AHA Scientific Statement

Fundamental Cardiovascular Research: Returns on Societal Investment

A Scientific Statement From the American Heart Association

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***Abstract*—**Recent decades have witnessed robust successes in conquering the acutely lethal manifestations of heart and vascular diseases. Many patients who previously would have died now survive. Lifesaving successes like these provide a tremendous and easily recognized benefit to individuals and society. Although cardiovascular mortality has declined, the devastating impact of chronic heart disease and comorbidities on quality of life and healthcare resources continues unabated. Future strides, extending those made in recent decades, will require continued research into mechanisms underlying disease prevention, pathogenesis, progression, and therapeutic intervention. However, severe financial constraints currently jeopardize these efforts. To chart a path for the future, this report analyzes the challenges and opportunities we face in continuing the battle against cardiovascular disease and highlights the return on societal investment afforded by fundamental cardiovascular research. **(*Circ Res*. 2017;121:e2-e8. DOI: 10.1161/RES.0000000000000155.)**

Key Words: AHA Scientific Statements ■ discovery science ■ drug discovery ■ heart disease ■ research (or laboratory research)

Age-adjusted mortality from heart disease has declined an astonishing 75% over the past 50 years.[1] Many patients who previously would have died now survive to enjoy happy and productive lives. Lifesaving successes like this provide a tremendous and readily recognized benefit to individuals and society.

Many who would have succumbed to heart disease previously now survive with an injured heart. Moreover, aging of the population has blunted the benefits of the drop in age-adjusted death rates. These considerations, coupled with deterioration in lifestyle-related behaviors and the epidemic of obesity, have culminated in robust increases in the prevalence of heart failure, a chronic condition that can persist for years, causing untold suffering and entailing considerable expense. Projections estimate that by 2030, >40% of the US population will have heart failure or other forms of cardiovascular disease, with direct plus indirect costs exceeding $1 trillion.[2] This problem extends beyond the United States; indeed, a worldwide epidemic is unfolding as a result of an increased prevalence of risk factors and changes in environmental and socioeconomic conditions and, in turn, cardiovascular disease. For example, because most patients with diabetes mellitus develop heart disease, the prevalence of diabetes mellitus (11%) and prediabetes (50%) in China (1.4 billion total population)

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is truly alarming.[3,4] Cigarette smoking, another major risk factor for heart disease, is on the rise in many parts of the world. Males in China currently consume some one third of the cigarettes on planet Earth, and 20% of these individuals will die prematurely as a consequence.[5] In the United States, 10 000 people will turn 65 every day for the next 17 years. Thus, even as we benefit from impressive successes in our quest to conquer cardiovascular disease, the challenges we face continue to evolve and expand.

Many lifesaving advances have emerged through research into mechanisms underlying cardiovascular disease pathogenesis, prevention, diagnosis, and therapeutic intervention. Furthermore, recent analysis of temporal data has identified that the observed reduction in coronary mortality results from both risk factor management and improvements in treatments.[6] Thus, society has derived enormous benefit from investment in cardiovascular investigation, with improvements in longevity, quality of life, and economic growth.

Historically, the National Institutes of Health (NIH) has dominated as a source of research funding for basic cardiovascular investigation. Support from private foundations (eg, American Heart Association, Howard Hughes Medical Institute) has complemented this NIH funding. Despite the demonstrated return on investment (ROI) of this support, which has saved hundreds of thousands of lives, we currently face an unprecedented decline in research funding (blunted slightly by a recent up-tick in NIH appropriations). Current levels of NIH funding resemble in real dollars those of 2001, representing an ≈25% decrease in purchasing power for research compared with 13 years ago. This decreased funding has led to delays in the age at which new investigators launch as independent researchers. Between 1980 and 2013, the average age of investigators receiving their first Research Project Grant increased by 6 to 8 years. For PhD investigators, the average age increased from 36 to 42 years (6 years), whereas for MDs, the average age increased from 38 to 45 years (7 years). The age at which MD, PhDs, on average, obtain their first Research Project Grant is now 44 rather than 36 (8-year delay).[7]

Lack of awareness of the benefits of research investment, coupled with an inadequate sense of the urgency of the problems we face among lawmakers, policy makers, and the public, likely contributes to this attrition of societal support for fundamental research. Competing demands present on all sides inevitably limit resources. To reinforce the case for continued investment in fundamental investigation, the research community needs to convey more effectively the societal benefits of what may appear to nonexperts to be esoteric research on seemingly incomprehensible problems. We must redouble our efforts to make this case convincingly so as not to jeopardize future discoveries. Furthermore, we must dispel the notion that healthcare innovations always drive up costs. Analysis is required of the contexts in which the opposite occurs, where "health begets wealth," such as when fundamental research improves the health of society (eg, vaccines, risk factor reduction strategies, improvements in socioeconomic disparities), leading to increases in productivity and societal prosperity. We begin here to evaluate and estimate the multifaceted rewards that society receives from investment in fundamental cardiovascular research.

