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Population health science as a unifying foundation for translational clinical and public health research

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A B S T R A C T

Separated both in academics and practice since the Rockefeller Foundation effort to "liberate" public health from perceived subservience to clinical medicine a century ago, research in public health and clinical medicine have evolved separately. Today, translational research in population health science offers a means of fostering their convergence, with potentially great benefit to both domains. Although evidence that the two fields need not and should not be entirely distinct in their methods and goals has been accumulating for over a decade, the prodigious efforts of biomedical and social sciences over the past year to address the COVID-19 pandemic has placed this unifying approach to translational research in both fields in a new light. Specifically, the coalescence of clinical and population-level strategies to control disease and novel uses of population-level data and tools in research relating to the pandemic have illuminated a promising future for translational research.

We exploit this unique window to re-examine how translational research is conducted and where it may be going. We first discuss the *transformation* that has transpired in the research firmament over the past two decades and the *opportunities* these changes afford. Next, we present some of the *challenges*—technical, cultural, legal, and ethical— that need attention if these opportunities are to be successfully exploited. Finally, we present some *recommendations* for addressing these challenges.

1. The transformation of translational research for public health and clinical medicine

1.1. The legacy of translational research

Translational research in clinical medicine has a long and distinguished history, reified in 2003 by the introduction of the NIH "Roadmap." (Zerhouni, 2006) With the overarching goal of finding new and better medical treatments for the gamut of diseases, the process has proceeded along the pathway depicted in Fig. 1.

Against an essential background of research aimed at understanding biologic mechanisms more broadly and developing tools to support research relevant to multiple disciplines (often referred to as "basic science"), translational scientists have focused on 1) describing the clinical characteristics of diseases, often facilitated by assembly of patient registries; 2) using these detailed observations as the foundation for development of animal models—or, more recently, *in vitro* systems, including organoids, derived from animal or human tissues—which become the foundation for 3) explorations of the unique biology of each disease, and 4) the search for targets to disrupt the disease process. With maturity of this work and experiments suggesting such interventions might be beneficial, 5) medicinal chemists search for compounds or other moieties that might achieve that benefit in humans at an acceptable cost in terms of side effects and risks. After such an agent or device has been deemed ripe for testing, 6) trials commence starting with first-in-human tests to determine whether the effects in humans resemble that in animals and assess the dose-related adverse consequences. With that evidence in hand, the typical next step is 7) the conduct of a

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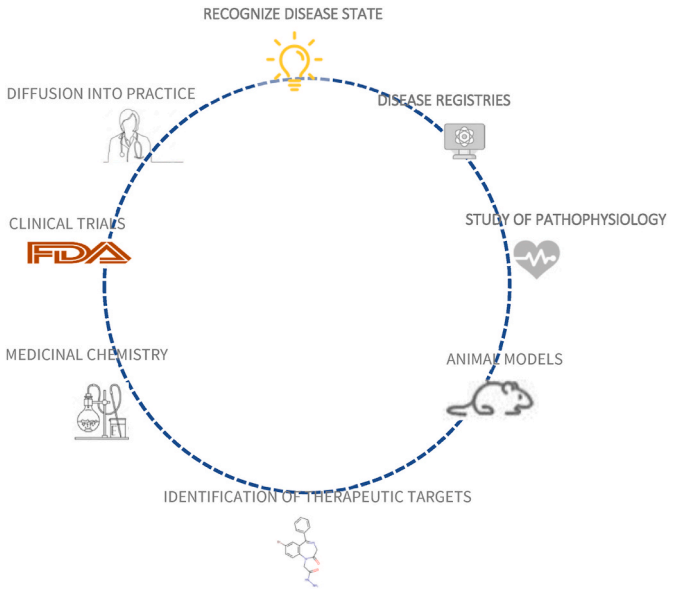

Fig. 1. The traditional pathway of discovery in clinical and translational medicine.

Translational research in *clinical medicine*, reified in 2003 by the introduction of the NIH "Roadmap" (Zerhouni, 2006), with the overarching goal of finding new and better treatments for the gamut of diseases, has proceeded along the pathway depicted in Fig. 1.

randomized controlled trial (RCT) of the new therapy compared to the standard of care or placebo.

By contradistinction, the search for evidence about public health interventions, such as nutritional supplements (e.g. Vitamin D in milk; fluoride in drinking water), environmental and occupational regulations, or policies to discourage harmful behaviors, historically has proceeded in a quite different way (Fig. 2).

Relying on vital records (births, deaths by cause, etc.), surveillance data, periodic community surveys, and assembly of large cohorts, epidemiologic research—cohort and case-control studies—became the primary tools for generating evidence to inform public health

Fig. 2. The traditional pathway of discovery in public health and epidemiology.

The search for evidence about public health interventions, such as nutritional supplements (e.g. Vitamin D in milk; fluoride in drinking water), environmental and occupational regulations, or the use of policies to discourage harmful behaviors, historically has proceeded in a quite different way than clinical research. This pathway is depicted in Fig. 2.

interventions. For example, observations of the long-term health of workers in various industries revealed the hazards of materials like benzene or asbestos; evidence of dose-related excess heart disease due to the public's exposure to fine particulate air pollution led to regulations to limit noxious exposures. Importantly, for many health problems, overlaps in efforts between clinical medicine and public health researchers occurred as analyses of different data sources suggested the utility of interventions at both the population and the individual level, e.g. vaccines.

Such projects engaged researchers from both fields, who brought different tools and perspectives to the table, for instance the effort to control HIV-AIDS (Piot & Quinn, 2013). Other times, differing perspectives generated some stress, highlighted recently by the tension arising over optimal application of initially scarce PCR tests for COVID-19: should they be used primarily for clinical diagnosis, or for surveillance to track spread of disease? But while some bridges have been built across researchers in clinical medicine and public health, until quite recently public health decisions have been grounded primarily on evidence from observational data, though learnings have often involved application of the underlying mechanisms involved, such as the pathways for disease transmission, biologic basis for risk, or mechanisms of action "borrowed" from medicine. Use of criteria such as those promulgated several decades ago by Bradford Hill and modified over time has rendered interpretation of observational research more consistent and palatable to those more confident of experimental approaches (Bradford Hill, 1965; Bradford Hill et al., 2020).

1.2. Sea changes in the last two decades

The past two decades have witnessed enormous advances in basic biology. Not only can we sequence an individual's genome at reasonable cost, we but we can measure the epigenome, transcriptome, metabolome and the scope and spectrum of the microbiome. Combining these advances in biology and those in data science, we can now scale the depth and breadth of our research to study large cohorts in which each individual's biology is characterized with petabytes of data, exemplified by the explosion of GWAS studies (Mills & Rahal, 2019). The concurrent expansion of biobanking has further afforded researchers the ability to quickly leverage new research modalities even for rarer patient populations (Ahadi et al., 2020).

The same vast expansion has occurred in the clinic as medical information has become digitized, essentially rendering complete health records part of the potential research quarry. Combining these two sources of information—clinical and biologic—has already yielded exceptional information about the role genes play in virtually every clinical condition (Tam et al., 2019). These analyses have also suggested that genes alone do *not* account alone for the fraction of disease believed to be heritable based on earlier studies (Boyce et al., 2020).

New opportunities in the era of big data are further enriched by the availability of vast, detailed, longitudinal data on environmental, social, physical, and behavioral factors that could link biology and *social factors* of populations with long-term outcomes (Rehkopf et al., 2016). Potential sources include not only the large *administrative* datasets held by government and private organizations, but also the troves of personal data collected *transactionally* on each of us every day as we use our phones, computers, credit cards, and customer loyalty program cards. Additionally, there are the rapidly growing repositories of "user-generated" data from fitness, health monitoring, and other apps; the geolocation data generated from geotracking technologies embedded in cellphones and smart watches; social media tracking of who we interact with, when, and where and the recordings made of our physical movement as we steer our car, move our computer mouse, or work the screens of our smartphones. In essence, we are all undergoing extensive psychometric testing all day, every day.

Deferring for now discussion of the myriad privacy concerns this raises, at least two previously unimaginable opportunities for

translational research become feasible. First, because these data are obtained in an ongoing fashion and many historical datasets have been digitized, following people and populations across the life course becomes possible beyond the older, painstaking strategy of long-term cohorts (Humphreys et al., 2018). Second, we can better link health to the many different ways we each—individually—lead our lives. Of course, this would be impossible but for concomitant developments in computer and data science. These huge leaps—e.g., the cloud and evolution of machine learning (ML)—elevate the analytical possibilities far beyond the traditional modeling methods upon which statisticians and epidemiologists have long relied (Chen et al., 2020a).

1.3. The opportunity for translational research

Numerous obstacles must be overcome in order to fully and responsibly realize the promise of the new data age for translational research. Before turning to these, we lay out the opportunity under the most favorable possible trajectory: all impediments can be overcome, and the resources needed to fulfill the promise can be garnered.

Fig. 3 visualizes a new paradigm for translational research in which the centerpiece is linkable, individual-level data derived from large populations. It depicts a research environment in which sources of biologic, clinical, physiologic, environmental, sociodemographic, transactional, and behavioral data are available for whole populations—serially—to facilitate a life course data panorama.

Many kinds of questions could be addressed within this data ecosystem. At the person level, data spanning the life course should allow linkage between conditions at early stages in life and later health. Each of the observed factors—medical, environmental or social—could be studied to generate hypotheses similar to the so-called "Barker hypothesis" that *in utero* exposure to food insecurity leads to later-life obesity (Almond & Currie, 2011). Every medical intervention could be traced forward into adulthood, indeed all the way to mortality. Complex aspects of life, such as work environment, social and neighborhood effects, life-long dietary exposures and habits, sleep patterns, and virtually every intervention that doctors and the health care system impose would become amenable to scrutiny in relation to virtually any short or long-term health outcome of interest. Where biologic and physiologic data on a sufficient sample are available and of high quality, not only the outcomes but the pathways between early causes and later outcomes might be elucidated.

Perhaps most exciting in this vision is the potential for "personalizing" our knowledge of these relationship based on our ability to predict likely responses to various therapeutic or preventive options. Failure of traditional studies to elucidate the optimal lifestyle suggest that "one size does not fit all" as we have begun to recognize for many drugs and medical treatments as well (Agarwal & Ioannidis, 2019; Markozannes et al., 2016). Average beneficial or harmful effects—the primary output of clinical trials and most observational studies—are exactly what the term implies: *average* effects across the population studied. Yet as we recognize the substantial diversity among us based on our unique biology and biography, what we want to discover are person- or person-type-*specific* treatment effects. This is most especially true in the realm of prevention, where presently most guidance regarding lifestyle, behavior, and environment is generic (one size fits all) (Arnett et al., 2019). This potential has already spawned speculation about the potential to personalize dietary recommendations (Topol, 2019).

2. The challenges

The data we anticipate will be central to the vision for Population Health Science as a unifying scheme for translational research are already being collected, some with the active consent and participation of the subjects, most passively. Collection of more or new data, per se, will *not* be critical. Making those data safely and securely available to the broad scientific community; creating new and refining existing computer and analytic tools; revolutionizing the culture and beliefs of the scientific and wider communities; and translating into practice the evidence they produce are the challenges that need attention (Leonelli, 2019). We approach these issues under three rubrics: technical challenges, cultural issues, and legal and ethical dilemmas.

2.1. Technical challenges

First, technical challenges must be surmounted to assure translational researchers access to relevant data and the ability to safely use and share them. Certain core principles have become axiomatic, frequently summarized by the acronym **FAIR** (Wilkinson et al., 2016). First, the data need to be **F**indable. In other words, there must be dataset search engines. The data need to be **A**ccessible, either to acquire or analyze on a suitable computational environment. To function as research data they must as well be structured in a format recognizable to each user, following a common data structure with shared data definitions, referred to as being **I**nteroperable.

