or losing ground—despite growing resources directed toward research and patient care. We need to accelerate progress, or at least demonstrate overall progress.

Here are some ideas that, as a cardiovascular disease and stroke scientific community dedicated to improving people's and society's heart and brain health, we might consider.

THE IDEAS

Promote Open Science

Before the pandemic, clinical scientists were slow to adopt open science principles. Data are the fuel for research and often the rate-limiting step. They are also a resource that is not depleted by use. In fact, the more use of a data set, the more that can be learned from it—and its utility may actually be expanded. Also, data generated in clinical research often do not age well because of concomitant changes in diagnosis and treatment, placing a premium on early use.

But what is the reality about clinical research data? In ordinary times, we scientists are reluctant to share data assets that we believe we have created. We tend to overlook the contributions of participants, funders, and collaborators and hold tight to what we believe is rightly ours.

My introduction to this culture occurred early in my career. I remember, at one of my first American Heart Association Scientific Sessions, tentatively approaching a senior investigator from another institution about the opportunity to work with data from a high-profile clinical trial. I was a first-year faculty member replete with ideas and eager for collaborations. My institution had enrolled patients in the trial. The response to whether I might be able to do any projects was a resounding no. I had a similar experience with other trials.

These experiences were emblematic of a viewpoint that restricts access to research data. To be honest, I also had the experience of holding tight to data—after all, I grew up in that culture. I know the mental model that I, as the investigator, own the data and have discretion over their use.[19–21]

A better outcome occurred with the Dig Trial.[19–21] This federally funded study had a bounty of data collection. Yet, for 5 years after the investigators published the landmark study, the leaders had resisted using the data for additional studies, even by study investigators. Then the National Heart, Lung, and Blood Institute's Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) made the data available.[22] By 2017, 20 years after the original publication, Angraal et al[23] in our group showed that researchers had published 75 articles from the Dig Trial, including 41 by outside investigators—and many in high-impact venues.

Our group created the Yale Open Data Access Project to promote the sharing of clinical trials.[24–27] Today, Johnson and Johnson shares all of its drug and device clinical trials through the Yale Open Data Access Project. They will do the same with their vaccine trial. Anyone with a science proposal can apply for access. Many scientists have produced publications with these data. Others in industry are sharing trials in different ways, although not all are complying.

But academia lags and much data remain locked up. Even results are not often shared. We did a study of academic centers, led by Ray Chen, and found that more than half of their completed clinical trials are never reported.[28] In another study of National Institutes of Health-sponsored trials, led by Joe Ross, we also found that fewer than half of them were reported even 30 months after trial completion.[29] The National Institutes of Health later replicated this study.[30]

Within our group, we are seeking ways to encourage a more open science culture. The lack of reproducibility in science hampers progress—a solution is greater transparency and more overt sharing so that others can build on the original work. But progress is slow, even for us. The goal ought not to be to build our reputations on sequestered data but rather to recognize that our common enemy is disease and that we ought to be sharing data and code routinely.

There are shining examples. Beth Israel Deaconess Medical Center, in collaboration with the MIT Lab for Computational Physiology developed MIMIC, a freely accessible critical care database. MIMIC-III has data from 61 000 intensive care unit stays and includes demographic and clinical data—and waveforms and numerics (second by second derived values from the waveforms).[31]

The Stanford Center for Artificial Intelligence in Medicine and Imaging has CheXpert, a data set of 224 316 chest radiographs, and EchoNet-Dynamic, a data set of over 10 000 echocardiogram studies, which are all labeled and being shared on request.[32] They have many more imaging studies that they share.

The highest accolades of our profession should go to those who best facilitate the work of others. We saw this spirit in the Human Genome Project, which was the work of many to make possible the work of many more.[33] In the parlance of outcomes research, we

should care about whether we have produced a benefit for patients and society at the end of the day.

The pandemic brought the importance of open science into bright relief. In the face of a global threat, open science is an imperative. But should not we be applying such a perspective to all global health threats, if not all health threats? The conditions we are routinely battling are, indeed, global threats. Thus, we, in the cardiovascular disease and stroke community, ought to be leaders in embracing open science and commit to data and code sharing, making it normative, and agreeing that we collaborate for progress. We do need to find ways to describe data provenance and credit those who created the data assets. Nevertheless, we ought to work together to ensure that scientists can gain access to data, properly configured to protect the interests of patients and study participants. This access should include registry data too. The goal is progress and to not have data be the constraint. The sharing of code also adds transparency to our efforts and enables more thorough evaluation of our work.

