Clinical and Translational Science: From Bench-Bedside to Global Village

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Introduction

Clinical and translational science has emerged as the cornerstone of biomedicine poised to actualize, during this decade, the healthcare value of national investments that fuel the ongoing revolution in modern science.[1] This integrative field, spanning across medical specialties, represents the pinnacle of the new biology, enabling advances in technology platforms to offer unprecedented opportunities in disease prediction, prevention, and even cure beyond the reach of traditional healthcare solutions.[2] Clinical and translational science is indeed primed to identify the most effective science-based healthcare decision systems that align clinical care with individual patient and community needs.[3]

The emergence of clinical and translational science, as the key paradigm to optimize medical as well as surgical products and services emanating from the intersection of discovery science and healthcare delivery, highlights the requirement for a unifying framework that bridges across the continuum of knowledge creation and deployment, converting discoveries to human application, advancing that information into clinical practice, disseminating best clinical practices into communities, and ultimately modifying the behavior of populations to improve global wellness.[4] Fundamental alignment of basic and clinical sciences; development of newer knowledge domains in health services research, comparative effectiveness, and dissemination science; creation of investigational teams bridging communities of patients and practice; and the reciprocal bidirectional flow of information and inquiry across those communities shaping and prioritizing knowledge domains are central to the broad and timely implementation of clinical and translational science, ensuring global availability of the best patient-centered algorithms for clinical healthcare delivery.[2,4,5]

Innovation Driving Clinical and Translational Science

Modern healthcare delivery is undergoing forced evolution, driven by the explosion of new information at the intersection of discovery, development, application, and dissemination sciences.[6,7] Discovery has been exponentially advanced by emerging enabling technology platforms including the "omics" revolution, targeted therapies, integrative systems biology, and the informational sciences, including biological and medical informatics, that provide previously unimaginable insights into molecular pathophysiology.[8,9] Integration of these potentiating platforms defines the critical path for best resolving the mechanistic processes underlying fundamental physiological programs that are corrupted in disease.[10] Identification of these processes offers, in turn, novel perspectives resulting in personalized diagnostics and therapeutics, molecular markers of disease prognosis, and clinical predictors of therapeutic responses, guiding the development of optimum management algorithms for patients and communities.[1,2,5,6] Continued deconstruction of physiological networks and deciphering molecular circuits central to disease pathobiology provide the foundation to pinpoint ideal pharmacological targets, and develop therapeutic devices or diagnostic approaches that offer rational, patient-centered healthcare solutions.

While the pace of fundamental discovery is accelerating, extension of the benefits of these innovations to patients and populations dramatically lags.[4,11] Hundreds of genetic variants for disease have been identified, yet few human genomic discoveries have been translated into evidence-based public health practices.[12] Further, it is estimated that only 5% of highly promising basic science discoveries are ultimately licensed for clinical use, and only 1% are actually used for the licensed indication.[12,13] These examples underscore apparent limitations and ultimately failures in translating knowledge generated by the new biology, impeding applications for disease control and prevention in patients and populations.[1,2,4–7,11]

The Continuum of Clinical and Translational Science

Advancing the benefits of fundamental discoveries in the laboratory to patients and populations has become the domain of clinical and translational science. As the concepts of clinical and translational science evolved, it became apparent that *translation* conveyed different meanings to different communities of practice.[14] For laboratory-based investigators, translation encompassed the steps that moved molecular discoveries from the bench to the bedside, to create new clinical knowledge.[12,15] In contrast, agencies and organizations focused on public health viewed translation as the processes generating the requisite evidence base to deploy new clinical knowledge beyond individual patients and academic healthcare organizations into community practices and populations.[12] These conceptual differences highlight the continuum of knowledge, processes, skills, and practice reflected by clinical and translational science, whose amalgamation and integration is essential to the successful application of new scientific discoveries to the creation of community wellness.

In that context, this continuum has been divided into discreet steps, revealed by gaps in the translational process and encompassing essential knowledge domains and skill sets (*Figure 1*). In T1 translation, new discoveries in the laboratory resulting from the revolution in the new biology are first translated to human application.[14] This initial step in the continuum recognizes the essential nature of advancing technology from the laboratory into humans and the difficulty of that transition, which has been labeled the *valley of death*, reflecting the challenges of resourcing to support early translation.[16] It encompasses unique skill sets that bridge the laboratory and clinic, including divergent domain-specific lexicons, practices,

