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Environmental Health Sciences in a Translational Research Framework: More Than Benches and Bedsides

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Environmental Health Sciences in a Translational Research Framework: More than Benches and Bedsides

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Background: Environmental health scientists may find it challenging to fit the structure of the questions addressed in their discipline into the prevailing paradigm for translational research.

Objective: We aim to frame the translational science paradigm to address the stages of scientific discovery, knowledge acquisition, policy development, and evaluation in a manner relevant to the environmental health sciences. Our intention is to characterize differences between environmental health sciences and clinical medicine, and to orient this effort towards public health goals.

Discussion: Translational research is usually understood to have evolved from the bench-to-bedside framework by which basic science transitions to clinical treatment. Although many health-related fields have incorporated the terminology and context of translational science, environmental health research has not always found a clear fit into this paradigm. We describe a translational research framework applicable to environmental health sciences that retains the basic structure that underlies the original bench-to-bedside paradigm. We propose that scientific discovery (T1) in environmental health research frequently occurs through epidemiological or clinical observations. This discovery often involves understanding the potential for human health effects of exposure to a given environmental chemical or chemicals. The practical applications of this discovery evolve through an understanding of exposure–response relationships (T2) and identification of potential interventions to reduce exposure and improve health (T3). These stages of translation require an interdisciplinary partnership between exposure sciences, exposure biology, toxicology, epidemiology, biostatistics, risk assessment, and clinical sciences. Implementation science then plays a crucial role in the development of environmental and public health practice and policy interventions (T4). Outcome evaluation (T5) often takes the form of accountability research, as environmental health scientists work to quantify the costs and benefits of these interventions.

Conclusion: We propose an easily visualized framework for translation of environmental health science knowledge–from discovery to public health practice–that reflects the crucial interactions between multiple disciplines in our field. https://doi.org/10.1289/EHP4067

Introduction

The notion of translational research is usually described through the bench-to-bedside application of basic research discovery to clinical treatment. This framework typically describes the "translation" of a scientific discovery to a result of improved patient (and population) health. For example, a laboratory bench researcher makes a basic discovery, such as a protein playing a key role in a disease process. Organisms with varying expression of that protein can be engineered, processes observed in disease model organisms with the protein added or blocked, and so forth, through to formulation of a drug that modifies protein expression and the testing of that drug—first in animal and then in human studies—through to clinical trials and finally to adoption in recommended clinical practice. Based on this canonical translation, medical researchers can describe the transition of a discovery at the bench to a meaningful improvement in human health. This transition is then one of the ways that the value of basic science is communicated to the general public (Collins et al. 2016).

Although the field of translational research still feels relatively new, the groundwork for this field was laid nearly 50 years ago. In 1974, Dr. Stewart Wolf described "The Real Gap between the Bench and Bedside" in an editorial for the *New England Journal of Medicine* (Wolf 1974). The first versions of this bench-to-bedside paradigm to use the language of "translation" included a model with just two stages. The first stage described the bridge between basic science research (the bench, which included animal and preclinical studies) and human clinical research, including clinical trials. The second stage transitioned from human clinical research to clinical practice (the bedside) (Sung et al. 2003). This model has become more complex over time. Subsequent analysis (Khoury et al. (2007) described four stages of translation, and recent work describes at least five (Drolet and Lorenzi 2011). Depending on the author and perhaps the context, these five stages are alternately titled T1 to T5, or T0 to T4. Regardless of the numbering system, these recent descriptions include a first stage of discovery, typically understood to be basic science research. This stage is then followed by a second stage focused on understanding the human applications of the discovery, followed by the development of clinical applications, the development of clinical guidelines and interventions, and, finally, evaluation.

Over the past two decades, the idea of translating basic science findings into measurable health improvements has become an essential component of the NIH's vision for transforming medical research initiatives in the United States. This transformation was described in 2004 in the NIH Roadmap for Medical Research, a collection of far-reaching initiatives organized around New Pathways to Discovery, Research Teams of the Future, and Re-Engineering the Clinical Research Enterprise (Schmidt 2004). One outcome of the aim to re-engineer clinical research was the conversion of the National Center for Research Resources (NCRR) into the National Center for Advancing Translational Sciences (NCATS), a transition that occurred in 2011. Most major American academic medical centers now house NCATS Clinical and Translational Science Awards (CTSA) programs (NCATS 2018).

Although these programs are intended to revolutionize drug development frameworks, it is clear that in both historical and contemporary societies, most major improvements in life expectancy and decreases in human suffering are attributable to environmental and public health interventions rather than novel drug development (CDC 1999). Thus, environmental health scientists can feel frustrated with the clinical goals and focus with which

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the translational paradigm is typically presented. This frustration raises the question: How can we think about the translational research paradigm in a way that is relevant to public health, and in particular to environmental public health?

Objective

In this commentary, we describe an approach to modify this translational framework to be applicable to environmental health sciences while retaining the basic structure that underlies the original bench-to-bedside paradigm.