Finally, the data need to be **R**e-useable by new investigators. This requires extensive documentation, generally referred to as "meta-data"

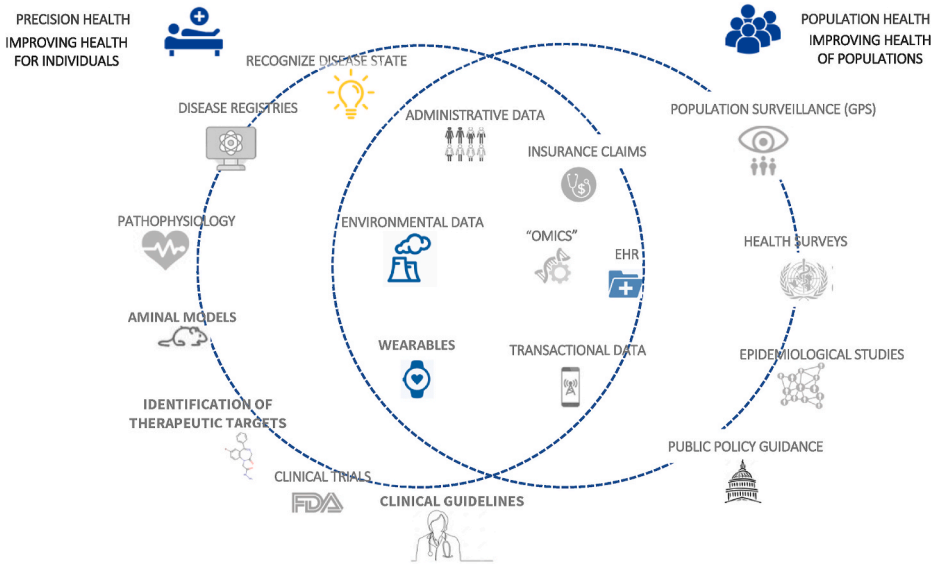

Fig. 3. A new paradigm for clinical translational research with large, linkable, individual-level datasets as the substrate.
Fig. 3 visualizes a new paradigm for translational research in which the centerpiece is linkable, individual-level data derived from large populations. It depicts a research environment in which sources of biologic, medical, physiologic, environmental, sociodemographic, transactional, and behavioral data are available—individually and longitudinally—for whole populations. Critically, while each byte of data is collected at a single point in time, those measures that change over time can be performed serially. Moreover, data from other points in time, including links to past administrative data, might be identified—imagine old tax and census records, birth and death certificates—and incorporated in such a way as to facilitate a life course data panorama.

which ensures all users know the assumptions, limitations, choices and concerns of the originators of the data. Only in this way can analyses be reproduced and replicated.

Government-held data meeting these standards, such as vital records, census, immunization registries, and all-payer claims data represent troves of unique researcher interest. While several federal agencies have collaborated with the Census Bureau to support the Federal Statistical Research Data Centers (FSRDC) (The Federal Statistical R, 2020) in making these granular data, including identifiable variables, available for research, the process remains cumbersome and expensive—all work must be done on site at one of the 31 centers—hence serving only a fraction of the potential research demand (Jarmin, 2021).

These requisites are also becoming a reality for the now more than 60 million individual datasets in wide use around the world that do **not** include proprietary, highly sensitive or otherwise personally identifiable information (PII). The challenge for health research is to extend such work to these sensitive datasets as well. While it is generally not necessary for a data *analyst* to have access to any directly identifying feature, the ability to merge datasets together—for example, to look at environmental measures in relation to health outcomes—demands that a data *manager* retains the means to link the files. In many cases precise geo-spatial information is sufficient. But even after the identifiers themselves have been stripped, the greater the number of variable fields on each subject, the easier re-identification becomes (Harron et al., 2017; Wirth et al., 2021).

Most often, at present, we evaluate requirements for datasets that do not include identifiers specifically enumerated in privacy laws by having institutional "experts" who render a judgment at the institutional level regarding privacy, hosting security and specific stipulations about user-access based on training and research credentials. The lack of standards for such classification is problematic, and the process fraught with potential for unwanted variation (McGraw & Mandl, 2021).

Of course, many datasets *are* high-risk. Efforts to mitigate their risks have proliferated, and are generally discussed under the concept of differential privacy, achieved by creating "synthetic" data—datasets with the same distributions as the original but in which no single file is unaltered (Boedihardjo et al., 2109). While possibly expedient in the short-term, such mitigations result in a sharp reduction in the long-term utility of the data, e.g. blurring geospatial coordinates, as have been done with many surveys to limit re-identification. Many partial technical fixes are evolving, institution by institution, from which hopefully will evolve a small number of best-in-show products that could be commonly adopted.

2.2. Cultural challenges

Four aspects of the present "culture" of the translational research community demand attention if the proposed vision for population health science can be achieved. First, there needs to be more universal expertise in the principles of this science among all those who contribute. Second, the present academic incentive structure for appointments, promotions and other rewards heavily rewards individual prowess and successful "labs," where teams are more likely to succeed going forward. Third, present deep biases in the relative value and utility of observational evidence, as opposed to that from randomized controlled trials will need to be reevaluated, and finally, the value of creation and sharing of critical research datasets must be more heavily rewarded. We discuss each in turn:

2.2.1. Training in population health science for translational researchers

Presently, research training in our academic medical centers (AMCs), and associated universities is well suited for the historic approach, illustrated in Fig. 1. Translational scientists, selected and promoted based on *individual* research prowess, garner the resources to embellish knowledge, typically in a narrow area, identifying collaborators with necessary ancillary skill sets or methods as needed. Core precepts, such as "prediction," "cause," or "standards of evidence," are relegated to specialists in those areas—biostatisticians and informaticians—and often adopted uncritically. Translational researchers in training, including MD/PhD candidates and post-doctoral fellows among others, have historically been taught far more about genetics and immunology than about applications of data science to clinical and population health problems, or causal inference; most are assigned to a wet lab very early on. Yet as we shift from the old paradigm, heavily dominated by development of animal or *in vitro* disease models in wet labs to the "information age" these imbalances and omissions will have to change.

Even as translational researchers increasingly make use of large datasets either as clinical research or in addition, they typically get more training in computer coding than in fundamental issues such as sampling strategy or analysis, or the difference between *predictors* of a health outcome and its (potentially treatable) *causes*. Invariably such investigators leverage the assistance of a colleague in informatics or statistics to apply the newest algorithms for machine learning or statistical testing, but revealingly, discussion sections of final reports focus more on putative biologic mechanisms —assuming the result is true— than critical assessment of the potential biases and limitations of study design (Giovannucci et al., 2008; Narod et al., 2019).

Two fundamental shortcomings stand out: 1) understanding the meaning of the "population" exploited for such research, and 2) confusion between *prediction* and *cause*. We elaborate on these two issues to illustrate the critical need for *all* translational researchers to be co-trained in data science broadly as, in the past, all have been trained in basic human biology.

So what is a "population," anyway? The term is now widely used to describe any large number of people with one or another feature in common, for instance: all 3 million people who have received care at a particular hospital; 12,000 patients with inflammatory bowel disease assembled from multiple patient registries; 10,000 participants in a public survey; or all children born in Denmark (Bengtsson et al., 2019).

No machine learning algorithm will discern, or alert an unprepared investigator to recognize, that inferences drawn from each of these "populations" will be different: some more representative than others of a larger population to which inferences may later be applied.

A parallel problem is the increasing, but potentially uncritical use of predictive models appearing in the biomedical literature (Luo et al., 2016). User-friendly statistical packages and their increasing availability make such analyses easy to conduct, but both users and consumers of resulting studies may lack understanding of what the models imply. There are many reasons one characteristic of a subject might "predict" a subsequent event: Fever in is a strong predictor of sepsis, but hardly a cause. Zip code is a strong predictor of excess hospital utilization but not a viable intervention target for individual patients (Chen et al., 2020b). Many of the strongest correlates of risk from Covid such as race and ethnicity have proved largely due to other, initially unmeasured factors such as essential occupation (Asfaw, 2021). Even strong correlates of outcome can be badly confounded, like serum beta-carotene, shown repeatedly to be a strong predictor of low cardiovascular and cancer risks, yet when tested as a supplement in an RCT it proved lethal (Omenn et al., 1996; Shekelle, Liu, Raynor, Lepper, & Maliza, 1981).

This is not to say we require knowledge of causal pathway or mechanism of action to optimally prevent or treat. Indeed, as we will discuss below, one of the putative benefits of RCTs as a source of evidence is that they typically *don't* require many assumptions about why one arm of a trial may prove more successful than another. But what we do want to have is evidence that modifying the single factor on which we intervene will (at least on average) improve an outcome of interest.

2.2.2. Translational science as a team sport

Many institutions recruit trainees and faculty for translational science using the principle of "best athlete"; the individuals most likely to achieve stellar personal success. Even where overall balance of faculty is

considered, the aim is not team building but breadth. And while most learn quickly the importance of cross-specialty input in preparing grants and papers—adding a statistician here, an economist or engineer there—the incentives for success are squarely on the "PI," who will be judged by the impact of their first and last authored papers in journals deemed of highest value to the PI's department.

Recognizing the limitations of such a structure, the notion of "team science" as integral to translational medicine research has achieved some cache over the past decade. Two distinct meanings have evolved. One is the concept of "broadly engaged team science" referring to the critical inclusion of all of the actors in late-stage translation, from trials to implementation. The focus of these teams is on inclusion of nonmedical professionals, patients, and members of stakeholder communities (Selker & Wilkins, 2017).

The second meaning refers to teams of scientists of very different skills and motivations who assemble to address problems that extend beyond the scope any one discipline. The COVID-19 pandemic offers a striking example: virologists, immunologists, geneticists, chemists, physicians, demographers, epidemiologists, computer scientists, mathematicians, economists, engineers ethicists, legal scholars, health behaviorists, health communications experts, and political scientists all play major parts. But this effort occurred under the extreme circumstances of a shared public and clinical health crisis, and has not been normative. To fully realize this conception of team science will require reorganization of existing research organization, with configurations of transdisciplinary teams, not PI labs "with consultants." Efforts to explore how such teams form, function, and survive in an academic universe not optimized around outputs that transcend narrow disciplinary norms has begun (Committee Toward an Open Science Enterprise, 2018; Stokols et al., 2008), but remains in its infancy.

2.2.3. *Hierarchies of evidence: critical acceptance of observational research*

The availability of rich population-level data could serve to markedly advance the efficiency and interpretability of many RCTs. For one thing, established "cohorts," with proper respect for privacy, can offer a ready-made template for trial recruitment; the preliminary observational analyses may further suggest an ideal sampling frame, pre-specifying subgroups for potential differential responses to the treatment in a prospective manner, and for addressing issues in generalization from recruits to larger clinical populations (Westreich et al., 2017). Once the study group has been selected, comparison with the larger observed population data could provide critical insight into how the study volunteers may, once selected, differ from the other potential subjects, impacting the interpretation of results and offering insight into the generalizability of the treatment effect measured.

But by far the biggest "gain" from the envisioned data-centered translational research universe will come from enhanced attention to the observational data themselves. And it is in this regard that the (presently) limited conversancy with the theory and practice of population health science among researchers in translational science has become rate-limiting. A strong belief has developed within the research community in which the evidence from randomized controlled trials is considered of materially greater value to decision making than observational data, however thoughtfully collected and analyzed, however well supported by ancillary scientific data (e.g. effects in animals) and however plentiful (i.e. replicated). There are very sound scientific reasons that experimental (RCT) data have achieved this preeminence, most notably that random assignment *is* the surest way to avoid the many "confounders" as noted above. Confounders include easily recognized and measurable relationships, e.g., smoking in examining the relationship asbestos and lung cancer (Klebe et al., 2019), or much harder to assess factors, like diet or stress. Most vexing of all for observational research are the myriad sources of "selection"—people and their doctors make choices for all sorts of reasons that themselves may be associated with different outcomes and generally difficult to directly observe.

Without disparaging the extraordinary benefit conferred on population level research by randomization, we propose to bring a pause to the often unbridled enthusiasm for the RCT as a research tool (Wang et al., 2015). Notwithstanding the biggest problem—many critical questions are not amenable to RCT for ethical or practical reasons—trials also have significant limitations (Deaton & Cartwright, 2018). Two concerns appear most salient. First is the belief that because neither measured nor unmeasured confounding factors can, by design, be correlated with treatment assignment in an RCT except by chance, no bias can creep in unless studies are poorly conducted. While this may be true for an 'instantaneous' assignment, where the entire treatment immediately follows randomization (such as surgery vs. stenting for CAD), non-random treatment "drift" occurs in trials that require longer treatment periods, as patients (non-randomly) drop out, take other interventions to treat side effects or even seek a supply of the active agent being tested. Use of the "Intention to Treat" approach provides a conservative solution for small drifts, but not larger divergences between assignment and treatment (Robins & Greenland, 1994). While strategies to adjust for these "late" biases have been developed, they involve approaches not unlike those used to address bias in observational studies (Hernán et al., 2013).

