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True translational research: bridging the three phases of translation through data and behavior

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Abstract

Translational medicine has yet to deliver on its vast potential. Obstacles, or "blocks," to translation at three phases of research have impeded the application of research findings to clinical needs and, subsequently, the implementation of newly developed interventions in patient care. Recent federal support for comparative effectiveness research focuses attention on the clinical relevance of already-developed diagnostic and therapeutic interventions and on translating interventions found to be effective into new population-level strategies for improving health—thereby overcoming blocks at one end of the translational continuum. At the other end, while there is a preponderance of federal funding underwriting basic science research, further improvement is warranted in translating results of basic research into clinical applications and in integrating the basic sciences into the translational continuum. With its focus on the human and interactional aspects of health, medical practice, and healthcare delivery systems, behavioral medicine, itself a component of translational medicine, can inform this process.

Keywords

Translational medicine, Translation blocks, Translational behavioral medicine

Implications

Practice: Practitioners of behavioral medicine have the opportunity not only to introduce behavioral medicine topics onto the translational medicine research agenda, but also to guide development of a healthcare system in which the results of basic and clinical research are effectively translated into change in practice at the individual and population level.

Policy: To best advance translational medicine, investment in health information technology development should include development of methods, measures, and instruments relevant to behavioral medicine, and should be informed by expertise in this field.

Research: Behavioral medicine needs to position itself at all points along the continuum of research, from basic science to clinical studies, and to ensure that results are pushed forward into implementation.

TRANSLATIONAL MEDICINE AND THE TRANSLATION BLOCKS

The term "translation," now a well-worn buzzword in academic medical and policy circles, refers to the process in which knowledge newly generated in one sphere is applied in another sphere to advance goals in that area. Translational medicine was originally described as the implementation of "bench to bedside" research, i.e., research that moved new discoveries from the basic science laboratory toward patient care by developing clinical applications such as new drugs, devices, or biomarkers.[1] The vision was that of a bridge connecting the lab to the clinic, thereby expediting the transformation of clinical practice based on scientific progress, and ultimately leading to improvements in care and outcomes.

This vision, unfortunately, remains elusive. Obstacles, or "blocks," to translation at three phases have impeded the application of basic research findings to clinical needs and, subsequently, the implementation of newly developed interventions in actual patient care. In June 2000, the Institute of Medicine's Clinical Research Roundtable defined two translation blocks: the T1 block, occurring at the stage where "new understandings of disease mechanisms gained in the laboratory [are transferred] into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans;" and the T2 block, hindering "the translation of results from clinical studies into everyday clinical practice and health decision making."[2] The wider generalization of research findings occurs at a third translation phase, T3, which has been described as the "how" of healthcare delivery, the purpose of which is to ensure that evidence-based interventions effectively reach individuals and populations whose health can benefit.[3]

Hypothetical examples of T1, T2, and T3 research, respectively, are (T1) a basic science study that identifies a genomic marker for lung cancer susceptibility; (T2) development of this biomarker into a screening test for use in clinical practice; and (T3) evaluation of the impact of a

delivery model for this intervention that entails drawing blood samples from participants in Health Department smoking cessation programs, to test for the lung cancer biomarker. Behavioral science interventions might remediate blocks occurring at each of these levels of research by (T1) developing communication pathways and a "common language" that enables basic scientists to convey their finding and its implications to clinically focused colleagues, and to work together with clinicians to refine the biomarker so that it can progress to clinical study; (T2) examining clinical pathways and processes in primary care and lung cancer clinics, to make sure that the new test will be readily incorporated into routine care; and (T3) conducting focus groups to ascertain whether or not participants in publicly funded smoking cessation programs would be willing to undergo the screening test, especially if it involves a blood draw.

RATIONALE FOR A FOCUS ON T1–T2 TRANSLATION

Recent national support for comparative effectiveness research (more recently being labeled patient-centered outcomes research)[4, 5] represents, in large part, a strategy to eliminate the gap between T2 and T3 research, by determining which intervention, among existing alternatives, is superior and hence suitable for clinical adoption. Getting the "right care to the right patient at the right time" has become the mantra of the new decade.[6] Structures such as practice-based research networks (PBRNs) have been developed as a mechanism for moving research into clinical practice (T2 and T3); many PBRNs focus on creating a strong partnership between scientists and professionals in community health to advance widespread evidence-based translation and, in effect, overcome the T3 hurdle.[7] T1 science has yet to be well integrated into the continuum of clinical and health services research; a gap persists between basic science and its application at the individual patient, as well as the population, level. This paper focuses on the T1–T2 gap, a translation block which behavioral medicine can help to overcome since two primary tools for facilitating translation at this level–information flow and behavior change (discussed below)–fall within the purview of behavioral medicine.