Discussion

Discovery in the Environmental Health Sciences (T1)

All translational research paradigms begin with initial discovery. In this commentary, we posit that the most successful translations of public and environmental health research to disease prevention and increases in life expectancy have derived from discoveries made through epidemiological and clinical observation. With advances in molecular biology, it is increasingly likely that future bench-based discoveries will provide the impetus for interventions that prevent disease, but a paradigm that describes only bench discovery does not, in our opinion, reflect the existing reality of our field.

Current efforts to develop predictive toxicology methods hold promise for the identification of toxic hazards. Toxicology Testing in the 21st century (Tox21), a collaborative effort among EPA, NIH, and FDA, is one such effort that aims to more efficiently test environmental chemicals for their potential to disrupt biological pathways that may result in toxicity (EPA 2018). The promise of using short-term assays to identify hazards and prevent exposures and health effects has a long history dating back to the Ames Assay, and though there have been few victories to date, we believe that advances in technology may well prove useful in launching future successful public health interventions.

Despite this potential, in the field of environmental health sciences, it can be challenging to recount examples of effective public health interventions that we can trace to an initial discovery at the bench. In fact, although environmental health findings initiated by bench discovery have occasionally spawned well-meaning efforts to drive policy to protect health, they may instead result in decisions with little benefit. One recent example is dietary exposure to acrylamide from foods, such as French fries and coffee. In 2002, a group of environmental chemists in Sweden discovered that acrylamide could also be formed at elevated temperatures during cooking (Tareke et al. 2002). This discovery caused immediate concern, as acrylamide is currently considered a Group 2A carcinogen by the International Agency for Research on Cancer (IARC 1994). Interestingly, acrylamide's Group 2A designation was also driven by discovery at the bench. Numerous animal studies have demonstrated that acrylamide induces gene mutations and chromosomal aberrations in germ cells of mice and chromosomal aberrations in germ and somatic cells of rats *in vivo; in vitro* studies have demonstrated that acrylamide induced gene mutations and chromosomal aberrations in cultured cells (IARC 1994). Together, these bench discoveries establish both the biological plausibility of acrylamide as a carcinogen and a potentially prevalent exposure pathway for humans.

These bench findings have led to a bedside result—under the Safe Drinking Water and Toxic Enforcement Act (Proposition 65), California will now require that coffee be sold with a cancer warning label due to the presence of acrylamide (OEHHA 2019). This warning is required despite the fact that epidemiologic studies do not demonstrate a consistent or compelling relationship between acrylamide exposure and cancer and that coffee consumption itself is not associated with cancer (Graff et al. 2018; Kotemori et al. 2018; Pelucchi et al. 2015, 2016, 2017; Wilson et al. 2012; Sobel et al. 1986; Collins et al. 1989; Loomis et al. 2016). Based on the translational paradigm we suggest here, we would argue that having the right balance of expertise at the table is necessary to result in appropriate and evidence-based policies. Instead, the case of labeling coffee because of acrylamide appears to be an example of unbalanced expertise in which laboratory findings were inappropriately weighted over available observational epidemiologic research.

In contrast, most of the important discovery that occurs in environmental health is driven by seminal epidemiological or clinical observations, which has been true from our earliest environmental and public health successes. John Snow's discovery of the source of London's cholera epidemic in the mid-1800s was driven by his observation of the geographical distribution of cases in the area served by the Broad Street pump. Observational studies also spurred our understanding of the risks of occupational exposure to asbestos. Merewether and Price published the first epidemiologic study of the asbestos industry in 1930. They observed nearly 400 workers in asbestos textile mills in the United Kingdom and found that 25% of these workers had signs of serious respiratory disease and that among those who worked at the trade for more than 20 years, the proportion was 80% (Merewether and Price 1930). Our understanding of the importance of fluoridation of drinking water in cavity prevention stems not from bench science, but from observations made by Drs. McKay and Black in the early 1900s about the brown stains and lack of dental caries in the teeth of children consuming water with high levels of fluorine (NIDCR 2018).

The value of observational studies in the generation of important public and environmental health discovery continues over time. Prospective cohort studies from the 1970s and 1980s demonstrated the potential for neurobehavioral effects of lead exposure among children at much lower exposures than previously acknowledged (Needleman 1982). We understand the relationship between low-level arsenic contamination in drinking water and cancer due to discoveries made through observational research (Sambu and Wilson 2008), and our understanding of the effect of second-hand smoke exposure on low birth weight is the result of multiple well-designed observational studies in the late 1980s, with remarkably consistent findings (Rubin et al. 1986; Martin and Bracken 1986).

Furthermore, observations related to public health incidents have originated from sources other than clinicians and epidemiologists. Public health practioners, regulators, and community members have often provided initial observational insights that have heralded important environmental public health issues. For example, undertakers and florists first observed the effects of the Great London Smog event of 1952; after running out of coffins and fresh flowers due to the requests for funeral arrangements, these community members were weeks ahead of the registrars in understanding the magnitude of this public health crisis (Laskin 2006). Epidemiologic research now continues to further our recognition of the health effects of air pollution through prospective cohort studies that engage the exposure sciences, clinical sciences, and environmental epidemiology in the 21st century (Kaufman et al. 2016).

