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Clinical Translational Science 2020: Disruptive Innovation Redefines the Discovery-Application Enterprise

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Vaccines, analgesia and antibiotics embody some of the most enduring therapeutic breakthroughs that have transformed medicine. Building on such fine paradigms of biomedical innovation, the evolution of technologies has increasingly sparked spectacular advances across the continuum of wellness and disease spanning medical and surgical specialties. Discovery science - fueled by government and private sector resources - has systematically instituted the principles of modern healthcare delivery ensuring that medical practice is based on up-to-date scientific evidence. The harmony between science, technology, and resources has culminated in a golden age of discovery and translation, eradicating infections, curing cancers, and palliating endocrine and metabolic diseases. Indeed, proven therapeutic and preventive approaches have progressively moved into everyday practice.

The success of the science-medicine union has spurred public and private sector investments, further fueling the engine of discovery and enabling technology. This integration produced 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. Modern science offers outstanding opportunities to probe the innermost workings of the human body, and to understand how events at the subcellular and molecular levels influence the functioning and integrity of the individual as a whole.[1,2] Remarkable progress is being made in understanding the molecular, genetic, and cellular origins of disease, and opportunities now exist to uncover practical uses for this new knowledge, particularly in the realm of personalized medicine.[3,4]

Unexpectedly, however, acceleration in enabling technologies and the resultant insights into basic pathophysiological mechanisms has outstripped the capacity of current scientific and clinical structures to efficiently manage their

translation into new paradigms to improve the health and quality of life of individuals, communities and populations.[5] In that context, federally-funded research programs have produced hundreds, if not thousands, of new disease-related molecular targets that represent potential diagnostic and therapeutic targets for tailored disease management.[6] Unfortunately, their applications remain only a distant promise, reflecting a limited capacity in structures, resources and the specialized workforces required for their translations into new healthcare paradigms. Compounding these challenges is the reality that 95% of promising therapies brought into clinical development in the private sector ultimately fail because of limitations in efficacy or unacceptable toxicities. Further research is needed to identify, measure, and validate targets and pathways that have been detected in basic studies, and then to develop new clinical applications and rigorously evaluate their effectiveness and safety. Indeed, further understanding of the translation process itself must occur to expedite and expand the adoption of biomedical advances into clinical practice and individual health behaviors.

Recognition of the need to rebalance the equation, and bring translation into register with the power, progress, and pace of discovery science and associated enabling technologies is reflected in the recent enactment of the ***Cures Acceleration Network*** (***CAN***), legislation that seeks to bridge the chasm between basic scientific discoveries and new health treatments.[7] Part of the ***Patient Protection and Affordable Care Act***, ***CAN*** mandates that the ***National Institutes of Health*** (***NIH***) advance the development of highly needed cures by reducing barriers between research discovery and translation. The ***CAN*** provisions grant NIH flexibility to carry out therapeutic development projects and underscore the expectations of Congress and the American public that the NIH

will have a catalytic role in moving scientific discovery along the continuum that ultimately creates advances in human health.

The leadership of the NIH, embracing this mandate to accelerate translation inherent in ***CAN***, charged its **Scientific Management Review Board** with defining a path forward to rebalance the equation. Those deliberations resulted in the near-unanimous suggestion by the SMRB to constitute a new ***National Center for Advancing Translational Sciences***. The charge of this new Center will include:

- Advancing novel molecular discoveries across the translational *Valley of Death* into promising technologies with a more favorable risk-benefit ratio that will appeal to the private sector for further development into novel modalities that change patient care.[8]
- Consolidating the considerable resources already existing in NIH programs and cores that can facilitate the development of molecular science across the translational continuum. These will include the ***Molecular Libraries Program (MLP)*** which offers access to high throughput screening capabilities and libraries of compounds useful for research and as therapeutics. For example, the ***Chemical Genomics Center***, part of MLP, provides a robotic, high throughput screening system and a library of >350,000 small molecules to interrogate fundamental cellular mechanisms. The ***Therapeutics for Rare and Neglected Diseases*** program provides resources for preclinical drug development centered on rare disorders with limited commercial interest. Finally, ***Clinical and Translational Science Awards*** offer a linked nationwide network of institutions providing the infrastructure and workforce to advance the development of therapeutic through patient and community-based studies.[9]

- Nucleating interactions between public and private sectors that maximize the utility of technology resources, distribute risk to lower barriers to commercialize diagnostics and therapeutics, and orchestrate the appropriate organizational transitions (e.g., academic-government, government-pharmaceutical company) along the developmental continuum to optimize translational efficiencies.
- Leading the development of the next generation of clinical and translational investigators. Rebalancing the equation to equilibrate discovery and translational science will necessitate developing a cadre of investigators fluent in the lexicons of the laboratory and clinic.[10] They must understand the widely different paradigms underlying laboratory-based experimentation and clinical diagnosis and therapy, enabling integration of these structures in which critical unmet gaps in patient care drive the evolution of science. Moreover, they will require a transformation in professional culture that incents science practiced as part of multidisciplinary teams, rather than the current silos which reward individual contributions.[11,12]

The creation of the ***National Center for Advancing Translational Sciences*** evidences a broad contemporary vision of the investigational continuum from molecules, to patients and populations. It anticipates the evolution of translation from a science focused on new therapeutic modalities for disease palliation, to the assessment of risk and the science of wellness and disease prevention.[13,14] The Center will leverage existing and emerging resources to maximize productivity in the form of better health and quality of life. Moreover, it brings divergent stakeholders to the table, across traditionally insular communities of practice, and invests them in a public-private partnership and an envisioned

future in which science is the engine driving translation and clinical development to amplify efficiencies and reduce risks associated with improving patient care.