And machine learning needs training sets, so labeled data sets have utility. We should be working together, as Stanford and BIDMC/MIT have, to produce the fuel for future breakthroughs. Those of us in academic institutions have a special responsibility to promote society's best interests. Working together, throughout our research ecosystem, this approach can be a way to accelerate progress.

Improve Journals and Expand Preprints

In prepandemic days, peer-reviewed journals performed a vital service but also slowed the communication of scientific findings.[34] The cost of the delay was considered to be offset by the filtering function of these journals. Many authors, who seek peer-reviewed publications for academic credit, tolerate the delays as a necessary penalty.

The delays accrue for many reasons. Journals generally rely on volunteer reviewers, which can be challenging to recruit and may be tardy in their reviews. From my perspective, reviewing journals is a substantial commitment and requests have grown in volume to the point that many arrive daily. These requests compete with inquiries about grant reviews, promotion reviews, and program reviews. It is common for papers to undergo submission to multiple journals before acceptance. And even with a revise and resubmit request, the cycle can begin again. One paper, that I believed to carry timely insights, was held by a journal for more than a year as it evaluated a revision. I ultimately withdrew the paper and submitted it elsewhere.

In our study of National Institutes of Health trials, the median time to publication was 23 months.[29] We tend to think about high-profile trials that are simultaneously presented and published as late-breaking trials. But many more trials are completed and buried—or reach publication >2 years after completion. We conducted another study of the age of the data in published trials, led by Welsh et al.[35] In this study, we restricted ourselves to the top journals. The median age of the data at the time of publication was 34 months—and even for trials with a follow-up period of only 30 days, the median time was 30 months. In these top journals, the median time from completion of data collection to publication was 15 months. About one in 5 trials published in these top journals had a publication time of 2 or more years.

Other fields have managed this issue. The leadership of Brian Nosek from the Center for Open Science and Ron Vale with ASAPbio (Accelerating Science and Publication in Biology) oriented me toward preprints as a solution.[36] The story of preprints starts with Paul Ginsparg and Joanne Cohn, 2 physicists.[37] Ginsparg tells of how his colleagues would post articles in progress on their office doors in hopes that others would comment on them. Cohn used early file formats to email physics papers that had not yet undergone peer review.

In 1991, Ginsparg created a central repository mailbox stored at Los Alamos National Laboratory so that other scientists could access work. It soon expanded from physics to include astronomy, mathematics, computer science, quantitative biology, and statistics. Originally, it had the domain name hep-th@xxx.lanl.gov. In 2001, it moved to Cornell and Ginsparg changed the name to arXiv.

Since those early days, preprint servers have grown. bioRxiv is the main preprint server in the life sciences.[38] In November 2013, bioRxiv was launched and has posted about 100 000 manuscripts from 200 000 institutions and 130 countries.

Economists and other social scientists have also embraced preprints. They realize that publication in their esteemed peer-reviewed journals is a mark of accomplishment but can take years. They want to be able to disseminate their science, use it for job talks and grants, leverage it to build new collaborations, and archive it to establish the provenance of new ideas. As a result, they preprint their work while it is undergoing peer review.

Preprint servers also combat publication bias.[39] Anyone can easily post study results, thus providing a more complete picture of the scientific study landscape.

Such a mechanism and culture were missing from clinical research. It could be argued that time is more important for our field because of the more direct applicability of our science for clinical, public health, and public policy decision-making. The consequence, however, of posting preprints that could fuel misinformation is also greater.

I set out to build such a clinical medicine preprint server with Joe Ross from Yale, Theo Bloom and Claire

Rawlinson from BMJ, and Richard Sever and John Inglis from Cold Spring Harbor Laboratories. The idea among this group of cofounders was to build a platform with all the advantages of a preprint server but with safety features that provided guardrails.[40]

In June 2019, we launched medRxiv.[41,42] The landing page has a disclaimer that the content has not been peer-reviewed. We require evidence of an ethics approval for the study. Authors must register all clinical trials. We ensure that people in studies do not have identifiers. We review each preprint to determine if there is a possibility that it could cause harm. If there is a concern, we contact the authors and suggest that it is better to take it through peer review as a first option.