Because many advances in reducing human morbidity and mortality originate with scientific discoveries initiated by clinical observations and epidemiological approaches, we argue that a translational research framework with relevance to public health and environmental health sciences must acknowledge observational studies as a major genesis of health improvement. Although this framework has been acknowledged in other models of translational research (e.g., Surkis et al. 2016; Pettibone et al. 2018), we

propose a model for the translational science paradigm in which T1 explicitly emphasizes the substantial contribution of observational research for the environmental health sciences (Figure 1).

Health and Policy Implications (T2 and T3): Cross-Disciplinary Work in Environmental Health Sciences

In many translational frameworks, including that proposed here, the next two stages of translational research, T2 and T3, focus on identifying the practical implications of the T1 discovery (see, for example, Trochim et al. 2011). In the traditional bench-to-bedside model, these stages together represent the transition from basic science to human clinical research. In modern manifestations of the translational paradigm, T2 typically represents identification of prevention and treatment possibilities, whereas T3 represents actual clinical treatment of individuals and the identification of larger implications to clinical practice.

We propose a parallel process for the identification of the implications of the initial discovery to population health and policy. In the context of environmental health sciences, the initial discovery most often takes the form of an observation of an environmental exposure that has the potential to cause harm to human health. This exposure may be to a chemical, a metal, or a physical agent (e.g., ionizing and nonionizing radiation, or the effects of climate change such as heat, extreme weather, etc.), or features of the social, natural, or built environment. The T2 stage of environmental health translation first requires confirmation of a causal link between the exposure and the outcome.

In our experience, establishment of a causal relationship between a given environmental exposure and an increase in the prevalence or severity of a given disease requires a unique integration of disciplines. Exposure scientists are needed to identify and document relevant routes of exposure and to model exposure pathways. Exposure biology is required to unravel interactions between the exposure and other toxicants, metabolic processes, toxicokinetic dynamics, lifestyle factors, and genetics. Biostatisticians must be included in study design and planning and data analyses as well as the development of valid exposure and health-effect models. Toxicology plays the essential role in describing the mechanisms that constitute the adverse outcome pathway and that confirm biological plausibility, clearly crucial to establishing causality. Toxicologists further investigate the potential dose–response relationships, which can both strengthen the case for causality and define important exposure benchmarks. In addition to these disciplines, an important role exists here for human clinical research in some settings to confirm health effects in the species of interest and to understand exposure–response relationships without the perils of interspecies extrapolation. When ethical, estimation of biological half-lives, toxicokinetics, and measurement of reversible end points in human subjects strengthens a causal argument in a way that is difficult to replicate in animal studies (Rom et al. 2013).

This interdisciplinary cross-fertilization is a distinctive component of our view of the translational research paradigm in the environmental health sciences (Figure 1). Each component informs the others, resulting in an iterative advancement from discovery to health and policy implications. To be successful, this work must exist within a collaborative space, where an advance in one area necessarily motivates subsequent efforts in another.

It is here that we observe the bench component of environmental health science playing an indispensable role, defining the molecular underpinnings of hazards, identifying more and less risky exposures, and articulating a dose–response relationship. Bench research is also needed to understand molecular signatures of environmental hazards, establishing the proteomic, metabolomics, and transcriptomic patterns in tissue response to an exposure, all of which have applications to toxicology, exposure science, exposure biology, and epidemiology. We also understand a role for bench science in understanding genetic susceptibility and the role of potential pharmacological interventions. However, the potential for such advances to provide public health impacts is still largely in its infancy (if not mostly speculative) and typically inefficient in comparison with simply reducing exposures. In our opinion, in the environmental and public health arenas, the role of primary prevention must always be a paramount objective.

We can take, for example, our evolving understanding of the health effects of lead exposure over the past 100 years. Although our understanding of the acute effects of lead poisoning dates back to Roman times, the idea that lead could be safely used—in gasoline, paint, pipes, food cans, and toys—persisted well into the 20th century (Johnson and Mason 1984). Part of the failure to address lead exposure earlier can be attributed to strong efforts by industry to maintain its use, but another part of this failure may be attributed to the complexity of the exposure–response relationship. Fully understanding the exposure–response relationship, the T2 stage of translation, has been complicated by a multitude of factors, including the apparent lack of a level of exposure at which there is no adverse health effect (Needleman 2009), complex toxicokinetics including multiple compartments and nonlinear dose–response relationships (Bowers and Beck 2006), and the complexity of the dose–related continuum of toxicity (Needleman and Landrigan 1981). Modeling the relationship between low-level lead exposure and difficult-to-measure health outcomes, such as infant development, is further complicated by thorny issues regarding confounding and covariate selection (Bellinger et al. 1985). A truly interdisciplinary team of epidemiologists, toxicologists, biostatisticians, and clinicians–as necessary to solve the complex problem–has developed the information needed to model the relationships and provide inputs to risk assessment and public health policy.

Once the exposure–response relationship is established and understood, the T3 stage of environmental health translation can be framed as identifying appropriate interventions to reduce the exposure and improve health outcomes. This component of the translational framework is directly analogous to the development of clinical trials in the more traditional drug-development framework. In other words, what needs to happen to reduce or prevent exposures? Should we substitute a product? Reduce industrial emissions? Ask residents to wear masks? The answers to these kinds of questions form the substance of the T3 stage.