Perhaps the deeper limitation, though, relates to the output of RCTs: *Average* treatment effects (ATE, the absolute difference between prespecified outcomes in treated vs. control arms). Neither biographical not biologic attributes of subjects that may lead to heterogenous responses can be confidently estimated even for prespecified subgroups of interest because such subjects are typically too few compared to what could be observable in a study with real world data, such as post-marketing observations once an intervention is approved. As a result, RCTs have limited value in the effort to actualize "precision" or "personalized" medicine. Efforts to exploit large observational datasets as an alternative to exploring for heterogeneous effects have begun in earnest (Bodnar et al., 2020; Daoud & Johansson, 2019).

In the (Bayesian) scientific framework in which every study is premised on a foundation of prior beliefs, the notion that observational studies can only provide hypotheses for subsequent experiments is no longer tenable. Respectable observational studies demand a well justified conceptual framework in which all known or suspect causes, and their suspect inter-relationships are as prespecified as design of any RCT (Hernán & Robins, 2016; Robins, 1987). More than one hypothesis can be tested, with careful attention to statistical inference when multiple outcomes are considered simultaneously (VanderWeele et al., 2020; Vansteelandt & Dukes, 2020). In particular, where N is large and observations are rich, specific relationships between subject characteristics and outcomes of intervention can be tested. Methods have evolved over the last several decades to address biases, such as substitution for actual assignment by so-called "instrumental variables" (Marra & Radice, 2011; Rodu & Baiocchi, 2001) long used in economics—and dynamic marginal structural models for time varying covariates of concern (Robins, 1986). Newer methods are under exploration which would exploiting increasingly-available biologic "intermediate endpoints" (Athey et al., 2019). A novel contribution to the methodologic armamentarium, exploiting large data sets which have been genotyped, is "Mendelian randomization"—using the random assignment of measurable alleles as an instrumental variable to study environmental factors known to be directly impacted by that gene (such as variants of Apo E) (Smith, 2010). Myriad limitations of observational studies continue to be highlighted (Collins et al., 2020; Davey Smith & Phillips, 2020), while relevant concerns for interpretation of RCTS are typically ignored or downplayed.

In the end of the day both RCTs *and* observational studies are invaluable tools for translational research. No one doubts the importance of RCTs for definitive testing if new therapies confer more benefit on average than harm, as is apparent in the rush to treat COVID patients in the present pandemic. That said, much about the impact on health of human behaviors and exposures—including the role of medical

interventions and treatments—may best be learned from skilled analyses and inferential reasoning of increasingly rich person-level data.

2.2.4. Data sharing challenges

The transition to a research universe built on rich observational data cannot occur unless researchers can actually access these data. One persistent access barrier is the prevailing tendency of the research community to hoard academic assets once they are generated or obtained (Tenopir et al., 2011). Such hoarding not only detracts from the potential of population health science to generate new discoveries, but also hampers efforts to reproduce and replicate findings.

Presently, markets for research data appear to be absent from the academic marketplace. Researchers in all fields have historically exchanged data resources among small groups of collaborators, but in most, the practice of open data sharing has not evolved into a buoyant data market. Because the accumulation of academic reputation and credit is garnered primarily by high-impact publications (Nosek et al., 2012) and pioneering discoveries (Strevens, 2003), scientists are disincentivized to share research data. In addition, scientists in some fields face disincentives to act as customers of openly available data due to a perception that papers using such data are less impactful than primary (Wickham, 2019).

Over the last decade, the importance of data sharing for reproducibility, transparency, accelerated discovery, and collaboration has been recognized among stakeholders, including funding agencies, science agencies (Committee Toward an Open Science Enterprise, 2018) and academic journals (Alberts et al., 2015; Nosek et al., 2015). A growing number of journals encourage (and some mandate) making data supporting articles available (Vasilevsky et al., 2017).

Despite efforts to "open" data (and hence science), academic data exchanges to date lack an essential precondition for functional marketplaces: thickness (Roth, 2007). Too few scientists participate, because the data market is disconnected from the academic markets of scientific credit (Merton, 1973; Pierce et al., 2019) hiring and promotion (Moher et al., 2018). Shifting the culture to foster more data sharing will require research institutions to revise criteria for advancement to include production and sharing of high-value datasets. It will require journals to strengthen and enforce data-sharing requirements, and funders to better recognize the potential long-term value of expensive, laborious efforts to prepare high-quality data for use by others and facilitate its broad sharing.

2.3. Legal and ethical challenges

Of course, no matter how collaborative the research community becomes, much of the most relevant data arises not from academic research per se but from administrative data collection and curation as in health care and other daily business and government transactions. Access to—and responsible use of—the observational data crucial to the future of population health science hinges on our ability to address a spate of legal and ethical issues. Chief among these are concerns about data privacy and security and data use agreements (Ienca et al., 2018; Metcalf & Crawford, 2016; Mikal et al., 2016; Mittelstadt & Floridi, 2016; Rothstein, 2015; Stahl & Wright, 2018; Vayena et al., 2015).

2.3.1. Data privacy and security

Repeated reports of large-scale data security breaches has drawn attention to one harsh reality of the modern world described dispassionately above: we all live "under surveillance." Although reasonable people could debate the degree to which this is relatively benign or worrisome, it is clear that individuals have limited ability to control how much information is collected about them and how it is used. Some have curtailed their digital footprint by keeping Alexa and her friends out of their homes, limiting use of apps and online services, and setting their devices to strict "do not track/do not share" modes. But they do so at the expense of all of the services these apps and devices could provide, for free or at very low cost. Others concerned about data security and privacy have pushed for more regulation, in the form of strict limits to which data can be collected and how those data may be used. Yet others have pushed for a more market-driven solution, in which all personal data would reside legally and exclusively in the possession of the person *on* whom—not *by* whom—they are collected, leaving individuals in a position to sell or license some or all to bidders of their choice (Sonin et al., 2021).

The *privacy* of health information is only one among many related issues about big data that are currently under societal debate, but it has achieved particular salience. This stems in part from special protections given health data by law in most countries—so-called "health data exceptionalism." Also relevant is the widespread perception that health information is more intimate than information about other aspects of our lives, despite evidence that people may be even less forthcoming about, for example, their income (Tourangeau & Yan, 2007). In the realm of data *security*, health information actually has lower salience: it is less valuable to hackers than personal information that more directly facilitates lucrative crimes. It is relatively easy to identify potential harms caused by improper use or disclosure of health data. What is more difficult to measure is the opportunity cost of *failure* to use these data to their highest and fullest extent. As population health science advances three thorny privacy-related problems must be resolved.

First, the commercial-sector data ecosystem is too opaque. Most individuals have little or no awareness of the nature, scope, and value of the data trades they make every day when they use the internet and their devices. Put simply, "nearly everything done online involves trading personal information for things of value" (Cohen & Mello, 2018). Even information that is not, on its face, about health (for instance, income or neighborhood of residence) is useful—and increasingly used—to support modeling and inferences about health (Cohen & Mello, 2018). The world of commercially traded data is especially difficult to penetrate, but individuals may not even be aware of how their EHR information is used and passed on to third parties by their healthcare providers (Cohen & Mello, 2019). Nor are most individuals aware of the potential value of making these data—with proper privacy and security protections—available for observational research studies. Both sides of this issue should be elevated in the public consciousness so that those designing regulations and making everyday decisions about sharing their personal information can weigh the advantages and disadvantages in a more informed and deliberate fashion. For example, while few would doubt the public benefit that has accrued from the efforts to corral and analyze data on COVID-19, many would be disturbed to learn that no public tracking system in the US provides health investigators routine ongoing access to which individuals received the various vaccine preparations which would enable active adverse event case reporting reminiscent of a much earlier era in public health (Centers for Disease Control and Prevention, 2021).

Second, despite the potential for more informed decision making, there is reason for skepticism about perpetuating an information privacy regulatory scheme that leans on the notion of individual consent (McGraw & Mandl, 2021). Privacy laws in the US and abroad seek to ensure that individuals have an opportunity to authorize uses of their data to the maximum extent possible. The federal Health Information Privacy and Accountability Act (HIPAA), for example, provides that healthcare providers who collect identifiable health information electronically cannot disclose it to others, except for narrow purposes relating to treatment, healthcare operations, and public health reporting, unless patients authorize the disclosure. For research purposes, designated "Privacy Boards" (typically institutional review boards, doing double duty) can grant a waiver of this requirement, but only if several conditions attach, such as the impracticability of seeking patient authorization.

While the idea that patients should be able to control uses of their health information has strong intuitive appeal, it consistently falters upon execution (Canino, 2016; Kim, 2013; Meinel, 2016). Every patient

who has been asked to sign a HIPAA authorization form would agree that the process of reviewing and agreeing to these wordy, legalistic documents bears little resemblance to meaningful informed consent. Executing individual consent in the online context is even more farcical: research demonstrates that consumers do not read online privacy policies and end-user license agreements; moreover, even if they did, online service providers offer few or no alternatives to agreeing to the terms. In short, these permission-giving rituals are often hollow exercises that fail to effectuate the goal of meaningful consent and control over personal information. Yet, privacy law continues to rely upon them (California Office of the Attorney General, 2018; Wolford).

Third, health information privacy regulation relies on an outdated notion of "deidentified" data (McGraw & Mandl, 2021). When data are shared without personal identifiers attached, the transfer and use do not implicate the regulatory frameworks we have relied on for decades to protect individuals: federal human subjects research regulations and federal and state privacy laws (Cohen & Mello, 2018; Kaye, 2012). These laws date to a time in which reidentifying data that lacked personal identifiers was a practical impossibility, but advances in computing have greatly enhanced the technical feasibility of re-identification through data triangulation and hashing (Cohen & Mello, 2018; Kaye, 2012; Price & Cohen, 2019; Stead, 2017). "Deidentified" is increasingly recognized as a relative condition. Companies routinely approach health delivery systems to obtain "deidentified" patient health data (Farr, 2018). Although the datasets can be rendered "anonymized" based on deletion of PII, techniques to link the records with existing data are abundant (Harron et al., 2017; Wirth et al., 2021). Although such linkages have the potential to elucidate important and otherwise unanswerable questions about the relationships between social behaviors and health, the proposed arrangement would likely raise patients' hackles, but does not violate US law, suggesting the need for approaches to more thoughtfully weigh and adjudicate trade-offs.

Recently enacted privacy laws such as the CCPA (California Office of the Attorney General, 2018) and GDPR (Wolford) impose more stringent standards for considering a dataset deidentified, but do not decouple information privacy regulation from a determination about whether or not data are identifiable (McGraw & Mandl, 2021). Because current privacy laws push investigators to strip identifiers from datasets in order to reduce the risk that a privacy board or institutional review board will require them to seek individual consent for new uses of the data, they undercut potentially productive uses of data and limit the prospects for population health science. Consequently, scholars have suggested a need to reorient the law to "protect privacy while minimizing the cost to innovation" (Price & Cohen, 2019).

It is not even clear that the current regime addresses the concerns that animated its adoption. Although many consumers are concerned about potential consequences that may flow from wrongful disclosure or misuse of their identifiable personal information, for others the mere awareness that their personal data are accumulating on servers and in clouds of various organizations, including government, without their explicit consent, is *in of itself* a "harm" (Sonin et al., 2021). These individuals would *not* in general be willing to allow the use of their data even in putatively deidentified form. Indeed, some resist even participating in the U.S. Census and would not likely volunteer their data for any initiative without strict control over all present and potential future uses. While it is unclear what fraction of any population shares this perception, the moral weight of their argument offers a potent challenge to the open accessibility by researchers to population data.

2.3.2. Data use agreements

One factor impeding the efficient flow of data between data generators (including government agencies, private companies, and academic researchers) and secondary users in the research community is the length of time it takes to execute data use agreements, or DUAs (Major et al., 2020). These legal contracts, which spell out the rights and responsibilities of data generators and users and the remedies available to each party for breaches of the agreement, are negotiated on behalf of academic researchers by university administrators, and by legal counsel on behalf of nonacademic institutions. They are complex contracts, which augurs lengthy wait times for negotiation and execution (Microsoft, 2022; O'Hara, 2020). This can deter many investigators from seeking access to the best sources of data for their scientific question when inferior but more accessible sources appear to suffice (Mello et al., 2020). The exigencies of negotiation also may lead to compromises on DUA provisions that threaten researchers' academic freedom or ability to share data with others in the scientific community (Kanous & Brock, 2015).