Now, medRxiv has over 12 000 manuscripts and is growing at a faster rate than bioRxiv at a similar stage.[42] The pandemic rapidly accelerated the growth and I believe that medRxiv played a critical role, especially at the outset, in enabling researchers worldwide to share study findings. It also enabled the research community to engage in public critique of these studies. Almost all journals joined ranks and endorsed the use of preprints, including the New England Journal of Medicine and the Lancet. In June 2020, Massey et al[43] from our group led a study of the preprint policies of the 100 top-ranked clinical journals. The study reported that almost 90% explicitly allow preprints. The New England Journal of Medicine stated for severe acute respiratory syndrome coronavirus 2 manuscripts, we also encourage authors to submit their work for posting on preprint servers.

There are other actions that journals can implement to reduce friction and speed scientific peer-review throughput.[44] Authors spend countless hours formatting papers for each submission. An alternative would be to enable authors more flexibility on the format for initial submission, instead spending the time meeting specific format requirements once the journal expresses interest.

The New England Journal of Medicine offered other ideas for severe acute respiratory syndrome coronavirus 2 manuscripts.[45] They stated that they expected authors to share information with public health authorities as soon as possible. They encouraged authors to share their original data. They opted to make the articles freely available to the public on the day of publication. For rejected papers, they offered to facilitate transfer to other journals, with reviewer comments.

These ideas, including the use of preprints, are not uniquely helpful against the pandemic, but to all global health threats. Is the suffering from cardiovascular disease and stroke so different from that of coronavirus disease 2019 (COVID-19)? If there is an urgency to combat the pandemic, should not we be applying these tools more broadly?

In the cardiovascular disease and stroke community, should not we push for uniform adoption of these suggestions for all our research? I think so. Reduce the friction on scientific communication. Embrace preprints. Make it easy to submit and transfer papers for peer review. Ease restrictions on communications with public health officials.

Strengthen Experimental and Observational Studies

The pandemic has raised awareness of the heterogeneity in the quality of science. Earlier this year we did a review of COVID-19 studies registered on ClinicalTrials.gov[46] led by Pundi et al.[46] These studies were a combination of experimental and observational clinical studies. We determined that the vast majority were unable to provide strong evidence. Then, we had 2 highly visible studies, one published in the New England Journal of Medicine and one from the Lancet, retracted because of uncertainty about the integrity of the database.[47,48] We find ourselves needing rapidly to strengthen our experimental and observational studies.

Experimental studies have issues. Experimental designs reduce the risk of bias and enable causal inferences. But our experimental research infrastructure is slow and expensive. Even to this moment in the pandemic, we have failed to execute clinical trials at scale.

With the notable exception of the RECOVERY trial (Randomised Evaluation of COVID-19 Therapy), led by Martin Landray and colleagues, and the WHO Solidarity Therapeutics trial, we have not had a surfeit of large, experimental studies.[49,50] Meanwhile, trials of other conditions have been suspended or slowed, or even discontinued, during this pandemic period. This experience has revealed vulnerabilities, but also opened opportunities.

Retrospective studies also have issues. Real-world data and observational designs can provide insights into the experience of patients and the public and do so with great efficiency. However, they can also be performed in ways that are slow and over-engineered with data collection that is never fully utilized. Registries are labor-intensive, slow, and imprecise. There is limited ability to go back to the source data for clarifications.

Similarly, prospective studies have issues. They often require face-to-face visits and involve inconveniencing participants, as well as challenges surrounding participant engagement. The most successful studies often have to devote considerable resources to manually sustain contact with participants.

What if we were willing to innovate more avidly in our research designs? Many ideas have emerged, in part, through the American College of Cardiology Roundtables that I chaired with Jim Januzzi, including more use of remote enrollment and monitoring.[51] I am

collaborating on strategies that go directly to potential participants to enlist them as partners in the studies.

In particular, I, with others, have been pioneering an approach that gives people digital and real-time access to and agency over their data so they can enable it to be shared into studies in a timely way.[52] Many approaches can reduce, as possible, reliance on fixed sites. Sensors, surveys, and mailed-in biospecimens can go a long way to reduce the need for face-to-face encounters.