We emphasize that the T3 stage also requires the work of an interdisciplinary team (Figure 1). As in the T2 stage, this team includes epidemiologists, biostatisticians, and exposure scientists, but also expands to include risk assessors and policy experts, who may help to envision and evaluate options for appropriate interventions to reduce exposure and improve health. The example of lead remains pertinent as we consider the difficulty in finding consensus on the myriad interventions required to reduce lead exposure, heightened by the multitude of relevant exposure pathways and the social context and issues of environmental injustice inherent in this problem. Although obvious successes in lead interventions have taken place, from the ban on leaded gasoline to lead-paint abatement programs, the recent water crisis in Flint, Michigan, highlights the challenges in converting recognition of hazards into interventions sufficient to protect human health (Ruckart et al. 2019).

Translating Science to Practice (T4): Policy and Systems Change

In the traditional translational paradigm as applied to clinical medicine, the T4 stage typically focuses on outcomes and effectiveness (Fort et al. 2017), such as the development of broad-reaching clinical guidelines. In a public health context, T4 is centered on application within a community or societal setting, often as either a policy

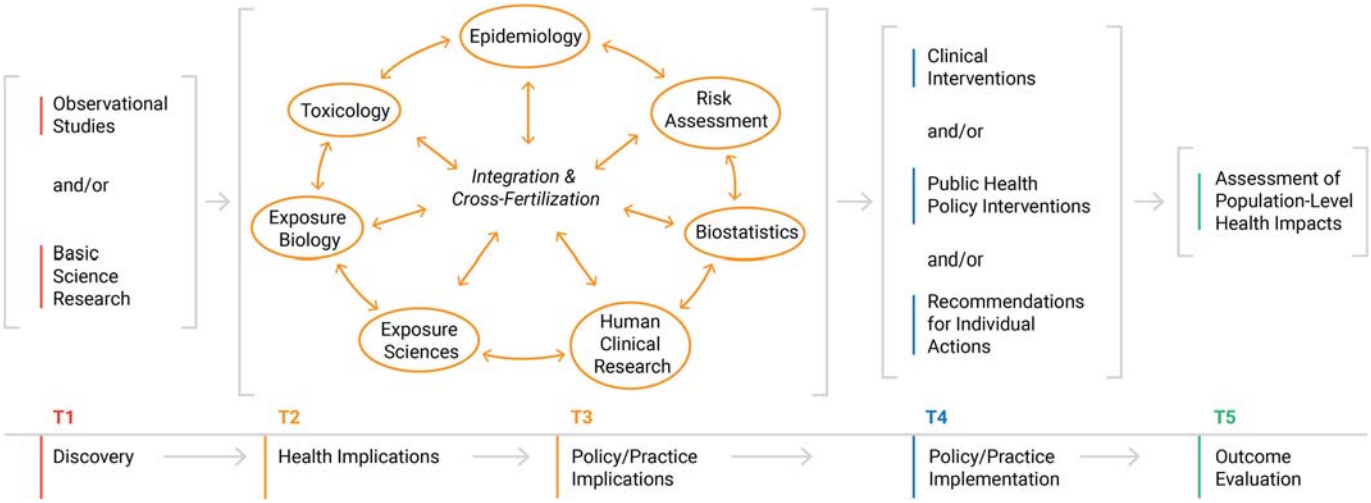

Figure 1. A proposed framework for translational research in the context of environmental health sciences. The bottom of this figure shows the phases of research translation, moving from Discovery (T1), to Health and Policy/Practice Implications (T2/T3), to Policy/Practice Implementation (T4), through to Outcome Evaluation (T5). Within the T2/T3 phase, key disciplines within environmental health sciences are located within ovals. For environmental health research translation to succeed, these key disciplines must integrate and cross-fertilize, and it must be understood that this entire group of disciplines are interdependent. The ordering and positioning of these disciplines is arbitrary and not intended to imply directionality or importance. This figure is not meant to assign greater or lesser weight or importance to specific disciplines, activities, or actions. (Graphic Credit: Sierra Wells).

intervention or recommendations for individual action. The most effective interventions are usually at the policy level (Brownson et al. 2009). For advancing evidence to achieve public health goals in the clinical practice realm, the U.S. Preventive Services Task Force has set a standard for moving from the grading of clinical trials to the grading of recommendations for system-wide changes in practice on a large variety of topics. These recommendations incorporate not only clinical trial data (rarely available in environmental health research), but also increasingly indirect evidence, observational data, and studies with intermediate end points as outcomes (Wolff et al. 2018). Ultimately, the recommendations need to incorporate concepts of cost–benefit evaluation and decision-making in the setting of uncertainty and individual preferences. The need to make this stage a collaborative cross-disciplinary process has become clear (Petitti et al. 2018).

