POLICY

Biology, biography, and the translational gap

Pamela Summers-Trio[1], Allison Hayes-Conroy[2], Burton Singer[3], Ralph I. Horwitz[1]*

Medicine-based evidence integrates a patient's biology and biography to improve individual medical care and to help eliminate the translational gap between research and the clinic.

The characterization of the *BRCA1* gene in 1994 and other genes associated with cancer suggested immediate applications in the early detection and treatment of cancers. Yet, almost a decade later, the National Institutes of Health's "Roadmap for Medical Research" highlighted critical scientific gaps that were blocking or delaying the translation of discoveries in the life sciences into improvements in medical care (*1*). The salience of this so-called translational gap was secured by a 2008 article suggesting that the gap between biomedical research and improvements in medical care had become an abyss in which breakthrough discoveries went to die, an abyss called the Valley of Death (Fig. 1) (*2*).

Understanding the source of the translational gap requires appreciating the role of randomized controlled trials. Randomized controlled trials have been useful for establishing the benefits of therapies or devices because they are considered the method most likely to generate results that are valid. Nevertheless, numerous problems have been noted. One problem central to the translational gap is referred to by Deaton and Cartwright (*3*) as the transportation problem. They argue that if the average treatment effect of a randomized controlled trial is, by chance, close to truth, then the truth referred to is for the trial sample alone. There is no guarantee that the average treatment effect of a randomized controlled trial would apply to other patients, who were not eligible for the trial or who were otherwise excluded from the trial. How does context created by an individual's biology and biography (life experience) account for the transportation problem and lead to the translational gap?

DOES BIOGRAPHY AUGMENT BIOLOGICAL AND CLINICAL DATA?

Consider this remarkable and forgotten story. In 1975, Lee Robins studied heroin addiction among Vietnam veterans returning to the United States. She found that approximately 20% of a general sample of soldiers became addicted to heroin while in Vietnam. She also reported that half of the soldiers who used narcotics at any time in Vietnam became addicted, but only 7% remained addicted after they reintegrated into their communities. Importantly, 84% of the veterans reported access to opioids at home, excluding accessibility as an explanation for the very high remission rates (*4*). Robins suggested that the high recovery rates (previously reported to be only 10 to 30%) were due, in part, to the specificity of the context supporting addiction. Soldiers became addicted under the stress of war, far from home and from the personal relationships and social structures that gave meaning to their lives. Robins wrote, "Society has overemphasized the importance of treatment for heroin per se, failing to pay attention to the multiple other problems that heroin addicts have…they have all kinds of social adjustment difficulties that are not entirely attributable to heroin. It is a small wonder that our treatment results have not been more impressive when they have focused so narrowly on one part of the problem" (*4*).

Robins highlighted the role of social, behavioral, and environmental context on the response to treatment, even for a problem as intransigent as heroin addiction. Methadone treatment to stop heroin usage has frequently been found necessary but not sufficient for rehabilitation of chronic heroin addicts. This has led to the incorporation of psychiatric and social support services in contemporary programs for opiate addiction (*5*). Treatment regimens are, of necessity, tailored to the individual patient. Robins's demonstration of the therapeutic value of a supportive social environment does not stand alone and is not limited to studies of addiction. In the past two decades, there has been an increase in understanding how varied aspects of biography—including one's individual social context and support—affect health states, disease risk, and treatment outcomes. Such work has varied in form and focus, and some of it has been driven by concerns over health disparities. For example, researchers now ask how experiences of discrimination, racism, and gender bias outside clinical settings produce diverse biological outcomes relevant to specific diseases or conditions and their treatments (*6*). Racism experienced by the individual patient has received particular attention for diverse effects on a wide variety of biological measures, including birth outcomes, premature biological aging, and disease risk among others (*7*).

Yet if biography, with all of its structural and cultural complexity, is a "missing link," then how do we use it to bridge the translational gap? Omics research gets us part of the way. For example, a 2008 study illustrated the interdependence of biology and culture among the genetically homogeneous Berber people of Morocco. Looking at individuals coming from urban versus rural communities, researchers found that up to one-third of the transcriptome was associated with different environments (diet, exposure to microbial organisms, and environmental stresses among other influences) (*8*). Meanwhile, epigenomic research on psychosocial stress also sheds light on the biological effects of social context on multiple generations. Such omics studies, however, cannot fully address the collusive effects of multiple biographical-biological factors over time and in different locations. Rich biographical narratives—recorded in individual patient