We are also seeing hybrid strategies that combine real-world data strategies with protocolized data collection. Use of real-world data for event ascertainment can provide investigators with the information to support adaptive designs. In this construct, data streams from real-world sources, ideally through a process that gives people access to their digital data, can come into the study to represent real-time information on health care events, experiences, physiological measures, physical activity, and functional assessments. An increasing number of studies are suggesting that traditional adjudications may not be necessary or add value commensurate with the time and resources they require, at least for some trial questions. Protocolized data collection can occur through decentralized sites for blood draws or other measurements that cannot be done remotely. The FDA is showing interest in all these new designs and is supportive of their use.

On the analysis side, the heterogeneity of quality in the pandemic is not so different from what we have seen in usual times, but it has highlighted the need for improvement. If it is important for the pandemic, then it should be important for all health threats.

A survey by Khera et al[53] on the quality of observational studies using the National Inpatient Sample of the US Agency for Healthcare Research and Quality revealed 85% did not adhere to one or more required practices, and 62% did not adhere to 2 or more. Many of these violations would invalidate the major conclusion of the paper.

The path forward must include adherence to standards that enhance validity and reproducibility and reduce bias, p-hacking, and publication bias.[54] Innovation in this space is growing organically from individuals who have assembled to advance observational research. People worldwide have come together for the Observational Health Data Science and Informatics group to share best practices.[55] The Observational Health Data Science and Informatics group is a multistakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics. All the solutions are open source.

The Observational Health Data Science and Informatics group launched the Large-scale Evidence Generation and Evaluation across a Network of Databases research initiative to promote standards and provide observational research examples that others can use. The Large-scale Evidence Generation and Evaluation across a Network of Databases group, of which I am a member, has promulgated a set of standard principles.[56,57] Some of the essential principles include the prespecification of the research question, the commitment to share all the generated results, the use of control questions, validation across databases, and full transparency, including the public posting of all code.

So, we have work to do on the way we conduct research and the pandemic is just an opening. We need to consider redesign of our approaches that address speed, efficiency, participant-centricity, validity, and reproducibility. The cardiovascular disease and stroke research community leads evidence generation; what will we do to strengthen our research enterprise, innovate and experiment with new approaches, and hold ourselves accountable for developing the pipeline of knowledge generation that we need?

Elevate and Propel Implementation Science

The pandemic galvanized action on implementing new workflows, with remarkable changes in practice. Who imagined that on a dime we could pivot to telehealth as a primary means of connecting with patients? The emergency showed what we can accomplish in short time frames if the moment requires it.

Before the pandemic, there were hundreds of reasons why telehealth stalled and the vast majority of our patient visits required people to find time during the day to come in (something that can be challenging for hourly workers or people responsible for others), sit in waiting rooms (sometimes for extended periods), and meet personally with health care providers (even if the visit did not require it). Suddenly, those constraints became much less formidable.

Is there a need for widespread change in the way we deliver health care? The results speak for themselves. There is much room for greater optimization of all aspects of the way we deliver care and conduct public health.

One of the biggest insights I had early in my career was the determinative importance of where you seek care.[58–64] The unfortunate fact is that how you do, whether you will have the correct diagnosis and treatment, and your likelihood of a good outcome may be dictated more by where you seek care than by many other conventional predictors of outcomes. Our guidelines focus on what to do for particular clinical situations but pay little attention to how best to do it. We neglect the how, in part, because of the paucity of evidence regarding how best to implement care. But there are some notable exceptions where we have changed care quickly with implementation science, remarkable for their rarity as much for their impact.

Primary percutaneous coronary intervention for patients with an ST-segment–elevation myocardial infarction is a prime example. The value of primary percutaneous coronary intervention for patients with a ST-segment–elevation myocardial infarction is minimized or eliminated when the door-to-balloon time is extended. The technically best interventional cardiologist in the world wastes her skills unless her entire team works in synchrony to diagnose, stabilize, and transport the patient to a catheterization laboratory that is staffed and poised to provide outstanding care.

Changing our level of performance and dramatically shifting the performance curve required some radical redesign of the process and the means to measure progress. The research entailed mixed methods, a design that involved quantitative and qualitative research studies. In the National Institutes of Health-funded research, we leveraged positive deviance, learning how the best places achieved results that were outliers in a positive direction.[65–72] We interviewed people at these sites and sought their secrets. We then tested our hypotheses in large-scale quantitative studies. We published the findings in the New England Journal of Medicine and simultaneously, at the American Heart Association meeting where we presented the findings, we launched a national effort to improve care that ultimately stretched across 1200 hospitals. Health care professionals around the country responded to the challenge and times improved—and mortality dropped.