Comparable processes are being adopted in the domain of environmental health sciences. Thus, similar to other models of translational research in the context of environmental health sciences (e.g., Khoury et al. 2007; NCATS 2018; Pettibone et al. 2018), we propose that this T4 stage of environmental health research translation involves movement from understanding the exposure–response relationship (T2) and development of intervention strategies (T3) into implementation in standard practice and policy. This process requires evaluation of the weight of the available evidence for the efficacy of various strategies, understanding of the acceptability of each potential intervention, consideration of alternative solutions and competing risks and benefits, cost-benefit analysis, and ultimately, policy development. Community engagement forms an important component of this stage of translational environmental health research. Here, too, we see the critical roles of dissemination and implementation research, policy and systems change. Implementation science is research that "supports movement of evidence-based effective health care and prevention strategies or programs from the clinical or public health knowledge based into routine use" (Colditz 2012). Recent work connecting implementation science, policy and systems change, and public health emphasizes the importance of envisioning implementation at the earliest possible stages of the intervention development process, considering the sustainability of the intervention and focusing on capacity-building efforts (Chambers 2018).

Of special interest in the T4 stage of environmental health translation is how policy decision makers evaluate the magnitude and quality of the evidence available to support various intervention strategies (Figure 1). Typically, for findings from clinical interventions to be included in guidelines, the highest grade of evidence is needed, especially when new recommendations are expensive, have extensive potential negative consequences, or may conflict with other standards of care. In environmental health sciences, definitive high-grade evidence may be elusive even when the weight of evidence indicates that public health action is warranted. Hence, the requirement for high-grade evidence may conflict with the precautionary principle—the idea that preventive action should be taken while some uncertainty remains (Kriebel et al. 2001). Here, a departure from the requirements of clinical practice to public health contexts exists.

Evaluating Population-Level Health Impacts (T5): Accountability Research

The original bench-to-bedside framework did not extend into the evaluation phase (T5), now viewed as an essential component of translational research in nearly all contexts (Trochim et al. 2011). However, just as evaluation and outcomes research has taken on increased importance in the clinical realm, this phase has special relevance for evaluating public health interventions. In environmental health research, T5 encompasses measurement of the effects of interventions after their implementation, in terms of both exposure and health outcomes, as well as reconsidering cost-benefit assumptions and need for changes in policy as new science emerges. Because environmental and public health sciences are often focused on preventive measures rather than treatment, the evaluation of population-level health impacts of community interventions and policy changes is particularly challenging. How do we measure the number of cases of cancer that did not occur? Even more daunting is the question, how do we attribute those cases to a specific action? This challenge can require comparing the present to a counterfactual possibility, and the methods behind the science of evaluating the magnitude of that which did not occur continue to evolve.

We see a number of promising examples of this science in action in the study of air pollution. For example, many metrics have been developed to attribute the quantifiable lives and dollars saved by the Clean Air Act. According to the U.S. EPA's report, *"Benefits and Costs of the Clean Air Act 1990–2020, the Second Prospective Study,"* by 2020 this legislation will have prevented over 230,000 early deaths and generated a savings of over $2 trillion (EPA 2011) Pope et al. have estimated that reductions in air pollution in the United States have accounted for as much as 15% of the overall increase in life expectancy in the last several decades (Pope et al. 2009). Other recent work has associated improvements in air quality with reduced mortality (Dominici et al. 2007) and positive effects on lung-function growth in children (Gauderman et al. 2015). In evaluating the effect of air-quality interventions, accountability research has been tested by lack of statistical power, complexity in background trends in air quality, and the difficulty of direct attribution of changes in air pollution and health to a single intervention among many regulatory actions (Boogaard et al. 2017). New causal modeling methods may help address these problems. This set of challenges speaks to the critical integration of the fields of biostatistics, exposure science, epidemiology, implementation science, and program evaluation in the T5 stage of environmental health sciences (Figure 1).

Other Translational Research Frameworks within Environmental Health Sciences

The model presented here is not the first conceptualization of environmental health sciences in the context of translational science. In 2006, the National Institute of Environmental Health Sciences (NIEHS) first began to include the idea of translating "research results into effective means to protect public health" as part of the NIEHS 2006–2011 Strategic Plan (NIEHS 2006). In addition, the NIEHS recently described a comprehensive model for "Expanding the Concept of Translational Research: Making a Place for Environmental Health Sciences" (Pettibone et al. 2018). This framework aims to expand the concept of translational research to incorporate environmental health sciences and envisions the translational framework as a series of five concentric circles, moving from a center ring titled "Fundamental Questions," to "Application and Synthesis," to "Implementation and Adjustment," to "Practice," and finally to an external ring representing "Impact" (Pettibone et al. 2018).

Our construction of the translational model shares many commonalities with the NIEHS framework. The importance of interdisciplinary cross-fertilization that we emphasize in the T2 and T3 stages of our model is reflected in the multiple nodes representing human, animal, and cellular research; risk assessment; and clinical testing within the concentric rings in the NIEHS framework. Both models recognize that bench-based findings are not necessarily restricted to the initial discovery stage but may in fact play even more crucial roles in what Pettibone et al. (2018) describe as the "Application and Synthesis" and "Implementation and Adjustment" rings. The two models also highlight the importance of implementation science and evaluation. The five stages that we propose and the five concentric rings of the NIEHS model run parallel in many ways. In addition, both models recognize that research becomes translational when it moves from one category to another, whether across the phases of our model or the rings of the model proposed by Pettibone et al. (2018).