Among the several underlying reasons for reduced support of basic cardiovascular research, we must consider whether we as advocates for patients with heart disease, both present currently and emerging in the future, have articulated adequately the ROI of societal investment. Society rightfully expects and deserves a clear, objective, and quantified explanation of the payoffs from taxpayer-funded research. Going forward, we must convey more convincingly to many of our political leaders the value of investing in fundamental discovery. We need to communicate better the distinction between investment in research and spending for consumption. Furthermore, we must recognize that, whereas the ROI is robust in many domains, it may lag in others. In sum, we must do a better job of quantifying and articulating the robust benefits afforded to individuals, society, and the economy by research in cardiovascular disease. This position paper aims to begin to address these questions.

Challenges to Gauging ROI

The difficulty with articulating the ROI on research investment starts with the impossibility of assigning monetary value to a year of human life. The full direct health value and secondary societal benefits from cardiovascular research thus defy easy absolute quantification. However, who would prefer returning to a time when cardiovascular death rates were quadruple those presently, reverting to a time when life expectancy was half of that today? In this context, it seems difficult to justify the current situation in which we devote 18% of the gross domestic product to health care, yet only 0.25% is devoted (federal dollars) to biomedical research. What private sector entity could survive and compete successfully by devoting only 1.39% of its total budget to research and development? Despite the multitude of gains that society affords, we invest a mere 2.5 cents per day per US citizen for research to attack the number 1 killer of men and women alike.

Investment in fundamental research increases the body of new knowledge. It trains skilled graduates joining the work force, creates new methodologies and instrumentation, and fosters the capacity for scientific problem solving, all benefits for society yet difficult to quantify. Another benefit to society is the transfer to the commercial sector of critical and yet unquantifiable elements of knowledge that facilitate complex problem solving. The "spinoff" of the knowledge base and sophisticated analytical strategies derived from basic research spurs innovation and advances in industry.[6] Despite the unquestioned merit of transfer of academic discoveries to the private sector, assessing its numerical value presents considerable challenges.

Economists have begun to wrestle with rigorous estimates of the ROI from fundamental research. Many such analyses have documented robust economic benefits of publicly funded basic research, roughly in the range of 20% to 40%.[8] In fiscal year 2009, the NIH funded 50 885 grant projects, which directly created >300 000 full- and part-time jobs.[9] In a particularly dramatic example, the WHI (Women's Health Initiative) is estimated to have led to >200 000 fewer cases of breast cancer and cardiovascular disease over the ensuing decade because of findings that fostered less use of hormone replacement therapy.[10] The economic return from the $260 million program has been estimated at $37 billion (assuming a societal value of $100 000 for each quality-adjusted life-year), yielding an ROI of 143:1.[10] Research has uncovered significant correlations between NIH funding and US health dynamics, focusing on cardiovascular disease, stroke, cancer, and diabetes mellitus.[11]

In a study of the ROI of National Health, Lung, and Blood Institute funding, measured as top 10% articles (articles cited more often than 90% of other articles on the same topic published in the same year) and peer review percentile, no association was observed between application percentile ranking and grant outcome.[12] These data document the difficulty in predicting the scientific outcome of National Health, Lung, and Blood Institute–funded projects, whether their peer review–determined merit scores place them in the 1st percentile or the 20th percentile. Such data suggest strongly that much potentially impactful research has gone unfunded in recent years.

Whereas definitive proof of a positive overall cost-benefit relationship between research investment and societal reward has proved challenging, a considerable body of evidence supports this proposition.[13] A Wellcome Trust and UK Medical Research Council study found that funding cardiovascular research provided an annual rate of return of ≈30%.[14] A more recent Canadian study examining health gains resulting from funding cardiovascular research identified a conservative annual rate of return of 21%/y in perpetuity.[15] The lag time from discovery to clinical impact was 13 years, relatively short compared with other domains.[16] Indeed, an estimated three quarters of the post-1995 increase in productivity growth in the United States derived from investment in science.[17] However, the inevitable complexities of the scientific enterprise itself, the unpredictability of its outcomes, and the variable time delays between discovery and impact are major factors underlying the uncertainty of these estimates.