Some problems contributing to delays in executing DUAs have ready solutions—for example, universities can increase staffing of the offices that handle them and create better portals for researchers to submit requests for a DUA (Mello et al., 2020). Some delays arise from persistent disagreements between the parties about particular provisions, however, e.g., data generators often demand data security architecture that is incommensurate the data risk profile or does not exist at universities (Mello et al., 2020; Saunders et al., 2015). For their part, universities insist on protecting researchers' rights to publish their research results, while many private companies are not acculturated to the importance of such freedom as a norm of academic science. On other matters, universities tend to resist making concessions with less justification: they may refuse to indemnify data generators in the event someone sues the data generator over some aspect of the research, for instance, although the actual risk of such a lawsuit is so low that it is not worth obstructing research over (Mello et al., 2020).

Perhaps the most fundamental obstacle to the timely execution of DUAs is that many private data generators, like academics, lack incentives to share data (Mello et al., 2020). Government and private companies generate an enormous amount of data of tantalizing research utility, but typically have no mandate or market incentive to allow researchers to use them. Possible exceptions include those in the business of healthcare itself, such as large public and private organizations that pay for healthcare or profit directly from it, such as pharmaceutical companies. Organizations in this sector have a positive incentive because of the economic value study results could produce, but also the reputational threat and potential liability that any breach or even public revelation of the research could present. For a great many other organizations, especially those in the digital-services business like Google and Facebook, managing, packaging and selling data for various kinds of analyses *is* a core business; there is no need to collaborate with academic researchers. Even when a company does perceive a business advantage from having a researcher answer a particular question, circumstances may change mid-course (O'Hara & Nelson, 2019). This creates an uncertainty hazard for the academic research enterprise, which relies on secure arrangements to assure completion of student projects and adherence to the rigid timelines of research grants and contracts.

3. Pathways forward

We have described a potentially exciting future for translational research, but also several challenges that must be surmounted to reach it. Next, we identify strategies for addressing the technical, cultural, legal, and ethical conundrums identified.

3.1. Addressing technical challenges

Simply put, the technical challenge is to achieve a state where qualified researchers working towards the broadest aims of translational clinical and public health research can avail data that are "**FAIR**" while at the same private and secure. While developments proceed on each component of this ideal condition—e.g., development of a standardized and automated instrument to assess re-identifiability of any data set, or machine learning tools that can rapidly "harmonize" data using differing data models—the ultimate ambition is to create safe research

ecosystems that incorporate these principles and are practicable in the research climate: It must be feasible, even attractive, for translational researchers in all settings to take full advantage. The trend has been towards development of "enclaves"—servers where the data of many relevant kinds are available with reasonable cost and effort, meet FAIR standards, and outputs of data off the enclave are surveilled for privacy risk.

Several specific efforts to achieve this merit special attention. First, the FSRDC model developed by the US Census Bureau, discussed above, is a useful exemplar for other governmental agencies to consider adopting (Jarmin, 2021; FSRDC, 2020). Importantly, not only are the number of available sites expanding but other governmental organizations in the US and around the world, are exploring smaller models, auguring a potentially rich role for the public sector in further development. (S special issue: data) The simple step of developing State All-Payer Claims Data troves for research now underway in many states, may be an important baby step in this direction (APCD Council, 2020).

Universities (Georgetown, 2022; Stanford, 2022) are also developing resources of this kind, if only as a stop gap to achieve data access to social and biomedical researchers on their own campuses. Nor is the private sector uninvolved: a consortium of private data vending and tech firms has been a leader in the provision of real-time, granular clinical and social data on the US population during the pandemic, providing a resource both to government and academic researchers when such data were not otherwise available (Datavant, 2022). Whether any of the non-governmental models is sustainable remains unproved, but momentum has been enhanced by the pandemic.

But to assure the future infrastructure of translational medicine will require that the major translational research funders—government and non-profit foundations—need to begin to enhance their investments and better coordinate their efforts. Presently, NSF, many of the NIH Institutes and Centers, and myriad foundations, global and domestic, have jumped into the fray to fund the underlying data science *methods*, for example novel approaches to differential privacy, or common data model development. But while advancing methods, including enhanced strategies for causal inference, are critical needs, they alone will not solve the broader infrastructure problem to achieve FAIR data, practicably available for all translational researchers.

3.2. Overcoming cultural barriers

The cultural barriers we have identified are possibly more formidable than the technical ones. Improving training in population health science; strengthening incentives for team science and data sharing; continuing to develop best practices for observational studies to build confidence that they belong higher up in the evidence hierarchy; and enhancing the incentives for data creation and sharing all must be pursued as part of the "long game" for translational research.

The most immediately actionable step is to begin enhancing the data and population science curriculum of medical and biomedical graduate students developing careers in translational research. For some training programs, such as MD/PhD programs, it might make sense to add such training as a prerequisite for admission rather than try to shoehorn it into the already crowded curriculum, or to encourage joint training programs with better established tracks in public health schools or programs. For others (e.g., post-doctoral research fellows in clinical departments), requirements and support for such training should become the norm. As these changes to training unfold, key allies of adding population science to the curriculum may be those waging the still-lonely fight to enhance scientific integrity and transparency.

Hiring, promotion, and recognition processes must further evolve to reward decisions to share rather than hoard, and to devote time and effort to creation of tools and resources that help others advance the field. The widely applied "impact" criterion could, for example, be interpreted broadly to include not just the ways in which scientists' research has changed thinking in the field, but also the ways resources they have created have enhanced the impact of others' research. Medical schools have already found ways to reward other material contributions faculty make, such as new technologies and intellectual property, patient referrals to trials, and the like; similar rewards could be developed for data-related contributions.

Two things need to happen first. There must be a simple way to count these contributions. The designation of standardized approaches to referencing datasets by journal editors, requirements that these be cited with every use of data, and establishment of standard ways of presenting them on CVs are crucial steps. Second, studies of "data markets" should be launched to establish the value to science of such contributions. The COVID-19 pandemic, which has brought unprecedented openness in the forms of preprinting and data sharing, may provide just such a natural experiment.

COVID-19 has also reinforced the value of team science: the problem is vast, multifaceted and not amenable to the solution a single lab could provide. Understanding the roles of host-factors, work, social behavior, and physical environment have been just as important to disease control as bringing vaccines to market at unprecedented speed. The value of team science will, in our view, win out over time without much additional deliberate intervention or promotion; our biggest immediate challenge is to train our workforce to adapt to and embrace this change. One idea to foster this is to re-examine the century-old split between schools of medicine and schools of public health, with an eye towards the emergence of "Schools of Health Science."

Finally, how can the culture of science be shifted to promote confidence in observational studies and disrupt established hierarchies of evidence? Clearly it will be important to further explore the limits of causal inference from observational data and develop of new methods and tools to address them. Research funders should earmark a pipeline of funding for this purpose. The ultimate objective is to enhance the utility of our growing trove of observational data and reduce reliance on RCTs to the settings in which they will add the greatest incremental value.

3.3. Approaches to the legal and ethical dilemmas

The legal and ethical dilemmas confronting translational science require a host of responses both short- and long-term. Increasing transparency around the "data trades" we make as consumers and improving public understanding of the actual and potential benefits of permitting responsible use of personal data, can and should begin now, while the pandemic experience is fresh in the public eye. Technical solutions to privacy problems should also continue to be pursued with vigor. New methods of safeguarding data and minimizing reidentification risks within and across datasets can help avoid wrenching decisions about whether to strip out useful but potentially identifying data fields from research datasets. They could also help build public trust.

A third short-term strategy for easing legal tensions is to promote standardization of the terms of data use in DUAs. Data generators and would-be recipients should not waste precious time haggling over points that should be non-negotiable (Mello et al., 2020). One promising development is the Federal Demonstration Partnership (FDP) project, in which 10 federal agencies and 90 research institutions are collaborating to identify ways of improving the efficiency of research; early efforts have focused on development of standardized DUA templates (Mello et al., 2020). In addition to supporting this approach, universities should increase staffing in the offices responsible for negotiating DUAs, recognizing that their workload has greatly expanded (Mello et al., 2020).

The long game for addressing legal and ethical tensions in observational research will be won by recentering our privacy protection regulatory regime so that it no longer balances precariously on the unstable pillars of individual consent and deidentification (McGraw & Mandl, 2021). In some contexts, such as prospective collection of observational data as part of a research study, it is both feasible and reasonable to require researchers to engage in an informed consent process with

prospective participants. But for secondary uses of information obtained for other purposes, whether online or in the physician's office, the hollow consent rituals that now dominate should be replaced, or at least joined, by deliberative, group consent approaches. As Cohen and Mello have argued in reference to secondary uses of EHR data, "Authorization that is individualized, upstream (i.e., obtained early), and typically one-and-done can be supplemented with governance that is group-based, downstream (i.e., obtained at the time of particular uses), and ongoing" (Cohen & Mello, 2019).

Two notable features of this approach is that the permission attaches not to the transfer of personal data but to specific uses; and that decisions are made by a multi-stakeholder committee that includes patient representatives but also experts in information technology and other fields who understand the potential privacy and security pitfalls associated with particular uses (Parasidis et al., 2019). Data ethicists have described other elements of a "systematic oversight approach" to data governance that would help undergird the oversight structure with more than the eroding concepts of individual consent and deidentification, and better balance the goals of protecting privacy and facilitating socially beneficial uses of personal data (McGraw & Mandl, 2021; Price & Cohen, 2019; Vayena & Blasimme, 2018).

Whatever permission-giving structures are adopted, it is clear that their remit going forward must include consideration of secondary uses of "deidentified" data. The assumption that uses of such data are risk free is simply outdated. Privacy laws should evolve to reflect this reality (McGraw & Mandl, 2021); their applicability or inapplicability to particular data transfers or uses should turn not on the presence of personal identifiers per se but on a broader assessment of risk and societal benefit. Further, these assessments should be made in a way that accounts for the rapid evolution of methods for triangulating and linking datasets.

In closing, we recognize the changes we propose are a tall order, and that resistance will continue to emerge from virtually every sphere. Rather than belabor the difficulty of that "squeeze," we choose to emphasize the "juice"—the enormous window of opportunity and potential benefit to every patient and individual who dreams of having decisions about their care guided by robust, highly specific evidence about patients like them while decisions around matters of public interest are guided by the best available evidence.

Author contributions

All authors shared in the design and approach to the paper. MRC was the lead author on this paper and responsible for the bulk of the writing. MB was made significant edits and contributed to sections on causality, LC made significant contributions to the conceptualization of the models in Figs. 1 and 2. IC, AO and SR contributed to the paper overall and made significant contributions to the discussion of data markets, legal and ethical issues around data sharing. RIH was made significant edits and wrote sections of the introduction and discussion, MM was largely responsible for the content sections on Data Use Agreements and Legal and Ethical Dilemmas.

Declaration of competing interest

The authors have declared that no conflict of interest exists.

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Common Models and Sub-Processes Inherent in Translational Research: Public Health Examples of Science for the Public Good

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Abstract

This study provides a formal review of eight of the most commonly cited models, frameworks, and approaches to translational research in public health. Translational research is defined as the process of moving scientific and other innovations into widespread use, and the authors suggest that such activities culminate in the use of proven practices to solve societal problems. Three critical subprocesses inherent in translational research are described: (a) knowledge generation, (b) translation, and (c) widespread implementation of proven practices. Implications for translational research professionals and organizations, mostly related to public health innovation and promotion of evidence-based practices, are discussed.

The purpose of this critical review is to understand how aspects of existing translational research models, frameworks, and approaches might guide self-identified translational research professionals and generate lessons that can be applied within organizations focused on translating scientific knowledge to practical contexts. Brownson et al. (2018) argued that individuals and organizations must be equipped with the capacity to effectively use evidence to promote public health and other interventions focused on enhancing well-being. Thus, the main focus of this study is process models and guidance related to the day-to-day activities of professionals engaged in developing and implementing evidence-based practices. The authors acknowledge that even though this review focuses predominately on public health innovation, there are many other segments of society (e.g., environmental science and policy) that engage in translational research.

This review analyzes practices employed by a center that conducts translational research within a research-intensive university in the United States. This center, referred to here as The Center, is the context for this case analysis. The Center has long been engaged in the implementation of evidence-based practices to address problems in schools, organizations, and communities. Typical projects focus on developing training resources, initiating program evaluations, and developing and implementing testing procedures to assess employee skills and competencies. Such projects are based on contractual arrangements that specify deliverables and dates when specific work tasks are to be completed. The development of an organizational strategic plan provided the impetus to revise The Center's mission and placed significant emphasis on what was referred to as "translational research."