The NIEHS framework also readily acknowledges the potential role of observational studies as a potential genesis of a translational research story. In the framework proposed here, we elevate the role of the observational study and argue that such study is not just one among many possible options for "discovery," but that in the history of environmental health sciences, the role of observation has been paramount. Our framework also places emphasis on the specific disciplines that must integrate to move along a translational pathway within our field, and our framework specifically highlights the unique role of exposure sciences—a discipline that is not necessarily present in other translational research contexts. Our framework and that proposed by the NIEHS share a common objective, which Pettibone et al. (2018) describe as "encouraging the translation of research from basic biomedical and environmental health findings to concrete strategies that protect and improve human health." However, we believe that the framework we have proposed provides a simpler and more visually compelling demonstration of the most typical translation pathway from discovery to public health improvement in the environmental health sciences.

Conclusions

We propose a translational research framework that spans from discovery to evaluation of public health policies. The overall linearity of this proposed model parallels the historical translational science paradigm, moving from an initial "Discovery" through "Implementation" to "Outcome Evaluation." This overarching linear framework, like those of traditional translational research models, acknowledges the basic construct of a process with a beginning and an end, wherein new knowledge instigates a series of events that ultimately, and concretely, lead to a measurable benefit to public health. This model also reflects unique aspects of our field, permitting environmental health scientists from many disciplines to recognize their key roles in the advance of knowledge from discovery to public health action. One such aspect is the clear recognition of the important role of observational studies as a key source of that new knowledge. In addition, this framework further recognizes the critical role of the interdisciplinary and complementary sciences that are most central to environmental health research: epidemiology, risk assessment, toxicology, biostatistics, exposure biology, exposure sciences, and human clinical research.

We believe the emphasis on the integration and cross-fertilization of our field's key disciplines within this framework provides a visually simple way for environmental health scientists and those working in related areas to see how and where their work belongs within a translational framework. The idea of the Discovery Phase (T1) still exists within this framework, but rather than solely recognizing discoveries made in the laboratory, this model reflects our experience that public health discoveries have frequently occurred through the observational sciences. This model therefore focuses on elevating the role of observation in environmental health sciences while still acknowledging that the cumulative contribution of basic science together with observational work provides the strongest foundation on which evidence-based impacts can be made. In this model of translational research in the environmental health sciences, the characterization of exposure–response functions and disease prevention strategies (T2 and T3, respectively) are then refined through a unique integration of toxicological research, exposure sciences, exposure biology, population-based studies, biostatistical methods, and human clinical research. Policy and practice interventions (T4) then take the form of clinical, policy, or individual interventions or actions, and outcome evaluation (T5) occurs as an assessment of population-level health impacts. With a framework reflecting the realities of the field, environmental health scientists can embrace the paradigm of translational sciences.

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References

Bellinger D, Leviton A, Waternaux C, Allred E. 1985. Methodological issues in modeling the relationship between low-level lead exposure and infant development: examples from the Boston Lead Study. Environ Res 38(1):119–129, PMID: 3841053, https://doi.org/10.1016/0013-9351(85)90077-5.

Boogaard H, van Erp AM, Walker KD, Shaikh R. 2017. Accountability studies on air pollution and health: the HEI Experience. Curr Environ Health Rep 4(4):514–522, PMID: 28988407, https://doi.org/10.1007/s40572-017-0161-0.

Bowers TS, Beck BD. 2006. What is the meaning of non-linear dose-response relationships between blood lead concentrations and IQ? Neurotoxicology 27(4):520–524, PMID: 16551479, https://doi.org/10.1016/j.neuro.2006.02.001.

Brownson RC, Chriqui JF, Stamatakis KA. 2009. Understanding evidence-based public health policy. Am J Public Health 99(9):1576–1583, PMID: 19608941, https://doi.org/10.2105/AJPH.2008.156224.

CDC (Centers for Disease Control and Prevention). 1999. Ten great public health achievements–United States, 1900–1999. MMWR Morb Mortal Wkly Rep 48:241–243, PMID: 10220250.

Chambers DA. 2018. Commentary: increasing the connectivity between implementation science and public health: advancing methodology, evidence integration, and sustainability. Annu Rev Public Health 39:1–4, PMID: 29272164, https://doi.org/10.1146/annurev-publhealth-110717-045850.

Colditz GA. 2012. The promise and challenges of dissemination and implementation research. In: *Dissemination and Implementation Research in Health: Translating Science into Practice*. Brownson RC, Colditz GA, Proctor EK, eds Oxford, UK: Oxford Univeristy Press, 3–22.

Collins FS, Anderson JM, Austin CP, Battey JF, Birnbaum LS, Briggs JP, et al. 2016. Basic science: bedrock of progress. Science 351(6280):1405, PMID: 27013720, https://doi.org/10.1126/science.351.6280.1405-a.

Collins JJ, Swaen GM, Marsh GM, Utidjian HM, Caporossi JC, Lucas LJ. 1989. Mortality patterns among workers exposed to acrylamide. J Occup Med 31(7):614–617, PMID: 2769457, https://doi.org/10.1097/00043764-198907000-00013.