ROI: New Drugs, Devices, and Therapeutic Strategies

Research across the spectrum of cardiovascular biology has culminated in a wide range of powerful drugs, lifesaving devices, and strategies of prevention, diagnosis, and therapy. We now have 11 classes of drug to treat hypertension and 12 classes of drug to treat diabetes mellitus, a formidable arsenal targeting 2 of the most important heart disease risk factors. Numerous discoveries have emerged of the biological effects of overloaded ventricular myocardium, raising the prospect of directly targeting those events within the cardiomyocyte of hypertensive patients. Statins, and more recently ezetimibe and the proprotein convertase subtilisin/kexin type 9 inhibitors, elicit drastic decreases in low-density lipoprotein, a causal risk factor for atherosclerosis. We now possess a powerful arsenal of antiplatelet agents, permitting control of a critical contributor to ischemic heart disease. Indeed, progressively increased risk of bleeding balances additional gains from newer agents. Thus, we have reached a plateau of success with diminishing returns going forward in targeting platelets, highlighting the need to explore other avenues to address the intolerable residual risk that remains despite current standard of care.

Societal benefits that have emerged from the support of fundamental cardiovascular research extend beyond pharmaceuticals. Fundamental, discovery science focusing on smooth muscle cell biology and cardiovascular inflammation provided the foundation for the development of standard-of-care second-generation drug-eluting stents and emerging biodegradable stents. Collaborations with biomedical engineers have culminated in numerous lifesaving devices such as pacemakers, implantable cardioverter-defibrillators, cardiac resynchronization devices, ventricular assist devices, and total artificial hearts. These advances all arose from explorations of fundamental mechanisms of disease-related ventricular remodeling, including structural, molecular, and electric events. Millions of patients worldwide benefit daily from these advances.

Looking to the future, advances in systems biology in terms of recognizing genetic variants (eg, proprotein convertase subtilisin/kexin type 9) and analyses of genome expression, including epigenetics, proteomics, and "big data," offer unprecedented opportunities to develop novel diagnostic biomarkers and to uncover innovative therapeutic targets.

ROI: Economic Benefits

Fundamental cardiovascular research has yielded not only the aforementioned health benefits but also substantial economic benefits. Prolongation of healthy and active life, a worthwhile end in itself, can increase productivity in the workforce. Jobs, products and goods, exports, and economic growth result. Furthermore, increased tax revenues derive from these additional years of productivity within the workforce, effectively reimbursing the government, both federal and state, for the upfront investment in research. Of note, the economic benefits of treating a disease that afflicts people late in life, as is often the case now, will not be as great as those seen during an age when acute heart disease commonly killed people in their 40s. However, chronic diseases in the elderly are extremely costly, not only because of direct healthcare expenditures, including hospitalization and medications, but also as a result of loss of productivity from family members and loved ones who care for the chronically ill. Thus, maintaining health improves quality of life and limits expenditure of healthcare resources.

Job creation per se is another apparent benefit from research investment, not just in academic, industry, and governmental laboratories. Fundamental research feeds a drug development pipeline in the biotechnology and pharmaceutical industries. These industries are enormous and generally quite profitable. The US biopharmaceutical sector employs >800 000 workers and supports a total of 3.4 million jobs across the nation. The estimated overall economic impact of the biopharmaceutical sector on the US economy totals approximately $800 billion on an annual basis when considering direct, indirect, and induced effects.[18] With rare exceptions, basic research in academia funded by the NIH and public institutions feeds the biopharmaceutical pipeline. A wide range of products, for example, research materials, infrastructure, pharmaceuticals, and medical devices, emerge from the development end of the research-and-development pipeline.

Figure. Research into disease mechanisms and novel therapies is critical to the urgent need to stem the tide of cardiovascular disease and to "bend the cost curve" of associated expenditures.

Apart from the health benefits afforded by new drugs and devices, these products have an important impact on the global economy.

ROI: Preparation for Future Healthcare Needs

Investing in the future distinguishes leading societies. For many years, the United States has led the world in biomedical research and education. This lead, however, has dissipated considerably in recent years, as investment in the United States has declined while increasing in Europe and Asia. We submit that investment in fundamental research boosts national standing and competitiveness and that our national position in this regard relative to other nations is eroding.