T1 studies that focus on developing basic science breakthroughs to the point where they are ready for clinical application were originally the main focus of calls for translational research and are amply funded. In 2002, the NIH budget totaling $22.1 billion included $13.0 billion for basic research, versus $787 million for health services research.[8] But despite massive federal (and industry) investment in the development of new applications that bring science to the market, major health breakthroughs have not materialized. We have yet to cure cancer, let alone prevent diabetes or other chronic diseases responsive to behavioral intervention. Why?

New understandings yielded by the basic sciences, even when used to create new interventions, are not in and of themselves sufficient to yield dramatic effects. Knowledge is necessary, but not sufficient, to improve practice and health outcomes. Reductionist purity may actually be the Achilles heel of T1 efforts, for ultimately health outcomes are influenced not only by basic biological mechanisms but also by environmental and genetic factors, and by behavioral, psychological, and cognitive ones.

Personalized medicine, viewed through one interpretive lens, begins with an understanding that the process of healing for any given patient depends upon a host of factors specific to that individual. While in its original formulation, personalized medicine referred to the use of genomic marker-assisted diagnosis, and targeted therapies derived from an individual's molecular profile, to tailor care to the individual,[9] genomic and biomarker medicine (i.e., the use of genomic and biomarker laboratory tests to support individualized matching of interventions to patients) represents only one aspect of personalized medicine. When redefined to be in alignment with multidisciplinary models of care, personalized medicine requires the aggregation of multiple data types representing the entire biopsychosocial spectrum of data describing the individual. Only by spanning all levels of the translation continuum, through cross-talk among experts in human biology, genetics, epigenetics, environmental sciences, behavioral medicine, animal modeling, and other disciplines, can T1 research lead to the development of interventions that optimize outcomes for the individual patient (T2) and the population (T3). In an era of personalized medicine, a "combinational, interactive approach" is needed.[10] And behavioral medicine must be at the table.

THE PROCESS OF TRANSLATION: AN OPPORTUNITY FOR BEHAVIORAL MEDICINE

Arguably, conquering the T1 block–that is, using basic science insights to develop new treatment options–is the most straightforward and well understood of the three translational tasks. While best addressed through interdisciplinary collaboration, the challenges of T1 research remain primarily biological, methodological, and technological, whereas those of T2 and T3 involve the vagaries of human and organizational behavior. To move from the outputs of T1 research–novel interventions based on basic scientific discoveries–to changes in clinical practice (T2) and implementation in healthcare systems and public health initiatives (T3) necessitates two fundamental ingredients: *information flow*, that is, the availability and accessibility of data that can help guide change in practice and reform of systems, and *behavior change*, specifically,

instituting new communication pathways and new (oftentimes evolving) ways of using data and of providing care, based on new knowledge.

At T1, information flow refers to the transfer of applied basic science knowledge to the clinic and clinical care providers; it requires true integration of the clinical and research spheres. At the T2 level, this integration demands *bidirectional* communication from the patient and physician in the clinic to the research scientist in the laboratory, and back again, in an iterative cycle of hypothesis, question, answer, and testing of that answer in the real-world setting. When we achieve this cyclical process involving routine exchange of data, we will have succeeded in bridging T1 and T2. Extension of the bridge across T3, to include patients, the local health system, payers, policy-makers, community agencies and interests, and the population at large in adoption of new knowledge and practices, can be facilitated by "system integrators," such as academic health science centers; these agents can play a vital role in "filling the spaces between academic discovery, science, industry, and the general health-care delivery system."[11]

Increasingly, these spaces are created by gaps in data and informatics that constitute, as described by Califf and colleagues, bioinformatics blocks.[12] Reliable mechanisms to collect high-quality data directly from patients, present it to healthcare providers and researchers, and facilitate bidirectional flow of information back to patients are critical to bridging T1 to T2, as well as T2 to T3.[13], [14] Novel approaches to health informatics that integrate the currently disconnected spheres of bioinformatics, clinical informatics, behavioral informatics, etc., are needed; technical, cultural, trust, security, and data exchange challenges must be overcome. Regardless of their origin, closing these "spaces," or gaps, will require both novel data-related and informatics approaches and behavioral change in the biomedical community; conquering these blocks in a widespread and enduring way (i.e., at a population-based vs. healthcare system level) will require involvement of decision-makers in the larger sphere, such as legislators and reimbursement policy-makers.