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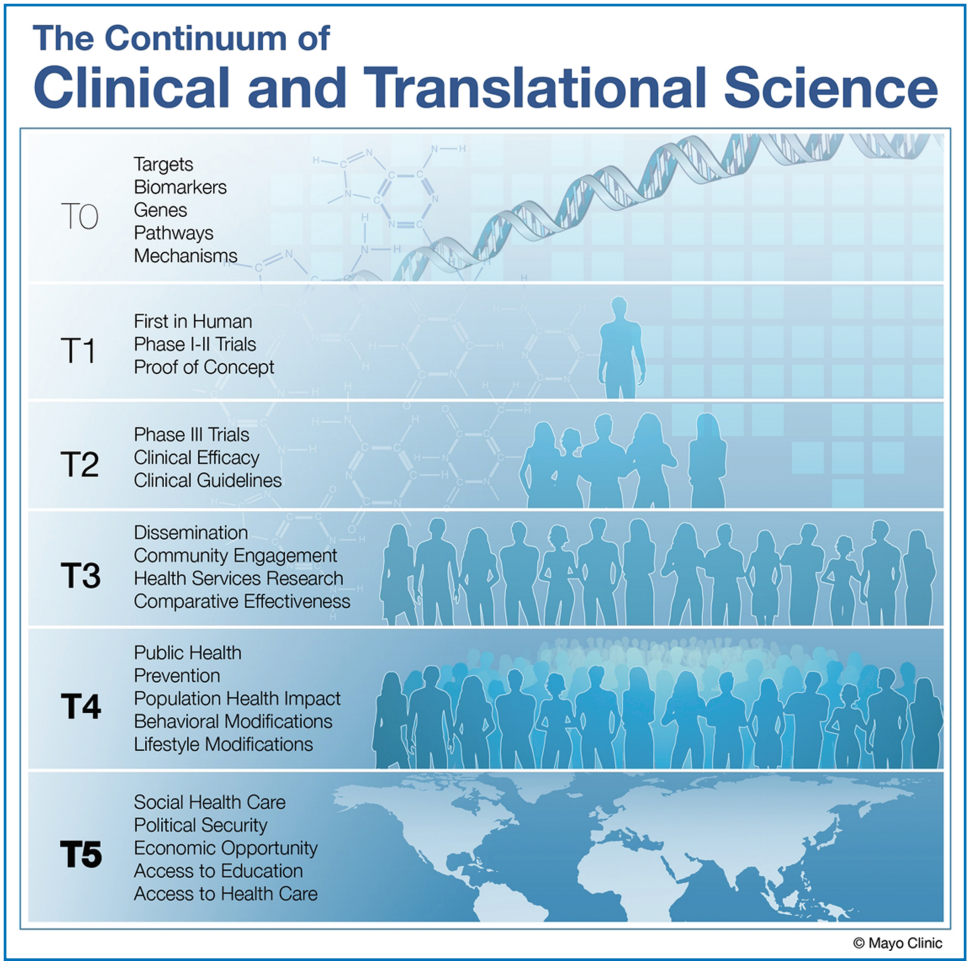

Figure 1. The continuum of clinical and translational research. Canonical steps include T1–T4 translation. This continuum has been expanded to include earlier (T0) and later (T5) steps that are essential to optimize the efficiency and global impact of the clinical and translational enterprise.

and structures. It incorporates the well-established processes surrounding early-phase clinical development encompassing phase I and II clinical trials.

In T2 translation, candidate health applications emanating from the prior step progress through clinical development to engender the evidence base for integration into practice guidelines. These paradigms also span the laboratory-clinical divide,[16] reflected in the essential integration of key molecular endpoints that stratify risk and reveal therapeutic responsiveness of patients and populations, forming the critical path to developing the most comprehensive evidence base for maximized safety and efficacy of new therapies. This step bridges the well-known skill sets supporting phase III clinical development of therapeutics and the analyses of resulting data sets to establish practice guidelines.

In T3 translation, new knowledge surrounding the clinical application of discoveries revealed in T1 and T2 must be disseminated into community practices.[17] This critical step, and the associated gap and essential unmet clinical need, was only revealed once it was recognized that breakthrough discoveries failed to translate into community practice. For example, the efficacy of statins in lowering circulating cholesterol levels (T1) and improving the evolution of coronary artery disease and survival (T2) are well established. Yet, a substantial number of patients with elevated cholesterol are not treated with statin therapy in the community-at-large.[18] Similarly, the benefits of beta-blocker therapy in improving recovery from acute myocardial infarction is well established (T2), yet only approximately 60% of eligible patients are treated with this therapy.[19] Moreover, the benefits of aspirin in treating unstable angina and preventing myocardial infarction are recognized (T2), but fewer than 40% of eligible patients are treated appropriately.[19] These examples underscore the gap in translating new evidence-based clinical knowledge into community-based patient-centered practice. This gap in dissemination represents one primary limitation restricting the application of new discoveries to global populations. While T1 and T2 translation involve well-established skill sets and processes, T3 challenges the enterprise to innovate concepts and methods to disseminate new clinical knowledge for integration into practice, including health services research, community-based participatory research, and comparative effectiveness research.[20,21]

Beyond incorporating evidence-based knowledge into clinical practice, T4 translation seeks to advance scientific knowledge beyond algorithms of palliation treating established disease, to paradigms of disease prevention through life-style and behavioral alterations in communities and populations. It is at this stage of translation that the enterprise undergoes a strategic evolution from the medical model of clinical practice (intervention), to the public health model of disease management (prevention). Here, the public health model focuses on information and education programs that eliminate deleterious behaviors at the community and population levels that produce disease susceptibility, for example obesity and tobacco use.[22] In essence, T4 research seeks to move health practices established in T3 into population health impact, associated with improved disease prevention and reduced costs for medical care.[12,14] Skill sets central to T4 translation include the well-established paradigms for public health and population research and emerging areas including outcomes research.

