

The Journey From Research Discovery to Optimal Heart Health for All



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TURNING FUNDAMENTAL DISCOVERIES INTO HEALTH

The tag line of the U.S. National Institutes of Health (NIH) is *Turning Discovery into Health* [1]. The phrase captures the importance of research translational steps that help turn discoveries into individual and population health impact. Without the discoveries from fundamental research in basic science to advance and expand our knowledge of the molecular, cellular, and physiological mechanisms governing health, our translational research efforts to underpin health promotion and the prevention and treatment of disease will falter. As Vannevar Bush pointed out in *Science, the Endless Frontier*, “Basic research leads to new knowledge. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn...” [2]. This new knowledge generation through fundamental discovery science occurs not just in the biological and other natural sciences but also in the social and behavioral sciences and encompasses research conducted in humans, animals, tissues, cells, and subcellular structures [3,4].

TRANSLATIONAL RESEARCH FROM BENCH TO BEDSIDE AND BEYOND

The journey from fundamental research discovery to optimal health for individuals and populations is an arduous one. The NIH Roadmap recognized the importance of supporting basic research but also highlighted the need to “translate” basic research findings more quickly into diagnostic and therapeutic interventions to be undertaken in clinical practices in support of patient care to promote health. Re-engineering the clinical research enterprise and supporting translational research core services were just as important as new pathways to research discovery [5]. In fact, as former NIH Director Elias Zerhouni noted, “exciting basic science discoveries demand that clinical research continue and even expand, while striving to improve efficiency and better inform basic science” [5]. This was the concept of the 2 major research laboratories—bench and bedside—and the related (T1 and T2) translational steps.

In their commentary on practice-based research as the “blue highways” on the NIH Roadmap, Westfall et al. [6] emphasized that the T1 and T2 translational steps from bench to bedside and from bedside to practice in the NIH Roadmap were inadequate to capture the crux of what happens in routine clinical practices. As they eloquently

stated, “What is efficacious in randomized clinical trials is not always effective in the real world of day-to-day practice” [6]. They proposed expanding the bench and bedside concept to include a third translational step (T3) involving research in ambulatory clinical practices [6]. Research generated in this third setting—practice-based research—is what Green has called for as necessary to make research relevant to the practice setting [7,8]. More recently, in alignment with the operational phases of translational research advocated by the National Academy of Medicine [9], we have built on these developments and highlighted the fourth translational step (T4), which embodies population-level outcomes research with an emphasis on implementation research outcomes (Figure 1) [10].

Collectively, what these translational research steps represent is a nonlinear, iterative process where one translational step informs as well as leverages insights from other steps through feedback loops in new knowledge generation; rigorous systematic evidence review, synthesis, and integration; clinical practice guideline development and deployment; and active dissemination and implementation research as one progresses from fundamental discovery science to population health impact. Each of these translational steps is important and features unique challenges that must be overcome to facilitate turning discoveries into health.

CHALLENGES IN EARLY-STAGE TRANSLATIONAL RESEARCH: CROSSING THE VALLEY OF DEATH

The valley of death is a well-described challenge in early translational research that spans the period after fundamental discovery and includes proof-of-concept research, product definition, prototype development and optimization, pre-clinical validation, and regulatory approval before the start of Phase I clinical trials. It refers to the proverbial challenge wherein basic research breakthroughs “languish and frequently succumb” [11] because of a lack of funding and/or expertise to turn the breakthroughs into commercially viable drugs, devices, and other products. Several current NIH initiatives provide the support necessary for proof-of-concept research, prototype building, product development and testing, and overall “de-risking” to make concepts and prototypes attractive to investors and thus help investigators and their innovations cross the valley of death [11-14].

Admittedly, the valley of death is not the only challenge faced in early translational research. As summarized by several authors [13-17], continuing cultural differences