Translational Research

Morris et al. (2011) noted that 17 years is often touted as the estimated time lag between the development of medical innovations and their application in practice. The authors of this paper note that convergence around an average time lag ignores the complexities of policy development and practice and the fact that some lags may even be beneficial. However, others argue that every effort should be taken to expedite the development and evaluation of evidence-based interventions that have the potential to address societal problems and enhance well-being. Translational research may serve such an accelerating function.

The National Center for Advancing Translational Sciences (2015) defines *translation* as the process of turning observations in the laboratory, clinic, and/or community into interventions that promote well-being. *Translational science* is the field of investigation focused on understanding the principles that

underlie the steps of the translational research process. Rubio et al. (2010) defined *translational research* as the multidirectional integration of basic research, patient research, and population research with the aim of improving the public's health. Woolf (2008) noted that, in large part, the focus of translational research is "harnessing knowledge from basic sciences" to produce new treatment options for patients (p. 211).

While most prominent in the medical sciences, translational research has gained traction in recent years in other fields that seek to use scientific evidence as a foundation for developing and implementing interventions to promote well-being. Reviews of the literature suggest a bevy of models, frameworks, and approaches for moving scientific innovations from concept to practice. For example, Tabak et al. (2012) identified 61 different models or approaches related to implementation and dissemination of knowledge. A recent review of the literature focused on public health intervention identified 41 translational research models described in literature published between January 1990 and December 2014 (Milat & Li, 2017). This review included a keyword search of PubMed—"(translational research OR knowledge translation OR evidence to practice) AND (framework OR model OR theory) AND (public health OR health promotion OR medicine)"—which resulted in the identification of 98 manuscripts.

Importantly, Milat and Li (2017) identified a number of commonly applied models in public health (see Table 1): (a) RE-AIM, (b) translational research continuum or T models, (c) knowledge to action, (d) promoting action on research implementation in health services (PARiHS), (e) evidence-based public health (EBPH), (f) stages of research progression, (g) the interactive systems framework for dissemination and implementation (ISF), and (h) the UK Medical Research Council (MRC) framework. This is but one example of the identification of approaches to translational research. For example, theory related to translational research has been incorporated in psychology (Provenzano-Haas, 2017), social work (Teater, 2017), education (Nadeem et al., 2018), criminology (Sullivan et al., 2017), and business (Wofford et al., 2011). Another example is McNie's (2007) review, in which the author examined literature from a variety of disciplines on "reconciling the supply of scientific information with users' demands so that scientists produce information that decision makers need and use in policy decisions" (p. 17).

Along similar lines, Teeters and Jurow (2019) pointed out that "research that links action across multiple scales of practice is particularly relevant for organizing consequential social change" (para. 1). The authors worked on an evaluation framework that included five dimensions of community-engaged research: (a) establishing partnerships, (b) developing trust, (c) working

Table 1. Commonly Applied Translational Research Models, Frameworks, and Approaches (adapted from Mitlak & Li, 2017)

Name	Descriptive Literature	Description of Steps, Phases, or Activities
RE-AIM	Glasgow et al. (2012), Glasgow et al. (1999)	**Activities related to five phases or questions relative to a specific intervention:** **(a)** reach, or participation in the intervention; **(b)** efficacy, or the success rate of the intervention; **(c)** adoption, or use of the intervention across multiple settings; **(d)** implementation, or use as designed; and **(e)** maintenance, or sustaining intervention over time.
Translational research continuum or T models	Glasgow et al. (2012), Khoury et al. (2010), Westfall et al. (2007)	**Five-phase research continuum:** **(a)** T0: problem definition; **(b)** T1: research allowing for the development of clinical interventions; **(c)** T2: research focused on health outcomes; **(d)** T3: research designed to increase uptake; **(e)** T4: research related to impact in real world settings.

Knowledge to action framework	Graham et al. (2006)	**Knowledge creation and action are the primary phases of activities. The action phase consists of seven steps:** **(a)** identifying the problem, **(b)** adapting knowledge to the local context, **(c)** assessing barriers to using knowledge, **(d)** implementing interventions to promote knowledge use, **(e)** monitoring knowledge use, **(f)** evaluating outcomes of knowledge use, and **(g)** sustaining knowledge use.
Promoting action on research implementation in health services (PARiHS)	Kitson et al. (1998)	**Three phases or dimensions are considered simultaneously:** **(a)** evidence, which includes a combination of research, experience, and acceptability; **(b)** context, which is the setting in which the intervention is implemented; and **(c)** facilitation, which refers to creating conditions that allow for implementation.
Evidence-based public health (EBPH) models	Brownson et al. (2009)	**Consists of a seven-step process:** **(a)** assessing the community, **(b)** quantifying the issue, **(c)** developing a concise statement of the issue, **(d)** determining what is known through the scientific literature, **(e)** developing and prioritizing responses, **(f)** developing an action plan and implementation, and **(g)** evaluation.
Stages of research progression model	Bauman & Nutbeam (2014)	**Four phases of activities:** **(a)** understanding the problem, **(b)** assessing outcomes of exposure to intervention, **(c)** assessing fidelity of implementation under real-world conditions, and **(d)** assessing rollout across jurisdictions and systems.
Interactive systems framework for dissemination and implementation (ISF)	Wandersman et al. (2008)	**Three interacting systems that engage in specific and complimentary activities:** **(a)** the Prevention Synthesis and Translation System compiles and summarizes information about innovations and converts scientific knowledge into user-friendly products, **(b)** the Prevention Support System provides general and innovation-specific support, and **(c)** the Prevention Delivery System implements innovations in practice settings.
UK Medical Research Council (MRC) framework	Craig et al. (2019)	**Consists of four primary phases or activities:** **(a)** development, or identifying the evidence base supporting potential implementation and pre-implementation planning; **(b)** establishing feasibility and piloting or testing procedures for acceptability and effectiveness; **(c)** implementation, or providing information to decision-makers and getting interventions into practice; and **(d)** evaluation, or assessing effectiveness.

with diverse linguistic practices, (d) planning for different forms of action, and (e) outcomes and dissemination. This framework allowed for the development of equity-oriented partnerships, a tenet of translational research in the social sciences. Additionally, Moullin et al. (2019) conducted a systematic literature review of the use of the exploration, preparation, implementation, sustainment (EPIS) framework. The authors concluded that the EPIS framework has been used in implementation research projects with some level of success. Other fields such as environment sciences and psychology have similar frameworks (e.g., Cash et al., 2003, focused on knowledge systems, and Wandersman et al., 2008, promoted the interactive systems framework). However, more work is needed to better operationalize the factors inherent in translational research and grow its application and network of users. Identifying common features might assist in achieving this goal.

Subprocesses Inherent in Translational Research

The models, frameworks, and approaches listed in Table 1 share several common subprocesses. First, most acknowledge the importance of scientific investigation, or what their authors call "knowledge generation," as the foundation for the development of interventions that solve or address specific problems. For example, in the MRC framework, Craig et al. (2019) defined "development" in terms of creating theory and modeling intervention processes and outcomes. In EBPH models, understanding the scientific literature is a key step in identifying interventions that address recognized community problems (Brownson et al., 2009). Similarly, ISF includes a component referred to as the "Prevention Synthesis and Translation System" that compiles and synthesizes scientific knowledge (Wandersman et al., 2008).

Second, the models, frameworks, and approaches highlighted in Table 1 place significant emphasis on the subprocess of translation. Review of these models, frameworks, and approaches suggests that implementation is a formal step in the translation process. For example, the RE-AIM model emphasizes implementation of evidence-based interventions consistent with design specifications (Glasgow et al., 1999). The EBPH model describes a seven-step problem-solving process that proceeds from problem definition and culminates in implementation and evaluation of a specific intervention (Brownson et al., 2009). Similarly, Graham et al. (2006) described the knowledge to action framework as a seven-step process that proceeds from problem definition, to implementation, to evaluation of problem-solving efforts.

Third, the models, frameworks, and approaches summarized in Table 1 are designed to facilitate the development of policies at the local, state, and/or national levels that promote widespread use and maintenance of evidence-based or proven practices. For example, the Centers for Disease Control and Prevention (CDC; 2014) refers to "institutionalization" as a formal outcome of problem-solving consistent with the knowledge to action framework. The CDC defines *institutionalization* as the maintenance of an intervention as an established activity in an organization, community, or other social system. The translational research continuum (Khoury et al., 2007; Westfall et al., 2007) and the stages of research progression model (Bauman & Nutbeam, 2014) refer to research related to real-world impacts and the assessment of rollout across multiple settings, respectively.

Based on these observations, we identified three subprocesses that appear to be inherent in translational research: (a) knowledge generation, (b) translation that includes implementation as a distinct step, and (c) policy development designed to promote widespread use of proven practices. The authors of this paper contend that each of these subprocesses is well understood and is performed routinely in universities, government agencies, and nonprofit organizations. Further, the authors of this paper contend that each of these subprocesses can be described more precisely in order to develop a more thorough understanding of translational research. Finally, the authors of this paper suggested that integrating these functions may provide an opportunity to streamline the process of translational research and enhance problem-solving at the local, state, and national levels. We describe the subprocesses inherent in translational research is provided below.

Once again, similar frameworks can be found in the environmental sciences (e.g., Cross et al., 2019; Daniels & Walker, 2001; Karl et al., 2007) and other disciplines. It may be that translational research as operationalized in these other fields contains similar components. For example, Griffin et al. (2010), Bamberg et al. (2010), and Nadeem et al. (2018) have focused respectively on promoting physical activity in older adults, building evaluation capacity in a community health

coalition, and implementing school-based mental health clinics. This review is not sufficient to claim that translational research procedures transcend disciplines. However, evidence is beginning to accumulate that such is the case. At a minimum, the conceptualization of translational research advocated by the authors of this paper may have utility to local problem-solving across a variety of fields.

Knowledge Generation

Knowledge generation can be defined as developing and/or testing scientific advances to determine if potential interventions are appropriate for translation or implementation in specific problem-solving contexts (Wilson et al., 2011). There are numerous descriptions of the process of scientific investigation or knowledge generation. Odom et al. (2005) suggest that scientific investigation proceeds from the development of preliminary ideas, hypotheses, and observations; to pilot studies; to controlled laboratory experiments; to real-world demonstration studies; and finally to randomized control studies. Our conception of knowledge generation also includes packaging and testing interventions in forms that are user-friendly (Wandersman et al., 2008) and implementable in local settings and assuring the utility of these interventions is adequately supported by evidence.

Translation

Translation focuses on the processes or steps necessary to ensure effective use of evidence-based practices, programs, or policies (Wilson et al., 2011). An *evidence-based* practice, program, or policy is defined as an intervention that is likely to produce a desired outcome given a specific set of circumstances, in which the likelihood of producing a desired outcome is based on the best available evaluation and/or scientific evidence (American Psychological Association, Presidential Task Force on Evidence-Based Practice, 2006). As noted above, translation subsumes *implementation*, which is defined as the process of using a known entity or intervention (Fixsen et al., 2005). However, translation includes additional activities that provide a structured process for problem-solving. A variety of processes could be used to ensure the effective use of evidence-based practices in specific problem-solving contexts. For example, Cash et al. (2003) advocated for a more literal meaning of "translation" whereby scientists help ordinary people comprehend scientific jargon.

The Center has adapted the rational problem-solving process to promote the use of evidence-based practices (Alexander, 1984; Allmendinger, 2009). The rational problem-solving process adopted by The Center consists of seven steps, as illustrated in Table 2. The Center's translational research professionals suggest that translation is a distinct subprocess inherent in translational research and proceeds from problem definition, to values clarification, to solution generation and selection, and finally to implementation and evaluation. This series of steps provides a structured process that can be applied by translational research professionals to address problems in schools, organizations, and communities.