In addition, basic research is fundamental to the urgent need to tame runaway healthcare costs. The developed world has largely moved beyond singular focus on acute disease because chronic diseases now predominate worldwide in loss of productive life-years and as contributors to cost. Attacking the problem of chronic disease at the level of pathogenesis provides a proven way to "bend the cost curve" in our healthcare expenditures. We will never diminish the enormous and growing costs associated with Alzheimer disease without finding a cure. We will never reduce the costs associated with the pandemic of chronic heart failure without identifying novel underlying mechanisms (Figure).

ROI: Conquering Future Challenges

Despite the enormous gains achieved in recent decades, heart disease continues to be the number 1 killer of both men and women around the world. Somehow the problem continues to expand despite a steady stream of advances. How can this be? Much of this reality stems from the pandemic of obesity and diabetes mellitus occurring before our eyes. Furthermore, patients now survive episodes of heart disease that in a previous era would have proved lethal, as in the case of certain cancers. As a result of prolonged longevity, the insults of aging and comorbidities take a cumulative toll on the cardiovascular system. The steadily deteriorating environment of our planet, sadly likely to accelerate, also affects cardiovascular health: deteriorating air quality, the expected ravages of climate change, dependence on automobiles and technologies with consequent diminishing calorie expenditure, and substitution of processed foods for natural nutrition and food sources. In sum, despite enormous success, new hurdles have arisen that must be overcome, demanding an unremitting assault.

Indeed, present circumstances and opportunities give us every reason to anticipate significant ROI in the future. Recent years have witnessed a wide range of novel advances that set the stage for important new insights. The following list names just a few:

- Opportunities to explore and define the genetic basis of disease because of advances in sequencing technologies and bioinformatics; the cost of DNA sequencing has decreased 7 orders of magnitude in the past decade
- Big data ("precision medicine"), including novel "omics" technologies and analytical methods, paving the way for novel biomarkers, theranostics, and new treatment targets
- Technological advances, including gene editing technologies, notably CRISPR/Cas9; 3-dimensional molecular printing; nanoparticles for drug delivery; microfluidics; and mobile devices
- Advances in myocardial regeneration, including induced pluripotent stem cell technologies, progenitor cell biology, cardiomyocyte cell cycle control, and cellular transdifferentiation
- Robust advances in our understanding of the biology of vascular disease, endothelial progenitor cells, and aneurysm formation
- Insights emerging from bridging systemic disciplines such as cardio-oncology and cardio-nephrology
- Exciting insights into the robust benefits of exercise on the heart and other organs

To capitalize on these opportunities, affording unquestionable benefit to society, we must maintain singular focus on defining and articulating to society the ROI of the resources dedicated to these pursuits.

Novel Funding Solutions

As we pass through these financially constrained times, support from industry and nongovernmental foundations has assumed increasing importance. The total support for biomedical research in the United States in 2012 was approximately

$130 billion, of which $41 billion was from the federal government and $69 billion was from industry.[19] Although industry support for biomedical research is highly profit driven with a central goal of developing a new drug or technology, alternative means to support research outside the federal government by nonprofit funders have become increasingly vital. These nongovernmental organizations support the full spectrum of biomedical research from basic to clinical and place an emphasis on career development grants for new generations of researchers.

Recent declines in societal investment in biomedical research require other innovative approaches to supporting this vital mission. Could the NIH and private foundations reconsider the notion of funding investigators (proven track record of innovation) rather than specific research projects? Is funding investigators with multiple grants potentially more effective than funding multiple investigators with fewer grants? An increased role of private philanthropy also must be part of the answer.[20]

Opportunity Costs of Inadequate Investment

Just as robust benefit derives from investment in fundamental cardiovascular research, there is a price to pay for not investing. Shuttering of cardiovascular laboratories as a result of recent funding constraints leaves fewer professionals working to solve the riddles of heart disease as investigators abandon the field for other pursuits. Novel tools such as specialized animal strains, cell culture lines, and more may lie fallow. Fewer investigators are being launched to tackle the ever-evolving problems of the future. As a result, we foresee major challenges ahead in meeting the healthcare needs of our world; new discoveries, new therapies, and an adequate cadre of practitioners are all in jeopardy.