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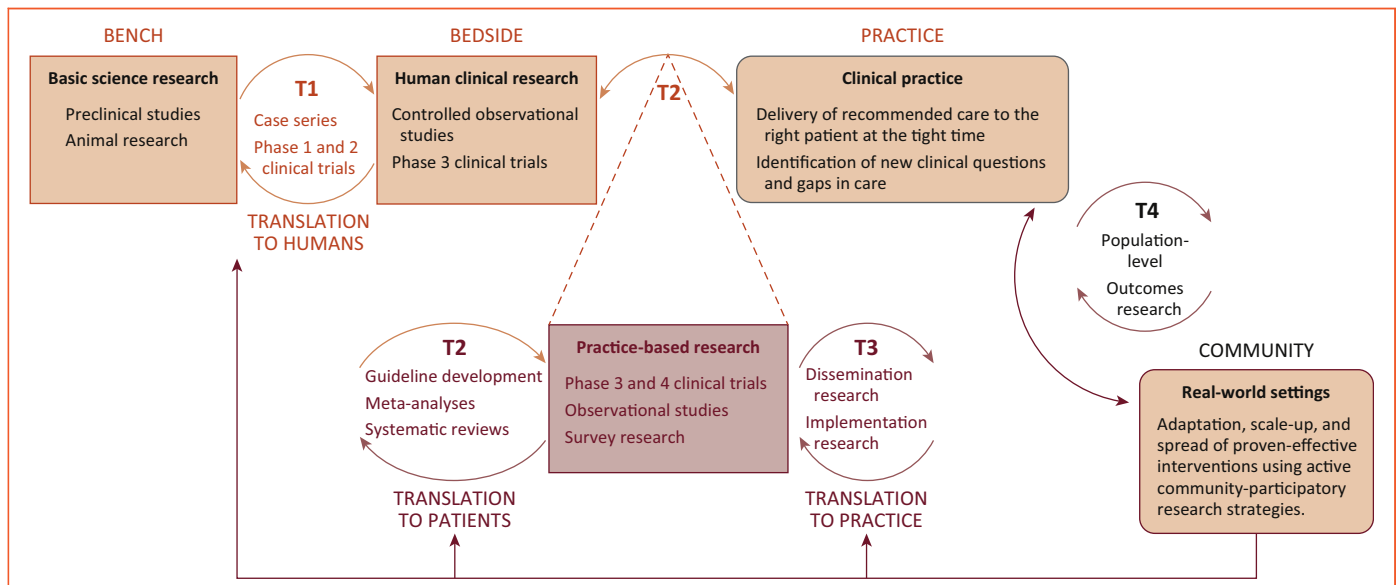


FIGURE 1. Research translation: from bench to bedside to practices to communities and back to bench research. Reproduced with permission from Westfall JM, Mensah GA. T4 translational moonshot: making cardiovascular discoveries work for everyone. *Circ Res* 2018;122:210-2.

between basic scientists and clinicians remain a challenge, and so do the complex regulatory environment, inadequacies in infrastructure and resource support, challenges in data access and sharing, limited training and mentoring opportunities, and inadequate numbers of trained interdisciplinary staff to support investigations throughout the early translational research spectrum. Again, there has been substantive support for early translational research, especially from the NIH, the United Kingdom's Medical Research Council and National Institute of Health Research, as well as other major research funding entities [5,9,17,18]. At the NIH, the establishment of the National Center for Advancing Translational Sciences (NCATS), with a fiscal-year 2012 budget of \$575 million, is one concrete example of the commitment to "re-engineer the process of translating scientific discoveries into new drugs, diagnostics, and devices" [19,20].

CHALLENGES IN LATE-STAGE TRANSLATIONAL RESEARCH AND IMPLEMENTATION SCIENCE

Far fewer initiatives and resources exist to address the challenges in late-stage translational research. Importantly, however, this phase is when strategies to increase the adoption and sustained use of these new drugs, diagnostics, and devices to optimize health impact are explored. At the National Heart, Lung, and Blood Institute, the establishment of the Center for Translation Research and Implementation Science was an effort to focus strategic attention on the challenges inherent in this phase of the translational research pathway and to stimulate interest in T4 translation research [21,22]. The myriad late-stage

translational research challenges include limited resources for rigorous systematic evidence review, evidence integration, and the development of trustworthy clinical practice guidelines; clinical, therapeutic, and knowledge translation inertia [23-25]; lack of tools and supports to facilitate guideline dissemination and effective implementation [26]; challenges in changing provider, health systems, and consumer behavior in adherence to established best practices and clinical practice guidelines [27-30]; and challenges in generating new knowledge in practice-based research to inform evidence-based practice to optimize population-level health impact [7,8,31].

Several articles in this issue of *Global Health* provide other examples of the important challenges encountered at this "tail end" of the translational research pathway in global health research and the implications they have for turning discoveries into population health impact. The examples span challenges in systematic data collection methods and data transparency [32]; importance of roadmaps that provide practical and effective solutions to improve detection, treatment, and control of hypertension and other cardiovascular risk factors [33]; context-specific health system factors that affect the patient's choices of medications and ability to adhere to dosing recommendations in the long term [34]; social and cultural conditions that vary between settings or countries and thus impact adaptation of proven interventions from one setting to another [35]; lack of relevant capacity and resource constraints [36]; and the importance of strategic partners at the local, national, continental, and global levels for the prevention, treatment, and control of cardiovascular diseases [37].

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