[1]Lewis Katz School of Medicine, Temple University, Philadelphia, PA 19140, USA. [2]Geography and Urban Studies, Temple University, Philadelphia, PA 19140, USA. [3]Emerging Pathogens Institute, University of Florida, Gainesville, FL 32610, USA.
*Corresponding author. Email: ralph.horwitz@temple.edu

Fig. 1. Circumnavigating the Valley of Death. The image shows the Zabriskie Point in Death Valley National Park, California. Just as gold prospectors saw their hopes for discovery die in the heat of the Death Valley desert, so too do many potential new treatments fail in the translation from discovery to clinical application. There are myriad reasons why this translational gap, the so-called Valley of Death, exists, but sole reliance on biology that ignores biography contributes to this persistent challenge.

profiles instead of assumed through zip code or income level—complement recorded information on disease severity, frequency, and types of comorbidity, cotherapies, and pace of disease progression. The combination is critical for clinical decision-making and facilitation of the recovery process for the individual patient.

BIOSOCIAL CONTEXT BRIDGES THE TRANSLATIONAL GAP

A well-known example of the importance of biography comes from Vincent Felitti, who directed the Permanente Medical Group's weight loss program. When Felitti began the program in 1982, it was believed that morbidly obese patients were not capable of achieving substantial weight loss. Felitti's program proved otherwise, because some patients lost as much as 300 pounds. However, a number of these successful patients ended up dropping out and regaining much of the weight. To understand why, Felitti interviewed 286 of the dropouts. A misspoken prompt offered a clue; when asking about a patient's age at first sexual intercourse, he mistakenly asked how much the patient weighed. Her response, 40 pounds, shocked him, and she subsequently described being raped as a young child (*9*). Felitti's discovery of sexual, physical, and emotional abuse as the antecedent cause for many of the patients to drop out of the weight loss program led to the ~10,000-participant study of adverse childhood experiences. This study confirmed the impact of early childhood adverse events on health and disease among adults.

We now know that life experience has profound implications for biological well-being, but just as Felitti's accidental discovery would never have happened without an intent to dig deeper into individual biography, biographical narratives cannot be replaced by standardized forms. Interdisciplinary methods that seek to understand biology and biography as they are unified in the body may help to overcome one cause of the translational gap.

APPLYING MEDICINE-BASED EVIDENCE

To accomplish this goal, methodological alternatives are needed to complement the traditional randomized controlled trial and the top-down approach that governs the analysis. The translational gaps can be bridged by careful consideration of the context in which treatment occurs. This involves using an evidence generation process that starts with profiling of a patient and then the assembly of comparison profiles from a large library through the clinician imposing approximate match criteria. We have previously referred to this alternative methodology as medicine-based evidence to distinguish the approach from the now standard evidence-based medicine that relies on average results from randomized controlled trials to guide clinical decision-making. Such a library would contain profiles of patients enrolled in a randomized controlled trial, patients who did not satisfy requirements for admission to a randomized controlled trial, patients enrolled in observational studies, and archived profiles from multiple medical centers. The variation in patient experience is of basic importance for identifying approximate matches when comorbid conditions, at least one of which is rare in the general population, and cotherapies are features of the patient at hand.

Medicine-based evidence is a new approach that is tuned to the fine-grained detail of the individual patient and establishes comparison populations using nuanced matching strategies to identify cases closely approximating the patient in question. Conceptual innovation derives from the integration of multimodal, multiscale, and multi–time point information from biology while using biography to provide essential information that is not part of the current canon of high-technology medicine.

Medicine-based evidence profiles the biological, clinical, and biographical features of the individual patient. Using a bottom-up approach, it is natural to seek guidance about management of the given patient from archived longitudinal profiles of closely comparable patient records that are approximate matches. This matching process starts with an "n of 1" and identifies an "n of many" that represents the clinically relevant comparison group for the patient in question. This process sharply contrasts with contemporary practice where subgroups selected from randomized controlled trials are used to approximate an individual patient. The difficulty with starting from an "n of many" and stratifying toward an "n of 1" is that the heterogeneity at the population level can lead to a situation where there are very few individuals who could be regarded as approximate matches to the patient at hand. This is precisely where evidence from randomized controlled trials presents a nearly insurmountable

translational gap between statements about what happens on average in a large population and the need for information focused on the idiosyncrasies of a particular patient. Only by expanding the scope of included patients and integrating biographical data about patients can data from randomized controlled trials begin to mitigate the translational gap.