Dominici F, Peng RD, Zeger SL, White RH, Samet JM. 2007. Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? Am J Epidemiol 166(8):880–888, PMID: 17728271, https://doi.org/10.1093/aje/kwm222.

Drolet BC, Lorenzi NM. 2011. Translational research: understanding the continuum from bench to bedside. Transl Res 157(1):1–5, PMID: 21146144, https://doi.org/10.1016/j.trsl.2010.10.002.

EPA (Environmental Protection Agency). 2011. Benefits and Costs of the Clean Air Act 1990-2020, the Second Prospective Study. https://www.epa.gov/clean-air-act-overview/benefits-and-costs-clean-air-act-1990-2020-second-prospective-study [accessed 6 June 2018].

EPA. 2018. What is Toxicology in the 21st Century (Tox21)? https://www.epa.gov/chemical-research/what-toxicology-21st-century-tox21 [accessed 6 June 2018].

Fort DG, Herr TM, Shaw PL, Gutzman KE, Starren JB. 2017. Mapping the evolving definitions of translational research. J Clin Transl Sci 1(1):60–66, PMID: 28480056, https://doi.org/10.1017/cts.2016.10.

Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, et al. 2015. Association of improved air quality with lung development in children. N Engl J Med 372(10):905–913, PMID: 25738666, https://doi.org/10.1056/NEJMoa1414123.

Graff RE, Cho E, Preston MA, Sanchez A, Mucci LA, Wilson KM. 2018. Dietary acrylamide intake and risk of renal cell carcinoma in two large prospective cohorts. Cancer Epidemiol Biomarkers Prev 27(8):979–982, PMID: 29760239, https://doi.org/10.1158/1055-9965.EPI-18-0320.

IARC (International Agency for Research on Cancer). 1994. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 60. https://monographs.iarc.fr/ENG/Monographs/vol60/mono60-16.pdf [accessed 6 June 2018].

Johnson BL, Mason RW. 1984. A review of public health regulations on lead. Neurotox 5(3):1–22, PMID: 6542973.

Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. 2016. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet 388(10045):696–704, PMID: 27233746, https://doi.org/10.1016/S0140-6736(16)00378-0.

Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore CA, Bradley L. 2007. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? Genet Med 9(10):665–674, PMID: 18073579, https://doi.org/10.1097/GIM.0b013e31815699d0.

Kotemori A, Ishihara J, Zha L, Liu R, Sawada N, Iwasaki M, et al. 2018. Dietary acrylamide intake and risk of breast cancer: The Japan Public Health Center-based Prospective Study. Cancer Sci 109(3):843–853, PMID: 29288560, https://doi.org/10.1111/cas.13496.

Kriebel D, Tickner J, Epstein P, Lemons J, Levins R, Loechler RL, et al. 2001. The precautionary principle in environmental science. Environ Health Perspect 109(9):871–876, PMID: 11673114, https://doi.org/10.1289/ehp.01109871.

Laskin D. 2006. The Great London Smog. Weatherwise 59(6):42–45, https://doi.org/10.3200/WEWI.59.6.42-45.

Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, et al. 2016. Carcinogenicity of drinking coffee, mate, and very hot beverages. Lancet Oncol 17(7):877–878, PMID: 27318851, https://doi.org/10.1016/S1470-2045(16)30239-X.

Martin TR, Bracken MB. 1986. Association of low birth weight with passive smoke exposure in pregnancy. Am J Epidemiol 124(4):633–642, PMID: 3752056, https://doi.org/10.1093/oxfordjournals.aje.a114436.

Merewether ERA, Price CW. 1930. The occurrence of pulmonary fibrosis and other pulmonary affections in asbestos workers. J Ind Hyg 12:198–222.

NCATS (National Center for Advancing Translational Sciences). 2018. Clinical and Translational Science Awards (CTSA) Program. https://ncats.nih.gov/ctsa [accessed 6 June 2018].

Needleman H. 2009. Low level lead exposure: history and discovery. Ann Epidemiol 19(4):235–238, PMID: 19344860, https://doi.org/10.1016/j.annepidem.2009.01.022.

Needleman HL. 1982. The neurobehavioral consequences of low lead exposure in childhood. Neurobehav Toxicol Teratol 4(6):729–732, PMID: 7170036.

Needleman HL, Landrigan PJ. 1981. The Health Effects of Low Level Exposure to Lead. Annu Rev Public Health 2:277–298, PMID: 7348554, https://doi.org/10.1146/annurev.pu.02.050181.001425.

NIDCR (National Institute of Dental and Craniofacial Research). 2018. The Story of Fluoridation. https://www.nidcr.nih.gov/health-info/fluoride/the-story-of-fluoridation [accessed 6 June 2018].

NIEHS (National Institute for Environmental Health Sciences). 2006. NIEHS 2006–2011 Strategic Plan: New Frontiers in Environmental Sciences and Human Health. https://www.niehs.nih.gov/about/strategicplan/strategicplan2006/niehs_20062011_strategicplan_508.pdf [accessed 6 June 2018].