But what we achieved for door-to-balloon times—and had previously done for aspirin and β-blockers for the treatment of acute myocardial infarction[73]—we are not accomplishing for so many other conditions. The risk of readmission varies by institution. We established measures that are publicly reported and that were ultimately integrated into national incentive policies. But showed that where you are admitted influenced your risk of readmission as much as your clinical characteristics. The strongest evidence was based on a study in which we identified patients who had been admitted for the same diagnosis to different hospitals over 3 years.[74] When patients sought care at a hospital with worse performance on readmission, their likelihood of being readmitted within 30 days was significantly and meaningfully higher. Still, this study in the New England Journal of Medicine and evidence about what it takes to improve performance failed to produce major changes in the risk of readmission, with no recent improvements.

Even for more basic care, such as hypertension treatment, our performance often varies and fails. In a study led by Shahu et al,[75] we found that even within the context of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Clinical Trial), site matters. Moreover, participants from the sites with lower income performed worse in blood pressure control.

In a digital age, we ought to be able to program the identification of patients who are falling through the cracks. In fact, we are terming such research locally as the falling through the cracks project. In my institution, we leverage the electronic health record to uncover such patients. In a study led by Lu et al,[76] we discovered thousands of people with highly elevated blood pressure and inadequate follow-up. Among patients with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg, only 28% had a follow-up visit within 1 month (follow-up window recommended by the guideline), and only 20% achieved control targets within 6 months.

These quality gaps represent implementation failures. Improvement requires the courage to identify these failures and implement redesign, with a focus on improved performance and the drive toward better outcomes.

The next era of health care needs a focus on implementation.[77–79] The National Heart, Lung, and Blood Institute, under Dr George Mensah, has established the Center for Translation Research and Implementation Science, which plans, fosters, and supports research to identify the best strategies for ensuring successful integration of evidence-based interventions within clinical and public health settings.[80] We need to elevate this type of science.

The cardiovascular disease and stroke community ought to be at the forefront of these efforts to realize the ultimate translation of what we know into effective action on behalf of patients. We should end the era where patients need to shop for high-quality doctors and health systems. When you travel by air, you do not spend time shopping for which plane and pilot to choose, you depend on aviation to control for quality. The top 10% of doctors and health systems cannot care for 100% of the patients. The imperative is to take the lesson of the pandemic about what can change and in what time frame to attack the deficiencies in quality that are also causing suffering and preventable death and disability.

Attack Disparities as If It Were a Global Pandemic

The pandemic has, once again, demonstrated the inequity in the burden of death and disease. Again, communities of color and those with limited resources suffer more than others. With the pandemic, and at this time in our history, we have raised our voices about the importance of focusing resources, research, and solutions where the burden is greatest. Words are not enough, but awareness is an important step. The pandemic is galvanizing a response to the disparities, but

the cardiovascular disease and stroke community can also seize this moment to broaden the implications.

Our failures to bridge disparities is also a large-scale failure of implementation and quality. Not all people have the same opportunity to achieve good health. Structural racism, exposures, behaviors, access, and quality conspire against people, creating inequity in our society.[81,82]

Continued descriptions of the problem and even characterizations of root causes will not progress until we test and implement the last-mile strategies that address the problem. People suffer needlessly because of the structure of our society and the organization of our health care. The loss of life and function among those who struggle because of structural racism and tenuous financial resources is akin to a global pandemic.

What do we have in place at our institutions to track and address racism and all forms of discrimination? Do we know if Black patients wait longer for admission, experience worse quality care, have longer times to follow-up appointments—and are we able to identify and track episodes of discrimination? How can we implement a truly antiracist agenda without metrics to track?

What about our research teams?[83] How strongly are we seeking diversity and the creation of opportunities to amplify pipelines for under-represented groups, including people who grew up in poverty and have first-hand knowledge of oppression and disadvantage? Also, to what extent are we configuring research teams that include patients from communities bearing the most risk and disease burden? What are the strategies we are continually testing to address disparities? To what extent can we change a mindset from one that assumes inequity will inevitably be with us to one that believes we can eliminate it? Could we possibly elevate disparities to the status of a disease that needs active treatment and continued vigilance?