While this bold step marks a sea change in the way the science of translation is conducted in the United States, the leaders of the NIH continue their forward-looking vision, anticipating challenges that could attenuate the impact of the new center. Those considerations include:

- The science of translation will maximally benefit from the broadest participation of the widest communities of practice. Teams of clinical and translational investigators will cut across disciplines, guilds, and cultures where individual knowledge and skill sets are valued for their potentiation of the greater goals. Teams will include physicians, scientists, engineers, pharmacists, therapists and others contributing to the generation of new insights, their operationalization into new modalities of healthcare, and their dissemination across populations, communities, and the global landscape. Conversely, the science of translation cannot be the purview of any specific clinical and scientific discipline. Indeed, restricting the science of translation to ownership by a single discipline jeopardizes the success of the entire enterprise.
- The science of drug development traditionally has been the focus of the biopharmaceutical industry, which has been the primary source of new diagnostic and therapeutic modalities for managing patients.[15,16] Even in the face of their considerable innovation and expertise, the success rate for new drugs is less then 5%, and success is associated with a price tag topping $1 billion. One goal of the new center will to accelerate the translation of the hundreds of new targets into promising therapeutic compounds in early clinical trials. The goal is to

"de-risk" these targets and agents, to make them more attractive to biopharmaceutical partners, who will advance them into late stage trials in anticipation of regulatory approval and marketing. One central consideration in this model is how the new center and its partners will "beat the odds" inherent in drug development. Indeed, while the pharmaceutical industry has the deepest expertise in this field, invests as much, if not more, capital resources into research as does the NIH, and is powerfully motivated by profit and investor satisfaction for success, the success rate remains very low. The architects of the new center are considering novel models, paradigms, and collaborations that increase the success rate required to accommodate enhanced throughput represented by translation of the backlog of new markers and targets.

- A correlative consideration is the measurement of success in this new endeavor, a core consideration for the new center. While the goals for enhancing translational science are clear, the methods to measure enhancement are less straightforward. Logically, the gold standard would be the number of new therapeutic agents being translated into patient care algorithms. However, this is particularly complicated by the very long timelines inherent in the drug development process. Indeed, it can take up to 15-20 years for a new entity to move from discovery into late stage clinical trials and regulatory submission. More proximal surrogate metrics, for example numbers of new therapeutics advanced into clinical trials, suggest activity in the system but do not address whether this activity is optimally productive, or is even commensurate with the track record of the pharmaceutical industry, acknowledged leaders in this field. Thus, it will not be sufficient to show

metrics of utility or traditional markers of interim performance. Rather, the challenge will be to identify markers of performance that correlate closely with ultimate success. This is not a trivial task and the biopharmaceutical industry has been chasing this ideal, without apparent success.

- New center activities are decidedly focused on the earliest stages of the translational continuum. Indeed, the focus for this organization is on discovery, target validation, preclinical animal models, and early stage clinical trials, including T1 translation in which safety and tolerability are established, and T2 translation, in which efficacy is first explored.[1,17] However, equally important are T3 and T4 translation. In T3 translation, new knowledge surrounding the clinical application of discoveries revealed in T1 and T2 must be disseminated into community practices.[1,17] This critical step, and the associated gap and essential unmet clinical need, was only revealed once it was recognized that breakthrough discoveries failed to optimally translate into community 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. 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 lifestyle and behavioral alterations in

communities and populations. It is at this stage of translation that the enterprise undergoes a strategic evolution from a medical model of clinical practice (intervention), to a 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.[18] 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. Skill sets central to T4 translation include the well-established paradigms for public health and population research and emerging areas including outcomes research. Together, these considerations highlight the essential nature of the entire T1-T4 translational continuum to accelerate discovery into new paradigms for the management of patients and communities.

Formation of the new ***National Center for Advancing Translational Sciences*** represents a critical exponential step in the evolution of the science of translation.[19,20] It amalgamates national resources and programs whose centralization and integration will facilitate discovery and early development. It will nucleate public-private partnerships that hold the promise of accelerating new insights in molecular mechanisms underlying pathophysiology into novel diagnostics and therapeutics. Moreover, it will create a career path in clinical and translational science and medicine that will prepare the next generation of skilled investigators invested the culture of team science. This great promise and potential can only be realized in the context of solving the great challenges that work to minimize the impact of translation on the healthcare of populations:

inclusion of broad communities of practice, failure rates in drug development, metrics of performance, and covering the translational medicine continuum.

The new ***National Center*** can be viewed as one bold example of visionary ***disruptive innovation***, in which traditional structures are reconfigured in unanticipated ways to achieve exponential evolution in a field. In that context, the new ***Center*** provides an unprecedented opportunity to recast science and medicine in response to the evolving needs of our patients while sustaining affordable healthcare. Here, translational medicine represents the critical next evolutionary step in realizing the clinical value of the new biology in order to drive discovery into personalized health care solutions. By offering paradigms to predict, prevent, treat and cure disease, translational medicine will be poised to enable application of transformative diagnostics, prognostics and therapies that promote longitudinal wellness and advance health care for individuals and populations. The ultimate mandate for the new ***National Center*** is to secure early adoption of the integration of discovery innovation into clinical practice in response to patients and society who seek new products and services to address unmet needs.

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