Research is a vital element of preparing the next generation of cardiovascular practitioners. The rapidly evolving nature of our discipline in the present era renders training in clinical cardiology highly complex. The Accreditation Council for Graduate Medical Education promotes a competency-based approach for training, which places emphasis on integrating medical knowledge into clinical practice and on developing skills appropriate to patient relationships.[21] Now, as the technology and research in cardiology are advancing rapidly, trainees must master a growing list of topics to provide excellent clinical care and to perform complex procedures. Going forward, future advances in cardiovascular medicine depend critically on the emergence of specialists trained and equipped to conduct research. Although many cardiology training programs at accredited academic institutions place an emphasis on research during fellowship, the emergence of the next generation of cardiovascular physician–scientist leaders requires a program dedicated to structured mentorship and career development for fledgling faculty. Although most cardiologists do not pursue research along with their clinical work, it is critical to facilitate that effort among those so inclined. Achieving this goal requires a training environment that mentors trainees at early stages, invests financial support for early career investigators, and facilitates their transition into productive positions in academia or industry.

Thus, the success of the next generation of cardiovascular physician–scientists will depend on several factors: (1) established and organized training programs supporting research-oriented education during fellowship; (2) an effective mentorship program that actively integrates young cardiovascular scientists into the system of established investigators; (3) the availability of steady financial support to provide a measure of security for early career investigators; (4) more effective institutional "showcasing" of discoveries and the progress made by cardiovascular researchers so that our investors (the public) can see the return on their investment; and (5) the establishment of organizations that aim to facilitate the translation of discoveries and to promote entrepreneurship among cardiovascular researchers.

Path for the Future

The biomedical research community must do a better job of defining, quantifying, and articulating the ROI that society can expect from investment in basic cardiovascular research. We challenge ourselves and our colleagues to remain cognizant of our responsibility to society whose investment reaps benefits in the future and strive for continued improvement. As one approach to optimize ROI, some evidence suggests that enhanced interaction among researchers, clinicians, and the public fosters basic research with a clinical focus and that prospective mapping of pathways to achieve wide impact can enhance ROI.[22]

We also hope that efforts to quantify better the ROI on research will emerge in the future. As a first step, we provide here an overview of the funding landscape of cardiovascular science and issue a call to communicate more effectively with lay society. Happily, initiatives are emerging with prospective mechanisms of tracking and quantifying the societal impact of research investment.[23,24] These approaches aim to strengthen the evidence base for providing to society a response to the question, "What do we get in return?"

Critically, we do not recommend that funding by NIH or the American Heart Association target primarily short-term gain to society. Reaping the ROI in basic research requires a longer perspective. An NIH peer review group should certainly not assume the mentality of venture capital investing, seeking to support work with the greatest immediate return. Rather, fundamental research must occur in the context in which clinical or commercial benefit may not provide immediate tangible return. Watson and Crick did not solve the double-helix structure of DNA seeking short-term, economic benefit. However, no one would question the enormous gain to society that has accrued from their work. The seemingly esoteric fundamental research on retroviruses unexpectedly and urgently yielded dividends when HIV burst onto the scene in the 1980s. There are countless examples—fundamental work on G-protein–coupled receptors, cholesterol metabolism, inflammation, and microbiology to name but a few—for which similar benefit has accrued to society from basic research. Focusing on fundamental research, broadly speaking, Margaret Thatcher, former prime minister of the United Kingdom stated that "…although basic science can have colossal economic rewards, they are totally unpredictable. And therefore the rewards cannot be judged by immediate results.

Nevertheless the value of Faraday's work today must be higher than the capitalization of all the shares on the Stock Exchange!"[25]

Perspective

We face unprecedented opportunities and evolving challenges in the fight against cardiovascular disease, the number 1 killer on Earth. The current environment has re-emphasized the pressing need to articulate effectively to society the benefits of investment in basic research. Many in the research community may assume that these benefits are self-evident and that the dramatic declines in cardiovascular mortality speak for themselves. We argue here that we cannot rest on our laurels of success; rather, we must focus time, thought, and energy on explaining the continuing need for new advances. This document sounds the call to engage in this vital mission. Failure to do so will stall critical progress; success in communicating this message will afford worldwide benefits long into the future.

Disclosures

Writing Group Disclosures

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*Modest.

†Significant.

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Fundamental Cardiovascular Research: Returns on Societal Investment: A Scientific Statement From the American Heart Association

Joseph A. Hill, Reza Ardehali, Kimberli Taylor Clarke, Gregory J. del Zoppo, Lee L. Eckhardt, Kathy K. Griendling, Peter Libby, Dan M. Roden, Hesham A. Sadek, Christine E. Seidman and Douglas E. Vaughan
on behalf of the American Heart Association Council on Basic Cardiovascular Sciences; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Stroke Council

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