For progress against disparities, we will need to work in partnership with the affected communities.[84] Trust in health care and the government is not high in these communities and solutions cannot be imposed from the outside. These communities have wisdom about what is causing the disparities and what solutions hold promise. Community-based participatory research has much to teach us about collaborations with the communities we seek to strengthen. In my role with the Robert Wood Johnson Foundation Clinical Scholars Program at Yale, I learned from community partners about what I needed to understand, how important it is to listen, and how trust is essential to all progress.[85]

The bottom line for disparities is that they persist despite all the talk and the studies published about them. In our work led by Caraballo et al[86] and Mahajan et al,[87] we have evidence that over the past 20 years, we have not made progress in access to care or health outcomes. We have life expectancy differences that resist change—and health outcomes, including functional status, continue to show health differences by race and income.

What if we were to attack disparities as if they were a global threat? Bridging the gap in health by race and socioeconomic status would avert more suffering than any miracle breakthrough that I can imagine. And the problem is, any miracle breakthrough in our field, given our current realities, is unlikely to benefit all our subpopulations to the greatest extent. Unless we change the churn of history, most of our breakthroughs will benefit those with the lowest risk and the highest privilege, before they truly have the beneficial impact on those at greatest risk and with the greatest vulnerability.

This inequity exacts a toll that is disproportionate and unacceptable—and is truly global. As the Gates Foundation states, "All lives have equal value,"[88] and, yet, that is not the reality. If we want this to change, we must make the change. And that change requires new strategies. The cardiovascular disease and stroke community, which has described reprehensible disparities for decades, needs to be up for the task.

Ride the Digital Transformation

The pandemic has arguably done much to propel digital health since the widespread introduction of the electronic health record. The period has propelled remote monitoring, telehealth, and digital apps.

The powerful concept in the wings is that the digital transformation can finally create a real-time learning health system.[89] In this construct, we can configure our health care enterprise to learn from every interaction. In tech companies, algorithms get smarter with every interaction. The google search algorithm evolves with every search. Amazon's algorithms get better with every shopper. Tesla algorithms get better with every mile. In health care, we have yet to come close to integrating knowledge from the last patient to benefit the next patient. And yet, such a system seems within our grasp.

A presumption of this next age is that we can move to more sophisticated systems of decision support for clinicians, patients, administrators, and policymakers. We may look back on these days as we look back on the early days of aviation, which required the pilot to pay rapt attention to a small number of instruments, with high rates of mishaps. Today, sophisticated autopilot systems assist pilots in producing exemplary levels of performance and make safe flight routines. The systems have not eliminated accidents but have made them rare.

The digital transformation can help us discard antiquated disease classifications and yield to improved taxonomies that better characterize mechanism, risk, and response. How many different types of hypertension are there?[90] How many types of heart failure? Our crude classifications are inadequate for the phenotyping that we and our patients need.

For example, a digital age holds the promise of avoiding the misclassification of considering people with hypertension as clusters primarily based on the systolic and diastolic blood pressures or diabetes based on patterns of glucose levels. Guidelines in the future could depart from simple, 2- or 3-step rule-based recommendations and instead feed into more complex and nuanced algorithms that inform choices for individuals. We can and will move from one-size-fits public health strategy to steering people into systems that enable personalized decisions that best suit each individual's preferences, values, and goals.

The question will be the standards to evaluate these tools, and since they evolve, to continually assess what they produce. The monitoring for unintended adverse consequences, including bias, will be essential. We need appropriate regulatory oversight to enhance innovation and maintain the safety of these systems. Software as a Medical Device will take on ever greater importance and we need to engage in the regulatory science. But what may be most important is how we implement these tools and how we test their value.

The most significant opportunity may be to bring together discovery, improvement, and accountability—activities that in the past existed in separate spaces. With greater control of digital data, it will be possible to leverage data generated in the everyday conduct of health care and individuals' lives to accelerate and improve research, transform our ability to monitor health care performance, and fuel efforts to improve.

Engage in Health Policy

The pandemic has focused attention on the degree to which government leaders and policies can influence our health care systems' results. The failures of public health policy have had devastating effects on our ability to control the pandemic. Meanwhile, flexible and expanded reimbursement policies propelled changes such as telehealth.