OEHHA (Office of Environmental Health Hazard Assessment). 2019. Chemicals considered or listed under Proposition 65. Acrylamide. https://oehha.ca.gov/proposition-65/chemicals/acrylamide [accessed 11 March 2019].

Pelucchi C, Bosetti C, Galeone C, La Vecchia C. 2015. Dietary acrylamide and cancer risk: an updated meta-analysis. Int J Cancer 136(12):2912–2922, PMID: 25403648, https://doi.org/10.1002/ijc.29339.

Pelucchi C, Galeone C, Negri E, Bosetti C, Serraino D, Montella M, et al. 2016. Dietary acrylamide and the risk of endometrial cancer: an Italian case-control. Nutr Cancer 68(2):187–192, PMID: 26905095, https://doi.org/10.1080/01635581.2016.1142585.

Pelucchi C, Rosato V, Bracci PM, Li D, Neale RE, Lucenteforte E, et al. 2017. Dietary acrylamide and the risk of pancreatic cancer in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 28(2):408–414, PMID: 27836886, https://doi.org/10.1093/annonc/mdw618.

Petitti DB, Lin JS, Owens DK, Croswell JM, Feuer EJ. 2018. Collaborative modeling: experience of the U.S. Preventive Services Task Force. Am J Prev Med 54(1S1):S53–S62, PMID: 29254526, https://doi.org/10.1016/j.amepre.2017.07.003.

Pettibone KG, Balshaw DM, Dilworth C, Drew CH, Hall JE, Heacock M, et al. 2018. Expanding the concept of translational research: making a place for environmental health sciences. Environ Health Perspect 126(7):074501, PMID: 30024381, https://doi.org/10.1289/EHP3657.

Pope CA 3rd, Ezzati M, Dockery DW. 2009. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360(4):376–386, PMID: 19164188, https://doi.org/10.1056/NEJMsa0805646.

Rom WN, Boushey H, Caplan A. 2013. Experimental human exposure to air pollutants is essential to understand adverse health effects. Am J Respir Cell Mol Biol 49(5):691–696, PMID: 24024529, https://doi.org/10.1165/rcmb.2013-0253PS.

Rubin DH, Krasilnikoff PA, Leventhal JM, Weile B, Berget A. 1986. Effect of passive smoking on birth-weight. Lancet 2(8504):415–417, PMID: 2874412, https://doi.org/10.1016/S0140-6736(86)92132-X.

Ruckart PZ, Ettinger AS, Hanna-Attisha M, Jones N, Davis SI, Breysse PN. 2019. The Flint water crisis: a coordinated public health emergency response and

recovery initiative. J Public Health Manag Pract 25(Suppl 1):S84–S90, PMID: 30507775, https://doi.org/10.1097/PHH.0000000000000871.
Sambu S, Wilson R. 2008. Arsenic in food and water–a brief history. Toxicol Ind Health 24(4):217–226, PMID: 19022874, https://doi.org/10.1177/0748233708094096.
Schmidt CW. 2004. NIH roadmap for medical research. Environ Health Perspect 112(3):A165–A166, PMID: 15049313, https://doi.org/10.1289/ehp.112-a165.
Sobel W, Bond GG, Parsons TW, Brenner FE. 1986. Acrylamide cohort mortality study. Br J Ind Med 43(11):785–788, PMID: 3790460.
Sung NS, Crowley WF Jr, Genel M, Salber P, Sandy L, Sherwood LM, et al. 2003. Central challenges facing the national clinical research enterprise. JAMA 289(10):1278–1287, PMID: 12633190.
Surkis A, Hogle JA, DiazGranados D, Hunt JD, Mazmanian PE, Connors E, et al. 2016. Classifying publications from the clinical and translational science award program along the translational research spectrum: a machine learning approach. J Transl Med 14(1):235, PMID: 27492440, https://doi.org/10.1186/s12967-016-0992-8.
Tareke E, Rydberg P, Karlsson P, Eriksson S, Törnqvist M. 2002. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. J Agric Food Chem 50(17):4998–5006, PMID: 12166997, https://doi.org/10.1021/jf020302f.
Trochim W, Kane C, Graham MJ, Pincus HA. 2011. Evaluating translational research: a process marker model. Clin Transl Sci 4(3):153–162, PMID: 21707944, https://doi.org/10.1111/j.1752-8062.2011.00291.x.
Wilson KM, Giovannucci E, Stampfer MJ, Mucci LA. 2012. Dietary acrylamide and risk of prostate cancer. Int J Cancer 131(2):479–487, PMID: 21866549, https://doi.org/10.1002/ijc.26383.
Wolf S. 1974. Editorial: The real gap between bench and bedside. N Engl J Med 290(14):802–803, PMID: 4150016, https://doi.org/10.1056/NEJM197404042901411.
Wolff TA, Krist AH, LeFevre M, Jonas DE, Harris RP, Siu A, et al. 2018. Update on the methods of the U.S. Preventive Services Task Force: linking intermediate outcomes and health outcomes in prevention. Am J Prev Med 54(1S1):S4–S10, PMID: 29254525, https://doi.org/10.1016/j.amepre.2017.08.032.