One limitation of our proposed medicine-based evidence approach could be that its implementation may be hard to accomplish given that medical records are not standardized or interoperable and that many of the prescribed features of biography are not currently captured. Although we acknowledge the salience of this argument, it is important to note that medicine-based evidence can be implemented now. Randomized controlled trials typically collect social and behavioral data using well-validated indexes of social functioning such as the SF-36 survey of patient outcomes or the PROMIS (patient-reported outcomes measurement information system) tool. Using the data already being collected to create biographical profiles for each trial participant would be an important first step toward a more complete medicine-based evidence analysis of randomized controlled trials.

The more fundamental part of medicine-based evidence is unrelated to randomized controlled trials. It aims to use data from diverse sources (including randomized controlled trials, observational studies, disease registries, and electronic medical records) to create integrated biological and biographical profiles to guide the care of individual patients longitudinally over time when clinical decisions are revisited as the patient's illness unfolds. Tightly integrated health care systems can lead the way in making medicine-based evidence the standard for evidence generation that achieves the long-held hope for precision medicine.

The process of moving from an "n of 1" to a defensible comparison population "n of many" was initially exhibited in 1972 in the context of lung cancer. The concept was again highlighted in papers written a few years later by G. Engel (*10*). He examined how the biomedical model alone without the inclusion of careful interviewing and consideration of a patient's additional psychosocial factors is insufficient for understanding a patient's disease using the example of diabetes. Remarkably, these pioneering examples have, until recently (*10*), not seen any further development. Nevertheless, even these examples lack the richness of social environmental evidence that we have indicated to be a necessary ingredient for management of the individual patient. Such information has been used by clinicians since the dawn of medical practice, but it has now mostly been pushed into the background by the profound emphasis on biology, presented without the many links to biographical features of the patient. We are now ready to provide integrated profiling that jointly considers biological, clinical, and social environmental information to represent the patient. Such integrated profiles will be the basis for identifying a comparison population in a library of longitudinal patient profiles that can guide the personalized care of the individual patient. The emphasis on biography is a necessary development if we are to reduce the persistent effects of the translational gap that lies between biomedical advances and clinical application.

REFERENCES

1. E. Zerhouni, Medicine. The NIH roadmap. *Science* **302**, 63–72 (2003).
2. D. Butler, Translational research: Crossing the valley of death. *Nature* **453**, 840–842 (2008).
3. A. Deaton, N. Cartwright, Understanding and misunderstanding randomized control trials. *Soc. Sci. Med.* **17**, 30735–30739 (2017).
4. L. N. Robins, J. E. Helzer, D. H. Davis, Narcotic use in Southeast Asia and afterward. *Arch. Gen. Psychiatry* **32**, 955–961 (1975).
5. V. P. Dole, M. E. Nyswander, Heroin addiction—A metabolic disease. *Arch. Intern. Med.* **120**, 19–24 (1967).
6. C. C. Gravlee, How race becomes biology: Embodiment of social inequality. *Am. J. Phys. Anthropol.* **139**, 47–57 (2009).
7. J. M. Metzl, D. E. Roberts, Structural competency meets structural racism: Race, politics, and the structure of medical knowledge. *Virtual Mentor* **16**, 674–690 (2014).
8. Y. Idaghdour, W. Czika, K. V. Shianna, S. H. Lee, P. M. Visscher, H. C. Martin, K. Miclaus, S. J. Jadallah, D. B. Goldstein, R. D. Wolfinger, G. Gibson, Geographical genomics of human leukocyte gene expression variation in southern Morocco. *Nat. Genet.* **42**, 62–67 (2010).
9. V. J. Felitti, R. F. Anda, D. Nordenberg, D. F. Williamson, A. M. Spitz, V. Edwards, M. P. Koss, J. S. Marks, Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am. J. Prev. Med.* **14**, 245–258 (1998).
10. A. E. Wivel, K. Lapane, C. Kleoudis, B. H. Singer, R. I. Horwitz, Medicine based evidence for individualized decision making: Case study of systemic lupus erythematosus. *Am. J. Med.* **130**, 1290–1297.e6 (2017).

10.1126/scitranslmed.aat7027

Citation: P. Summers-Trio, A. Hayes-Conroy, B. Singer, R. I. Horwitz, Biology, biography, and the translational gap. *Sci. Transl. Med.* **11**, eaat7027 (2019).

Science Translational Medicine

Biology, biography, and the translational gap

Pamela Summers-Trio, Allison Hayes-Conroy, Burton Singer and Ralph I. Horwitz

Sci Transl Med **11**, eaat7027.
DOI: 10.1126/scitranslmed.aat7027