This critical importance of health policy, however, is not restricted to the pandemic and mandates our awareness of and engagement with health policy and government actions in health. Some of my early health care heroes engaged strongly in health policy. These people, such as Bernard Lown, Alexander Leaf, and Donald Berwick, recognized that good policies promote health and destructive policies can be toxic to health. One of my early insights was that bad policies could undermine even the best health care professionals—and good policies could strengthen immensely our ability to fulfill our mission to help people live healthier lives.

Our aspiration ought not to be the richest country in the world, but rather to have policies that enable us to be the one with the highest well-being and greatest health. Our work on well-being, in collaboration with Gallup and Sharecare, and led by Brita Roy and Carley Riley, is indicating that far too many Americans are failing to thrive.[91–93] Moreover, there are vast variations in well-being across the country connected to the way that communities are organized and opportunities are distributed. We need overt policies that give every person the chance to thrive. For cardiovascular and cerebrovascular health, success is closely connected to modifiable factors that are influenced by policy. The health status of Americans remains mired at less than ideal levels. We trail many other countries in standard metrics of health performance.

Moreover, too many Americans remain left out or are underinsured. Over the past 20 years, even throughout the implementation of the Affordable Care Act, we have not improved the percentage of people who defer or avoid care because of cost.[86] Life expectancy is not showing good improvement, and some population groups are going in the wrong direction. Meanwhile, costs are rising. Our work on the financial toxicity of health care is chilling, showing that many families suffer adverse economic effects from their care. This harm is an example of how policies can cause suffering on top of illness. With its financial stressors, the pandemic is likely to further stress a flawed system, with people suffering as a result.

The policies that affect health are not only about health care coverage. We should evaluate all policies for their potential effect on health. Air quality, the climate, food quality, and more all have health effects. The organization of our cities, with the built environment, can affect health. The safety of our cities and the inequity of opportunities affect health. Health cannot be an externality for other policies but an implication that we must take into account.

The pandemic shows the consequence of weakness in our health policies and the potential of wise interventions to support change. We have seen harm and the potential. We need to embrace the reality that policy has consequences and no aspiration to improve society's heart and brain health will succeed without the tailwind of enlightened policies. We also must recognize the need for experimentation, accountability, and learning as we optimize our approach. Despite political polarization, we need to coalesce around common principles that unite our profession and resonate with our patients.

The iron triangle—access, affordability, and quality—is what everyone seeks. And, an environment and community that supports people to thrive in their lives and their health is an almost universal desire. Our engage-

ment to contribute to the policies that support the realization of these goals is essential.

CODA

In summary, the pandemic has mandated our attention but has lessons beyond the current global threat. We need to help the nation and the world navigate the peril but also recognize the position we will be in when it is over. The global threats of cardiovascular disease and stroke will persist—and, even now, we should begin our thinking about how the experience with the pandemic shapes our response to these ubiquitous causes of preventable and premature death and disability.

We need to set audacious goals for the future as to how we will subjugate these threats. We have a lot of the knowledge we need to make considerable progress. What should be evident to us, however, is that our progress has been too slow and the results also disappointing. What should also be obvious is that change is possible.

For younger faculty and students, the baton is yours. It is time to reject assumptions about what is possible or how things should be done. Our community can be the spark. Help us change the approach: promote open science, expand preprints, innovate and improve research designs and methods, propel and strengthen implementation science, attack disparities as if they were a global pandemic, ride the digital transformation, and engage in health policy.

To return to the theme of outcomes research, we need to hold ourselves accountable for progress for our growing research funding and health care spending inputs. I have tried to share an abundance of ideas about where we should focus and paths to pursue that are different from the traditional paradigm. If we take approaches that we have always done and our progress is not what we expect, then now is the time for some radical redesign in generating and applying new knowledge.

The pandemic has given us a sense of urgency to change. It can be an inflection point in what we achieve for health if we do not restrict our view to a single infectious disease but instead broaden our perspective to include the entire range of disease and health. A year ago, we would never have imagined all that has happened since December. Now is the time to dream big about what may be possible a year from now. Never has there been a greater opportunity for redesign.

What do we intend to improve between now and then? How will we seize the opportunity from this crisis? How will we ensure that our curve of improvement is at a positive inflection point for the future? Surely, together, we can find a way.

ARTICLE INFORMATION

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