Widespread Implementation of Proven Practices

Widespread adoption and uptake of evidence-based practices is often but not exclusively predicated on the development and initiation of

Table 2. Adaptation of the Rational Problem-Solving Process Used in the Case Study

Step	Objective of Step
1	Formulation of goals, objectives, and deliverables
2	Collection of data and other pertinent information
3	Analysis of data and problem definition
4	Development of problem-solving alternatives
5	Clarification of values and selection of a preferred alternative
6	Implementation of the preferred alternative
7	Monitoring, evaluation, and intervention improvement planning

relevant policies (Wilson et al., 2011). A *policy* is a law, regulation, procedure, administrative action, incentive, or voluntary practice of governments and/or other organizations that enhances well-being or serves to promote the public good (CDC, 2015). Ideally, policy-makers rely on a structured process that produces recommendations driven by evidence and/or other information. This process is highly consistent with the process of translation described above. The major difference between the two is that translation focuses on a specific instance of problem-solving, while widespread implementation involves policy development sufficient to support implementation of an intervention across multiple sites and/or settings (Wilson et al., 2011).

For example, a specific community might engage in a structured planning process relative to opioid abuse and elect to implement a particular evidence-based overdose prevention program. From our perspective, this represents an example of translation. Meanwhile, a state legislature might engage in policy-making to assure that this evidence-based opioid overdose prevention program is available to all interested communities in the state. This represents an example of widespread use of a proven practice. The policy-making process typically includes a number of distinct steps: (a) defining the problem or issue, (b) supporting problem definition with data, (c) developing a policy or policies to address the problem, (d) budgeting and acquisition of resources to support implementation across multiple settings, (e) implementation, and (f) multisite evaluation (CDC, 2015). Thus, translational research can be defined as a comprehensive process that proceeds from knowledge generation, to problem-solving through the use of an evidence-based intervention, to policy development that results in the widespread use of proven practices.

Furthermore, this conception suggests that the progression of translational research can be expressed as a continuum from knowledge generation through widespread use. Such a continuum, shown in Table 3, is useful in that any project that involves the potential or actual

Table 3. Translational Research Continuum Used in the Case Study

Subprocess	Station	Description
Knowledge generation	1	Developing preliminary ideas and hypotheses
	2	Conducting pilot studies, controlled laboratory experiments, and randomized control studies
	3	Packaging interventions in user-friendly formats
	4	Establishing interventions as evidence-based practices
Translation	5	Defining the problem to be solved
	6	Clarifying values, generating potential solutions, and selecting a preferred alternative
	7	Implementing the preferred alternative
	8	Evaluating implementation and intervention improvement planning
Widespread usse of proven practices	9	Defining a problem across multiple jurisdictions or settings and supporting problem definition with data
	10	Developing a relevant policy or policies
	11	Acquiring resources to support widespread implementation and implementation across multiple jurisdictions or settings
	12	Multisite evaluation

development, implementation, and/or evaluation of an intervention can be located somewhere on it. A critical objective of translational research is thus to move interventions along from one station to higher stations on the continuum. It might be argued that, with regard to a specific intervention, the translational research process is complete when the intervention is being used as it was designed, across a variety of jurisdictions, to address the problem or issue for which it was developed. However, "complete" is a relative term. While the process of translation is never complete, use across multiple settings for the intended purpose represents a terminal outcome for evidence-based practices, programs, and/or policies.

Scaling up the implementation of innovations is considered a critical component of translational research (Feller & Menzel, 1977; Rogers, 2002). *Innovation* and *adoption* have become mundane words in a world where technological innovation and policy generation move at a fast pace. Rogers (2003) defines *diffusion* as "the process in which an innovation is communicated though certain channels over time among the members of a social system" (p. 5). There are four key elements that make up this definition: innovation, communication, time, and social system. Diffusion of innovation includes both the spontaneous spread of new ideas and planned methods of propagating new ideas (Rogers, 2003).

The integration of knowledge generation, translation, and policy development may be best understood in terms of actual examples from the portfolio of projects undertaken by The Center. Translational research projects at The Center typically focus on workforce development, juvenile justice, environmental degradation, behavioral health, teacher training, and many other fields. For instance, a team from The Center worked with a local juvenile court to develop and implement quality assurance procedures designed to produce outcome data related to the impact of court programming on youth. In terms of translation, the rational problem-solving model provided a formal process for defining the problem the court was trying to solve and, in turn, identifying quality assurance as a potential solution. The problem focused on using data as a source of information to improve programming. Data were collected that provided the opportunity to consider the extent to which the court's programs produced desired outcomes. Finally, in the policy development realm, the quality assurance process developed in conjunction with the court is in the process of being disseminated to the field in the hope that other courts will adopt similar procedures. In another example, a translational research team from The Center is working with researchers to address water quality related to farming practices. With respect to translation, the team has helped researchers use several project management tools to support project implementation. In addition, evaluation data have been collected to illuminate the extent to which the project has met its goals of addressing water quality.

Implications for Translational Research Organizations

This review of translational research models, frameworks, and approaches has significant implications for organizations concerned with the dissemination of evidence-based practices. First, we suggest that translational research is a complex activity that transcends several key subprocesses. We support a definition of translational research that encompasses knowledge generation, translation focused on the implementation of evidence-based practices in specific problem-solving contexts, and the promotion of policies supporting widespread implementation of proven practices. Thus, translational research is a process likely requiring sustained action over a relatively long time frame and the application of a variety of skills that transcend research, translation, and policy development.

It is important to note that this conception of translational research is not sufficient to specify the responsibilities and duties of translational research professionals. The distinct responsibilities of researchers, implementation specialists, and policy-makers are relatively well-developed, and the critical competencies associated with these roles provide insight into the subprocesses of translational research. However, it can be argued that a translational research process must integrate or bridge knowledge generation, translation, and policy development to result in efficient and effective problem-solving (Abernethy & Wheeler, 2011; Patel, 2018; Tageja, 2011). To the extent that these three subprocesses represent a comprehensive approach to problem-solving, this bridging function might be conceptualized in terms of managing the problem-solving process (Julian, 2017). Finally, organizations concerned with moving proven practices into widespread use must consider developing structural arrangements and policies to support the array of activities related to the three subprocesses inherent

in translational research. For example, The Center is guided by a formal strategic plan that defines translational research and specifies procedures consistent with the subprocesses defined above.

Implications for the Field of Translational Research

This review also has several key implications for the field of translational research. As noted above, moving scientific and other innovations into widespread use is a complex and time-consuming endeavor. It is likely to be best accomplished by interdisciplinary teams composed of researchers, implementation specialists, and policy professionals. Bridging or linking these specialties may necessitate the designation of a fourth professional role, consistent with the concept of bridging or integrating the subprocesses. Thus, translational research professionals might conceptualize their bridging function in terms of managing the problem-solving process in schools, organizations, and/or communities. Such roles would appear to have relevance to a variety of fields, such as environment science, education, mental health, and many other domains.

This discussion also raises issues of community involvement and power dynamics relative to problem-solving that are beyond the scope of this review. How can people with lived experience best participate in knowledge generation, translation, and policy development? Finally, as best practices related to translational research evolve, questions are likely to arise about the competencies necessary to bridge the subprocesses of translational research and function in the role of translational research professional (as distinct from researcher, implementer, and policy-maker). Thus, educational programs might consider investing in training resources focused on the role of translational research professionals. Additionally, this discussion highlights the need for college administrators and faculty "to engage their communities to improve conditions and the efficiency and effectiveness of government and nonprofit organizations" (Barth, 2018, para. 1). Finally, it should be noted that community-based participatory research allows stakeholders to get involved and contribute to addressing the needs and problems of a community, particularly in the field of public health. For example, Brown et al. (2019) described the community-based participatory research partnership and the resulting needs assessment of HIV-related services for infected individuals in rural communities of Tennessee.

In summary, higher education institutions, learning organizations, and training and development groups should consider employing translational research professionals who are able to investigate the extent to which the organizational structures and professional roles and procedures are consistent with the subprocesses described above. Such action may facilitate problem-solving in local schools, organizations, and communities. Ultimately, scientific investigation may yield a translational research process that leads to greater diffusion of information and perhaps more efficient and effective resolutions to complex social problems.

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The Promise and Challenges of Integrating Biological and Prevention Sciences: A Community-Engaged Model for the Next Generation of Translational Research

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Abstract

Beginning with the successful sequencing of the human genome two decades ago, the possibility of developing personalized health interventions based on one's biology has captured the imagination of researchers, medical providers, and individuals seeking health care services. However, the application of a personalized medicine approach to emotional and behavioral health has lagged behind the development of personalized approaches for physical health conditions. There is potential value in developing improved methods for integrating biological science with prevention science to identify risk and protective mechanisms that have biological underpinnings, and then applying that knowledge to inform prevention and intervention services for emotional and behavioral health. This report represents the work of a task force appointed by the Board of the Society for Prevention Research to explore challenges and recommendations for the integration of biological and prevention sciences. We present the state of the science and barriers to progress in integrating the two approaches, followed by recommended strategies that would promote the responsible integration of biological and prevention sciences. Recommendations are grounded in Community-Based Participatory Research approaches, with the goal of centering equity in future research aimed at integrating the two disciplines to ultimately improve the well-being of those who have disproportionately experienced or are at risk for experiencing emotional and behavioral problems.

Keywords Genomics · Neuroimaging · Prevention · Integration · Community-based participatory research

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Personalized health interventions based on one's biology are on the rise. Although advances have been made in personalized medicine approaches for disease conditions such as cancer (Simona et al., 2023; Singh, 2023), there has been limited progress on the implementation of personalized approaches for emotional and behavioral health problems such as depression, substance use disorders, or antisocial behavior. At the same time, the availability and impact of interventions aimed at preventing emotional and behavioral health problems have never been higher, as reflected in the number of emotional and behavioral prevention programs meeting criteria for being "evidence-based" on national registries. For example, more than 100 programs are listed on one national resource—Blueprints for Healthy Youth Development—as "promising," "model," or "model plus" interventions in terms of the rigor of their evidence base (https://www.blueprintsprograms.org/program-search/). The purpose of this paper is to describe advances in biological science approaches, with a focus on genomics and

neuroimaging, and to describe how these might inform current directions in the field of prevention science. To this end, the Society for Prevention Research convened a multidisciplinary task force charged with addressing the integration of biological and prevention sciences, one outcome of which is this manuscript.

We begin this manuscript by looking back to the turn of this century (2000), when biological methods and technologies were advancing rapidly in many domains. We describe new approaches for collecting and analyzing human DNA samples to understand genetic influences on behavior that were increasingly accessible to researchers, and in parallel, advances in neuroimaging methods that provided a new window into the brain. During this time, early studies that integrated biological science and prevention science approaches began to appear in scientific journals, including *Prevention Science* (e.g., Bruce et al., 2009; Sales et al., 2014). As the science advanced, so too did recommendations for the successful integration of these methods within prevention science (for additional reading related to addressing challenges linking research to practice and policy in prevention science, see Crowley et al., 2018; Fishbein, 2000, 2016; Fishbein & Dariotis, 2019; Fishbein et al., 2016).

Despite the excitement generated by these early studies and papers, efforts to integrate biological sciences with prevention science have faced a number of challenges. We review these challenges in the next section of this manuscript, and we explain why we suggest that biological science has not fully realized its promise of transforming prevention science to inform personalized health interventions. We highlight complexities in the science that pose real hurdles for true integration of the two disciplines while discussing the lack of diversity in participants and researchers, the need for collaboration with community partners, challenges in the interpretation of the data, and ethical considerations. This presents a realistic, albeit somewhat pessimistic, outlook on the barriers that must be overcome in order for the two disciplines to become integrated in a way that equitably advances science to improve human health and well-being using personalized approaches.

Our skepticism turns to optimism, however, as we enumerate specific approaches that we believe would allow for better, more equitable, and responsible integration of biological science into prevention science research and practice. This includes grounding such work in a Community-Based Participatory Research (CBPR) model; forming meaningful collaborations between community members, experts in biological science, and experts in prevention science; developing and deploying improved analytical approaches; committing to professional development-oriented conversations around racism (and other structural inequities) and biomarker science before embarking on such collaborations; and including transdisciplinary experts on grant and editorial board review panels. We follow this section with a description of proposed steps to apply a CBPR framework to research investigations that include prevention science and biological science methods, noting the benefits and challenges to communities and researchers in each step in the process. In the penultimate section of the manuscript, we provide several examples from the field of prevention science that have made advances in one or more of the areas of integration described in the prior section. We conclude with a discussion of ongoing barriers, future areas of opportunity, and recommendations.