SYNERGY OF HEALTH INFORMATION TECHNOLOGY AND BEHAVIORAL CHANGE TO FACILITATE TRANSLATIONAL MEDICINE

Truly translational medicine depends upon *continuous and dynamic* information exchange. This sort of information flow will not be possible without coordinated health information technology (HIT) systems that span former "silos" in the biomedical community, and that can collect and manage large volumes of disparate and heterogeneous data in order to drive the formation of research hypotheses as well as support clinicians' queries. In concert with these HIT systems, we will need to establish communication channels that advance hypotheses through collaborative inquiry, and that create transparency such that stakeholders can monitor progress in translating research findings into clinical practice improvements.

In a fundamental way, information flow depends on communication; it thus will require changes in both personal behavior and organizational culture; a new level of requisite participation and collaboration will call together scientists and clinicians across all phases of the translational spectrum. Behavior/culture change can be promoted (a) through the deployment of decision support mechanisms that help clinicians access and use aggregated data and new informatics-based approaches to improve care for their patients, and (b) by efforts to cultivate a sense of common mission, in which continuous inquiry leads to new insights and interventions which, in turn, result in improved care and outcomes.

It should be clear by now that behavioral medicine has a critical role to play in the advancement of translational medicine. As new capacities such as imaging technologies and genomics make it possible to study the mechanisms of human behavior in greater detail, behavioral medicine is joining the ranks of the biological and technological sciences as a basic science. Not only are behavioral medicine research questions themselves the targets of basic scientific study with translational implications–for example, a sound understanding of the mechanisms of pain relief could guide the development of clinical applications, such as cognitive behavioral interventions or acupuncture, to treat specific pain scenarios–but the knowledge base of behavioral medicine can also inform the architecture and processes of the new translational medicine system, for example, by helping ensure that the necessary behavioral and cultural changes among stakeholders occur. Moreover, behavioral medicine may be the appropriate discipline to lead evaluation of the impact of a translational medicine system and its processes on care providers, researchers, and patients.

Special attention should be paid to the role of patient-reported data. Bidirectional interaction with healthcare consumers, which includes learning about their interests, concerns, needs, and experiences, is critical to bridging the T1/T2 and T2/T3 gaps. Most obviously, data systems that interact with patients can be used to refine and target interventions, deliver tailored information expediently, and meet patients' information needs when they are most ready to hear and respond to the information; behavioral medicine research and expertise is critical to honing and implementing each of these steps.[15] Patient-reported data, in themselves, are becoming equally, if not more, important as a method of understanding patients as well as matching education and care to needs. Patient-reported outcomes (PROs) such as quality of life, symptoms, and perception of care are taking center stage as research

outcomes in comparative effectiveness research. Clinicians, patients, payors, and other healthcare decision-makers are demanding patient-defined evidence of the value of healthcare interventions.[13] Studying the reliability, validity, and use of PROs fits squarely in the domain of applied behavioral medicine with its focus on psychometrics and psychology. PROs are proving to play a critical role in the overarching data infrastructure needed to bridge the translation gaps; behavioral medicine must be at the table.[16]

REQUIREMENTS OF A TRANSLATIONAL MEDICINE SYSTEM THAT ENCOMPASSES BEHAVIORAL MEDICINE

Biological and technological breakthroughs, even when information systems support them, will not by themselves transform healthcare and revolutionize health outcomes. Current progress in developing a national HIT infrastructure underscores this point. For example, the Cancer Biomedical Informatics Grid (caBIG®)[17] championed by the National Cancer Institute has made great strides in developing infrastructure for large-scale data interoperability; this interoperability will make it possible to cross the long-standing boundaries between data in the basic sciences, clinical datasets, and the patient report. To enable use of caBIG® and its tools, however, we must make the data accessible, facilitate and support use of the data, and help users make sense of the data at the levels of basic science, patient, clinic and health system, community, and population. With respect to behavioral medicine, we must ensure that data elements meaningful to the behavioral medicine community are readily available, fully curated, and applied in research and clinical practice. An important step in this process is the development of the Grid-Enabled Measures (GEM) database,[18] which is web-based and built upon the caBIG® platform. GEM contains measures relevant to behavioral medicine and the social sciences generally, including PROs, and is intended to provide a set of common tools that are useful to researchers and that enable them to exchange harmonized data–a critical communication function that will help researchers to cross the T1–T2 gap.