Clinical and Translational Science and Team Investigation

The breadth and depth along the continuum of clinical and translational science mandates that no specialists has the complete knowledge base to execute across the entire spectrum of expertise to bring new discoveries from the laboratory to populations. Rather, this translation is best accomplished by teams

of investigators across communities of practice with knowledge domains that are complementary and synergistic.[14] These teams will, by necessity, comprise members who are scientists, clinician investigators, and practitioners. Further, they will benefit from experts in statistics, informatics, regulatory knowledge, ethics, community engagement, and health services research. They will be facilitated by electronic structures that efficiently link patients, providers, databases, and operational resources into integrated clinical and research data marts for efficient and streamlined deployment to address priority translational questions with the potential to advance the health of populations. Moreover, the full spectrum of translation, from discovery to disease prevention in populations, will best be served by integrating representatives from the community into investigational teams. Community integration establishes a basis for bidirectionality in translational research in which neighborhood representatives shape the research agenda and inform the prioritization of questions, individualizing medical research that is aligned with specific community needs.[20] This team approach to scientific inquiry represents a paradigm shift, particularly in the context of academic medicine, which has historically rewarded individual performance of investigators. In this new paradigm, the revolution in clinical and translational science associated with its focus on team science must entrain a coordinated evolution in the metrics employed to evaluate members of the team for appointments and promotions in academic medical centers. Evaluative criteria must include measures that go beyond traditional metrics of individual success, like senior direction on publications and grants. Indeed, they must incorporate measures of team participation and success, including nucleating and participating in multi-investigator teams to achieve research objectives, developing enterprise-wide programmatic resources, contributing to achieving investigational team objectives, executing complex multi-investigator projects, and disseminating research knowledge into the community.

Beyond the Boundaries of Canonical Translation

The current model for clinical and translational science encompasses a continuum divided into discreet steps (T1–T4) focused on specific knowledge domains and algorithms required to advance laboratory innovation effectively from its introduction into humans through application to disease prevention in populations. This model encapsulates the critical components that leverage essential scientific discoveries for the benefit of the greatest number of patients. Moreover, it represents a visionary departure from earlier models and a revolutionary step in concept and process that will maximize societal investments in research for the greatest good. Although much has been achieved, the enterprise, and our patients and communities, will benefit most from continuous evolution and enhancement of the paradigm.

The current model may benefit by expanding to incorporate communities of practice that do not currently live under the umbrella of clinical and translational science (*Figure 1*). While the current paradigm initiates at T1 translation, when discoveries are first advanced into human use, it may be particularly advantageous to incorporate a T0 step in the translational continuum. This recognizes the essential contribution of laboratory-based investigators at the origin of the enterprise. Further, it considers the key importance of laboratory-based investigators, and their concepts and skills, as members of the investigative team iteratively shaping and enhancing the technologies that progress through the stages of T1–T4 research. Moreover, it amplifies their central role in reverse translation, in which patient- and community-based observations are reflected back to the laboratory to generate new hypothesis revealing molecular processes underlying pathophysiology and novel approaches focused on diagnosis and treatment.

At the other end of the continuum, T4 research explores the translation of novel technologies to alter the behavior of entire communities and populations to effect disease prevention. It encompasses the concepts, processes, and practices that underpin community and population health sciences. However, the impact of these paradigms must extend beyond individual communities, to translate the maximum benefits of scientific and medical innovation to global populations worldwide. In that context, an envisioned T5 translation step goes beyond the public health model of care, extending to the social health model[22] that focuses on improving the wellness of populations by reforming suboptimal social structures. Indeed, fundamental societal issues that eclipse limitations in healthcare delivery restrict the distribution of the products of scientific innovation to populations in greatest need. Poverty, infectious diseases, social imbalance, political instability, warfare, man-made and natural disasters, sanitation, and hunger and malnutrition conspire to limit the translation of the new biology into algorithms for disease prevention to the most vulnerable global populations. Here, T5 translational teams must incorporate investigators with knowledge domains that extend beyond the laboratory and clinic, engaging political and social scientists, engineers, economists, anthropologists, and population biologists to define the critical path that maximizes investments in research for the good of the global village. The full potential of the revolution in clinical and translational science will only be realized in the context of an associated revolution in social and political science that for all people creates secure environments, provides global access to safe and meaningful employment, economically enables the pursuit of healthy behaviors, and provides equal access to education and healthcare.[22]

Conclusion

The emerging revolution in clinical and translational science is closing the gap between the explosive growth in scientific discovery and technology and the lagging implementation of this new knowledge to evolve patient-centered algorithms that improve the health of communities and populations. Sustained engagement of teams of translational investigators that bridge communities of patients and practice will enable these objectives, shape local and national research agendas, and provide bidirectionality of focus and insights that feeds reverse translation driving and amplifying innovation in the evolution of healthcare solutions. At the enterprise level, continuous process evaluation will provide enhancements that, ultimately, maximize the benefits of innovation for the global village.

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