Defining What We Mean by "Biological Science" in This Report

This paper focuses on two biological science methods advances of the twenty-first century: genomics and neuroimaging. We refer to these as "biomarkers" throughout this report, to indicate a biological characteristic that reflects variation in processes or mechanisms that can be objectively measured, such as a gene sequence from analysis of a person's DNA or a measure of gray matter volume from a scan of a person's brain. We acknowledge that there are many other approaches that can directly assay biology, such as electroencephalography (EEG), cortisol collections via hair or saliva, or measures of the immune system (e.g., Nusslock & Miller, 2016). These are not used as examples within this report, due to space considerations. Similarly, there are advances in genetically informed research designs (e.g., children of twins studies) that may be relevant to prevention science, but are not detailed in this report. Nonetheless, many sections of this manuscript could apply broadly across a range of biological science methods, and we encourage readers to consider the challenges and recommendations described in this manuscript with a view toward the specific biological science method(s) that they are using or plan to incorporate.

Advances in Genomics: DNA Sequencing, Genome-Wide Association Studies, Polygenic Score Computation, and Epigenetics

The completion of the Human Genome Project in 2003, which identified the DNA sequence (i.e., the sequence of nucleotides) of the entire human genome (Green et al., 2015), generated tremendous excitement about the possibility that knowledge of a person's DNA would provide information about their disease risk and their treatment response. Soon thereafter, the first genome-wide association study (GWAS) was published (Klein et al., 2005). Although approximately 99.9% of the genome is identical from one person to the next, the 0.1% that

is not shared represents three million genetic variants and all their combinations, giving rise to a wide range of individual differences in behavior, cognition, and risk for disease. This variation is captured in GWAS. Unlike candidate gene studies, which measured variation in a single gene at a time and have fallen out of favor due to replication failure (Duncan et al., 2019), GWAS measure hundreds of thousands to millions of gene variants (called single-nucleotide polymorphisms, or SNPs) across the genome. Statistical geneticists use GWAS data to calculate polygenic scores, which are weighted combinations of gene variants that, additively, account for meaningful proportions of variance in phenotypes of interest and have been used with modest success in individual risk prediction models (Murray et al., 2021). An advantage of this method is that scores can be transported to smaller, deeply phenotyped samples, thus enabling researchers to test hypotheses about gene-environment interaction or correlation. However, a downside of these polygenic scores is that they may provide little insight into the underlying mechanisms that may be driving the outcomes to which they are linked, undermining their translational value (Visscher et al., 2021). Thus, increased predictive power has outpaced biological insight. Regardless, polygenic scores derived from these GWAS are being used in clinical risk prediction models to improve our ability to predict and prevent disease.

In addition, researchers are attempting to model interactions between biological processes and environmental experiences by measuring epigenetic modifications or gene expression (Jones et al., 2018; Miller et al., 2009). Epigenetic marks, such as DNA methylation, are modifications to the packaging of DNA that can influence whether a given gene will be expressed, or "turned on." In contrast to the sequence of DNA, which is set at conception and for the most part is static across the lifespan, epigenetic markers and levels of gene expression can undergo dramatic changes over the course of development and in response to environmental exposures and life experiences (Jones et al., 2018). There are several reasons why it is challenging for researchers to determine whether epigenetic modifications and changes in gene expression play a causal role in the etiology or maintenance of emotional and behavioral health problems (Walton et al., 2019), including the lack of studies with repeated assessments of both DNA methylation and measures of emotional and behavioral health problems, the use of peripheral tissue (which can be sampled from live humans) instead of brain tissue (which cannot currently be sampled from live humans), and lack of ability to isolate epigenetic effects from other potential mechanisms (e.g., epigenetic patterns are heritable).

Despite these limitations, these advances in DNA assay and statistical analysis approaches have begun to be incorporated into prevention science research and present opportunities for the integration of biomarkers into prevention science studies (Li et al., 2022; Neale et al., 2021).

Advances in Neuroimaging

The 1990s was termed the "Decade of the Brain," and, in part due to the initiation of the Human Genome Project (1990–2003), sparked an explosion of interest in linking health and illness to brain structure and function (Jones & Mendell, 1999). This interest was fueled, in part, by the development of magnetic resonance imaging (MRI). Structural MRI uses magnetic gradients and electromagnetic fields to generate high-resolution images of biological tissue. Researchers can use structural MRI to examine relationships between the volume, thickness, or surface area of a particular brain region (or connections between areas when using diffusion imaging) with clinical outcomes or other behavioral and psychological variables. Studies involving structural MRI have reported that many mental health problems, including emotional and behavioral disorders, are characterized by individual differences in the structure of brain regions that generate and regulate emotions (e.g., Shackman et al., 2016; Treadway, 2016). In some cases, these structural brain differences pre-date the onset of the observed illness (Borgwardt et al., 2007; Foland-Ross et al., 2015), suggesting they may indicate pre-existing risk factors and can help identify individuals for possible preventive interventions (Rashid & Calhoun, 2020). Information obtained via structural MRI is limited, however, by its static representation of tissue. Functional MRI (fMRI) complements structural imaging by generating maps of possible neuronal activation that can be linked to more dynamic mental processes. Using fMRI, researchers can measure changes in brain function while participants perform experimental tasks, or at rest, and then relate these changes to clinical, behavioral, and/or psychological variables (Heeger & Ress, 2002). As with the advances in genomic methods, these new tools provided researchers access to data about the brain that was unavailable just a few decades ago and offer the potential for the integration of prevention science and neuroimaging approaches to inform precision medicine approaches.

The Promise of Translation

Consistent with a precision medicine approach, a goal of increased emphasis on biological risk factors and mechanisms has been to identify: (a) mechanisms through which mental and physical health problems emerge, (b) individuals who may be at higher risk (to be targeted via prevention), and (c) subgroups of individuals who may have similar symptoms, but distinct causes to their health challenges (e.g., Gratton et al., 2019; Insel & Cuthbert, 2015).

If biomarkers can help to identify these mechanisms, risk factors, and subgroups, they could lead to early identification of individuals for prevention purposes, targeted and personalized interventions for individuals with different causes, and/or new prevention and intervention targets via better understanding of the causes and mechanisms of health and illness (Hyde, 2015). Thus, at the broadest level, biomarker approaches offer new inroads for prevention science by offering new ideas on who to target, how to target, and what to target in prevention and intervention efforts. In addition, at the individual level, biological mechanisms may partially explain prevention effects and serve as putative mediators. Including biomarkers in the context of a prevention trial has the potential to inform our understanding of why prevention studies typically have small to modest effect sizes, and to help explain the heterogeneity in intervention outcomes. This information could then be used to guide refinements to existing prevention programs or to guide the development of new programs that focus on novel targets, with the potential to benefit more people when applied in the context of interventions with at least modest effect sizes, strong implementation, and high levels of participant engagement (e.g., Leve et al., 2010). These directions are discussed further in the penultimate section of this manuscript.

This precision medicine conceptualization of the utility of biomarkers for advancing the understanding of emotional and behavioral health problems is synergistic with the broad definition of prevention science as having a primary goal of improving public health by "identifying malleable risk and protective factors, assessing the efficacy and effectiveness of preventive interventions, and identifying optimal means for dissemination and diffusion" (Biglan et al., 2011). In particular, within the prevention research cycle (illustrated in Fig. 1, adapted from the Institute of Medicine, 1994), phase #1 includes conducting research to understand predictors of problem and positive developmental outcomes and understanding the epidemiology and natural history of the problem, phase #2 includes developing interventions to motivate changes in individuals, groups, and environments based on theories of human behavior and our understanding or mechanisms for behavior change, and phase #3 includes testing the efficacy of these preventive interventions and their mechanisms under tightly-controlled parameters and settings (Biglan et al., 2011; Fishbein, 2016). Examples of biomarker science that has been conducted within phases #1–3 of the prevention research cycle are presented in a later section of this report. Phases #4–5 involve testing effectiveness in real-world settings and dissemination efforts and are not a focus of this report because biomarkers have not generally been used in these phases.

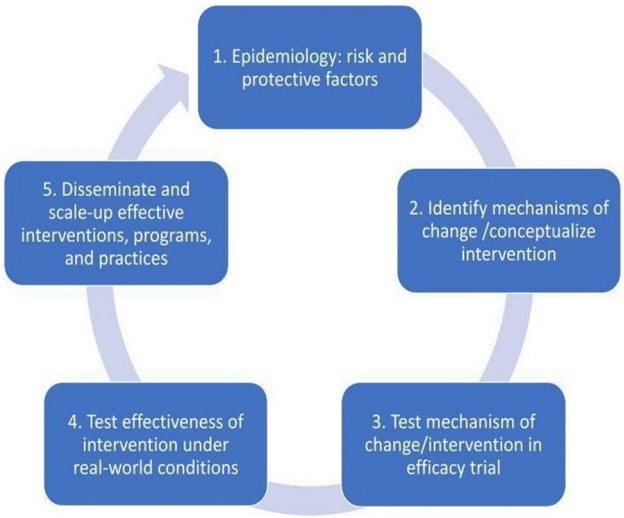

Fig. 1 Prevention Research Cycle. Note: Adapted from the Institute of Medicine (1994)'s five-step model for assessment, intervention, and dissemination

Where is the Field Today? Challenges in Advancing Integrated Biomarker-Prevention Science Research

Despite broad enthusiasm for integrating biological and prevention sciences to inform precision medicine approaches, implementing this vision has been challenging. We discuss four sets of challenges that have impeded progress in this section, before turning to strategies to address these challenges in subsequent sections.

The Complexity of the Science Exceeded Initial Expectations

A major challenge in advancing an integrated biological sciences-prevention science agenda is that linking biomarkers to emotional and behavioral health outcomes has been more complicated than initially expected. When the Human Genome Project was completed, researchers began looking for gene variants that underlie mental health problems. The hope was that a small number of gene variants would explain a large amount of variance in psychopathology outcomes, similar to genetic mutations like the *BRCA1* and *BRCA2* mutations implicated in breast and ovarian cancer. Initial efforts were also informed by experimental animal models, including mouse knockout and behavioral neuroscience studies that showed how behavior was affected when specific genes or neurotransmitter systems were effectively silenced (Cases et al., 1995; Murphy et al., 2001; Shih & Thompson, 1999). As a result, researchers initially focused their efforts on variants in genes such as the serotonin transporter (*5-HTTLPR*), monoamine oxidase A (*MAOA*), dopamine receptor 4 (*DRD4*), and dopamine transporter (*DAT*)

genes that were known to be associated with risk for various psychiatric problems, including depression, substance use disorder, and attention-deficit/hyperactivity disorder (ADHD; Caspi et al., 2003; Okuyama et al., 2000; Rowe et al., 1998). Yet, these single gene variants only accounted for a very small percentage of variance in emotional and behavioral health outcomes (2–4%), and frequently did not replicate in different cohorts (Risch et al., 2009) or in well-powered GWAS (e.g., Farrell et al., 2015; Flint & Munafò, 2013). Gradually, however, it became clear that individual differences in complex human traits were explained by hundreds or thousands of gene variants, each contributing a very small percentage of risk, and not by a small number of genes of large effect (Visscher et al., 2021). Moreover, as the science evolved, it has become apparent that the genetics of emotional and behavioral health (and many forms of physical health) do not follow a simple Mendelian pattern in which one gene is associated with one outcome. Polygenic scores that increase risk for one psychiatric disorder are usually associated with other disorders as well, and their effects may be contingent on both the expression of one or more independently inherited genes as well as the environment (Lee et al., 2019, 2021; Smoller et al., 2019). Even with large ensembles of genetic variation measured, the cumulative effects of these genes still only explain a relatively small percentage (< 10%) of variation in behavior (Gibson, 2010), highlighting the complexity of ways in which multiple genetic variants, combined with specific environmental exposures, likely influence emotional and behavioral health outcomes. It is possible that with new, theoretically driven multivariate gene identification methods, polygenic scores will begin to account for as much variance in emotional and behavioral health outcomes as some of the more robust social risk factors, such as socioeconomic status (see Karlsson Linnér et al., 2021, for more information on such approaches).