Though powerful, HIT alone cannot bulldoze the translation blocks and advance translational medicine; it, in fact, requires the perspective and involvement of experts in behavioral medicine and/or social sciences to guide its implementation, and thus to enable it to connect the T1, T2, and T3 dots. Healthcare is not a purely technical matter; rather, it is a human system, fundamentally dependent upon human understanding, acceptance, participation, and personal behavior. Change in these domains is a prerequisite for HIT to transform information flow, and thus to create a bridge from T1 through T3. Individual stakeholders in behavioral medicine need to be aligned behind the vision of translational medicine–through incentives to participation that are compelling to each. The RE-AIM (reach, efficacy/effectiveness, adoption, implementation, maintenance) framework is an example of a tool to facilitate the translation of research findings into practice, assisting researchers in behavioral medicine in designing studies so that their results are readily translated into practice.[19] RE-AIM addresses the T2–T3 block; similar approaches are needed to help bridge the T1–T2 hurdle.

Several requirements can be stipulated for a refined evidence development system that supports translational medicine. First, the system's infrastructure–primarily its data and HIT–needs to make sense to the human beings using the system (clinicians, staff, patients, administrators, clinical researchers, basic scientists). HIT must represent "value added" to the existing system from the perspective of each stakeholder. Second, interoperable data must be generated across domains and disciplines feeding data into the system, so that the system provides "grist for the mill" of inquiry; these data must be accessible and presented in a way that encourages their use. Third, to maintain confidence and hence participation, we must preserve the privacy, security, confidentiality, and sanctity of personal health information. And fourth, novel ways to understand new T1 information need to be developed; in addition to interpretation of traditional research results, these methods may include new approaches for visualization, decision support systems, Bayesian and other branched analyses, and *in silico* research. Current efforts, such as caBIG® and other data standards, focus on generating interoperable data; we also need to create human- and behaviorally focused systems that help people access, care about, question, understand, and use the data. Experts in behavioral medicine, together with colleagues from disciplines such as implementation and dissemination research and decision science, can lend insight into how best to promote adoption of new translational medicine approaches.

ROLE OF BEHAVIORAL MEDICINE IN TRANSLATIONAL HEALTHCARE REFORM

A critical next step in realizing the promise of translational medicine is to reorganize medicine at the point of care. Rapid learning healthcare, a vision first proposed by Etheredge[20] and subsequently explored by the Institute of Medicine,[21] describes a new model of the care environment that employs available data and linked datasets to support both research and clinical care; its methods help clinicians understand the data and routinely apply it as they tailor care for each individual patient.[5] Rapid learning is, in essence, the structural and functional manifestation of translational medicine. If implemented as envisioned, a rapid learning model will overcome the translation blocks at each level–T1/T2 and T2/T3–by continuously (a) feeding new knowledge from each sphere of inquiry into sub-

sequent level(s) and (b) returning results of implementation to the preceding level(s) to prompt further inquiry.[16] At this juncture, the development of well-functioning communication pathways and of methods for supporting behavior change are critical to achievement of the rapid learning vision.

Behavioral medicine is wisely preparing itself for participation in the data-driven framework that will underlie rapid learning healthcare, as evidenced by the recent formation of a Health Informatics work group within the Society for Behavioral Medicine. The addition of behavioral medicine research to the T1 phase of translational research, the ongoing activity of behavioral medicine researchers at the T2 phase, and the application of behavioral medicine insights to the process of T1–T3 bridging will undoubtedly help make translational medicine a reality. Thought leaders in behavioral medicine would be wise to (1) promote the conduct of, publish, and disseminate basic science studies with relevance to the practice of behavioral medicine; these will most likely appear across the biomedical literature, rather than solely in discipline-specific journals, but need to be brought to the attention of those within the field of behavioral medicine; (2) collaborate across disciplines to coordinate behavioral medicine interventions with the patient's full spectrum of care; these collegial efforts will likely be advanced by the availability of universal electronic health records that comprehensively capture patients' healthcare and outcomes; (3) develop data systems for behavioral medicine research and clinical care that are interoperable with those of Medicine's basic and clinical sciences, including genomics; (4) develop, promote, and contribute to the national discussion about PROs and electronic patient-reported data, including its central role in comparative effectiveness research; (5) develop evaluative systems to monitor the extent to which evidence-based behavioral interventions are translated into practice, and to encourage study methods designed to facilitate translation; and (6) join the national dialogue on rapid learning healthcare, to ensure that behavioral medicine, its purposes and unique perspective, are integrally incorporated into this emerging new paradigm for healthcare reform.

Implementation of rapid learning healthcare depends not only upon data, HIT, and research infrastructure but also on information flow, communication, individual behavior, and organizational culture. Among the disciplines, behavioral medicine is ideally prepared to inform healthcare redesign in these respects, thereby supporting translational medicine broadly while advancing translational behavioral medicine more specifically.

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