Unfortunately, things are not simpler in the brain, guided by neuroimaging research advances. Historically, structural and functional neuroimaging studies examined brain regions in isolation of each other. Although this approach was intuitively appealing and offered more direct explanatory power, simple findings linking the structure or function of a single brain region to emotional and behavioral health outcomes have not been replicated, nor shown consistent predictive power (Botvinik-Nezer & Wager, 2023). There is growing recognition now that emotional and behavioral health and illness may be driven by complex connections among these brain regions, rather than the size or activity in a single region (Bassett et al., 2018), and important advancements are being made in determining the best methods for characterizing such networks (Barack & Krakauer, 2021; Basset et al., 2018; Bassett et al., 2018). Further, and similar to genomics, individual differences in one brain region or circuit may be implicated in numerous different emotional and behavioral health conditions, reflecting transdiagnostic, rather than specific, biomarkers of risk (Insel & Cutherbert, 2015). Moreover, as with genomics, as neuroimaging identifies more and more complex brain patterns to be associated with outcomes, it is becoming clear that the effects are relatively small, thus requiring very large samples to identify relatively nuanced connections between brain and behavior (Feng et al., 2022; Marek et al., 2022). This complexity has made it difficult to identify biomarkers that can reliably identify vulnerable individuals and differentiate individuals at risk for one emotional or behavioral health problem from another. This complexity has also made it difficult to identify translational biological processes that can be targeted in prevention or intervention programs.

Lack of Diversity

A second major barrier to progress is a lack of diversity in existing biomarker science, including concerns regarding: (1) who is the focus of the research, (2) who is conducting the research, and (3) how is community involvement integrated into the research. These concerns are not unique to biomarker science and permeate other translational disciplinary efforts as well; challenges related to the integration with prevention science are described below.

Lack of Diversity of Participants Typically, partially due to cost, many biomarker studies, particularly human genomics, and neuroimaging studies, are conducted with convenience samples, often of relatively socioeconomically advantaged, primarily White/European individuals residing near major universities (e.g., a bias toward those living in suburban and urban settings versus those living in rural areas; Falk et al., 2013). This is an extension of the broad issue in social sciences of focusing on WEIRD (Western, Educated, Industrialized, Rich, and Democratic) populations (Henrich et al., 2010). Although some recent large-scale studies are leading to improvements in sampling (e.g., the Adolescent Brain Cognitive Development [ABCD] Study [Hagler et al., 2019]; neuroimaging with the Future of Families and Child Wellbeing Study [Goetschius et al., 2020]; the Environmental influences on Child Health Outcomes [ECHO] study [Knapp et al., 2023]), it is not clear from most published research to date who the research generalizes to because of the use of convenience sampling (Falk et al., 2013). Beyond the philosophical issue of generalizability, the field has also failed to include participants from diverse socioeconomic, ethnic, and racial groups, and studies often do not even report the demographics of participants (Qu et al., 2021). This poses challenges for translation to prevention science, given that focal populations for prevention efforts are often

from marginalized and/or underrepresented groups. What if associations between a specific biomarker and a measure of emotional or behavioral health differ between the extant literature and the population of focus in the prevention study? Racial and ethnic minorities are underrepresented broadly in biomedical research. White/European Americans make up 67% of the U.S. population, but are 83% of research participants (Taylor, 2019; Yates et al., 2020). Black/African Americans make up 13% of the U.S. population, but only 5% of participants, and Hispanic and/or Latino/a/x/e (hereafter referred to as Latine) represent 18% of the U.S. population, but less than 1% of participants (Yates et al., 2020).

Human genetics research faces the challenge that historically, GWAS have not represented population-wide genetic diversity. Over hundreds of thousands of years, different groups of people had different patterns of migration, adapted to different environments, and had different patterns of mutations and recombination, leading to distinct genetic signatures, reflected in patterns of linkage disequilibrium and allele frequencies. These genetic ancestry patterns are statistically correlated with social categories of race and ethnicity but are not identical. For example, genetic diversity is greater on the African continent than in the rest of the world combined, but most of this diversity has not been sampled (Choudhury et al., 2020). Thus, polygenic risk scores derived from individuals of European genetic ancestry do not capture the genetic variation present in individuals of, for example, African genetic ancestry and, as a result, are not as predictive of health outcomes (or any other phenotype) when applied to other ancestral groups (e.g., Duncan et al., 2019; Mars et al., 2022). Thus, there is the possibility that the use of these polygenic scores in personalized medicine from GWAS of individuals of European ancestry will exacerbate existing health disparities related to race and ethnicity (Martin et al., 2022), when considered in the context or a prevention trial. In recognition of this problem, there are new initiatives to increase the representation of diverse groups in GWAS (e.g., BioBank Japan, the Latin American Genetics Consortium, H3Africa Consortium, NIH's All of Us Research Program), new platforms for genotyping DNA from diverse groups, and new methods for analyzing GWAS data across ancestral groups and within groups of mixed genetic ancestry (e.g., Hispanic and/or Latine participants; Atkinson et al., 2021; Peterson et al., 2019). Recent reports are already showing that increasing ancestral and global diversity in genetic studies can help increase the discovery of core genes and increase the transferability of findings (Meng et al., 2024).

It is likely that the representation of marginalized communities is even lower in neuroimaging studies (Gard et al., 2020; Qu et al., 2021). This lack of representation is problematic as it undermines our understanding of "the human brain" and how variations in brain structure and function are impacted by experience and predict health outcomes. If biomarker studies do help to identify biological mechanisms that could potentially be changed through intervention (prevention research cycle phase #2), or test ways to personalize prevention based on a biological characteristic (prevention research cycle phase #3), but this science is based on a small, homogeneous subset of the population, then disparities in positive outcomes from prevention and intervention programs will increase. That is, the lack of proportional representation could potentially lead to interventions that are not efficacious in other populations (Yates et al., 2020), are not effective for many populations (Bass, 2020), or do not translate well into real-world use (Yates et al., 2020).

Lack of Diversity of Researchers Issues of inclusion and generalizability in genomics and neuroimaging study samples may be partially related to lack of diversity among those leading the research, both in their identities and in their training and expertise. Although we are unaware of an analysis that identifies the demographics of genomics researchers, people with racial and ethnic identities that are marginalized are under-represented in adjacent fields (e.g., psychology; Hur et al., 2017) and broadly in biomedical research (Ricard et al., 2022). Moreover, recent work has shown that, within neuroscience, White authors tend to disproportionately cite other White authors (Bertolero et al., 2020), and faculty with marginalized identities receive less federal funding than White faculty (Hoppe et al., 2019). Thus, our field underrepresents many racial and ethnic identities and there are clear barriers to success in the field for those with marginalized identities. Increasing researcher diversity is likely to broaden the range of questions researchers consider relevant, increase the ease with which researchers engage with participants from marginalized communities, and expose hidden biases in the interpretation of findings from biomarker research (Rowley & Camacho, 2015).

Beyond the lack of racial and ethnic diversity of researchers engaging in biomarker research and prevention science research, an additional challenge is the need to bridge sources of knowledge to ensure the multidisciplinarity of research on integrated biomarker-prevention science research. Many prevention scientists recognize that biological risk factors interact in complex ways with each other and with other non-biological risk factors (e.g., Fishbein, 2000). This recognition can lead prevention scientists to collect multiple forms of biological, social, and cognitive data in a desire to model this complexity. However, none of us can be experts in everything, and a challenge with successful interdisciplinary biomarker-prevention science research is forging collaborations that bring together the requisite expertise to elevate the research beyond the sum of its parts. These collaborations often take time to

establish and require researchers from different disciplinary backgrounds to establish common frameworks for defining key constructs and for thinking about key questions. Preferred publication outlets may also differ between the disciplines, as well as expectations around timelines and authorship roles. Moreover, individuals from different disciplines may value or have concerns about different types of approaches (e.g., community-based researchers may have concerns about biological approaches, biologically focused researchers may not see added value in community-based research). To promote successful interdisciplinary partnerships, a coordinated plan for collaboration and dissemination of the science must be established early in the research process.

A lack of interdisciplinary diversity, challenges with collaborating across disciplines (e.g., genomics, neuroscience, prevention science, community-engaged research, public health), challenges in obtaining training across these areas, and a lack of diversity among investigators has likely undermined the extent to which biomarker research has engaged directly with marginalized communities, underrepresenting those who might be more likely to benefit from selective preventive intervention studies and/or individuals who have been marginalized and oppressed in multiple ways (Gilpin & Taffe, 2021). This gap in the translational collaboration pipeline intersects with the lack of diversity among biomarker study participants, limiting the ultimate potential for equitable translation.

Lack of Community Engagement Adding to the aforementioned challenges is the fact that a lack of community engagement can perpetuate mistrust from marginalized communities. Without a history of positive collaboration with communities that may eventually engage with prevention or intervention efforts, biomarker researchers miss individual representation, but also their input. That is, studies involving genomics and neuroimaging rarely include representatives from the participant and community sides, and thus rarely take a community- or participant-focused approach. This unidirectional method of research can lead to interpretation biases (Tolwinski, 2019) and/or scientific directions that do not meet the interests or needs of the community. One example of this is when researchers collected blood samples from Havasupai Tribe members in Arizona to identify a genetic link to diabetes, but later used the samples without the consultation, input, or consent of tribal members, to study genetic linkages with other medical disorders, such as schizophrenia and alcoholism (Sterling et al., 2011). The broader scientific community is beginning to understand the harmful impacts of failure to engage the community in research, as evidenced by the prioritization of patient and stakeholder engagement in some funding priorities (e.g., https://www.pcori.org/engagement/value-engagement) and changes in consenting processes to include "broad consent" if the samples are going to be banked and used for future research.

Just as a lack of community and participant input can undermine the translational value of biomarker research, so too can the lack of collaboration with implementation scientists. Incredible amounts of research and funding are committed to biomarker research with the hope that this basic science can lead to important translation efforts later. Without thinking through how findings could be translated, research efforts may have low translational impact. For example, many of the current directions in biomarker research (e.g., large-scale polygenic scores, complex connectome brain imaging) may not be scalable, nor provide insights at the individual level that are relevant to prevention science. Moreover, many of these approaches are incredibly expensive or inaccessible if participants do not live near a major medical center or research university, leading to the question of whether a typical preventative intervention could have the funding, accessibility, and expertise needed to engage in the real world. That is, how could genome-wide or brain-wide methods be useful in a clinic or the community? These tools are incredibly costly; if a major site for prevention work is community health centers and on-the-ground providers of prevention services, what is the likelihood that these tools can realistically be used at scale in prevention efforts? Thus, it seems unlikely that tools like MRI will be used at scale in prevention work in community settings and thus, it is critical for biomarker researchers to be clear in their work about how it could inform translational goals.

Of course, the advantages that biomarkers promise for greater precision-based intervention may not lay within the use to these tools in community care settings, but rather, in their ability to identify underlying mechanisms that explain variation in responsivity across subtypes of individuals from a range of racial/ethnic groups. Using a neuroscience-informed framework, distinct neurocognitive trajectories that have been recognized as precursors to emotional and behavioral health outcomes could be targeted, and the change processes could be evaluated to inform causal hypotheses. This framework could also inform individualized assessments, intervention development, and outcome measurement in preventive interventions. If successful, the classification and diagnosis that guides prevention and intervention would not be based solely on surveys or interviews, but on sensitive tasks and stimuli previously used during biomarker testing and shown to consistently recruit regions or processes of interest (e.g., neurocognitive tasks, emotion processing indicators, and stress responses) that help us to better understand the key elements and neural mediators of different prevention programs, which could, in turn, help to personalize prevention and intervention and make it more successful. At

the same time, these approaches would need to be scaled up to have a broader impact, which is a challenge. Moreover, even in work where the goal is using biological science in empirical studies as a bridge to new and better prevention strategies, an issue remains that if biomarker studies are not done with communities that will be targeted eventually for a prevention trial, then generalizing the results to improve prevention may be challenging and will not reduce health inequities.

Challenges in Interpretation

A third challenge in prior biomarker research is related to challenges in interpreting the findings, specifically, concerns regarding sample sizes and measurement.

Sample Sizes and Effect Sizes Early failures with candidate genes (and more recently, with region of interest, task-based neuroimaging studies) and the small effect sizes that have resulted from studies using biomarkers to predict emotional or behavioral health outcomes have led to an acknowledgement of the increased statistical power needed to conduct rigorous and replicable research in this area (Duncan et al., 2019; Marek et al., 2022; Poldrack et al., 2017). This can be a challenge within prevention science, as the costs of implementing interventions often preclude the use of very large samples (particularly in effectiveness trials, within prevention research cycle phase #4 activities). Increasingly, data sharing consortia (e.g., Early Genetics and Lifecourse Epidemiology [EAGLE] Consortium; Middeldorp et al., 2019) and multi-site coordinated data collection efforts (e.g., the ABCD study [Volkow et al., 2018]; HEALthy Brain and Child Development Study [Volkow et al., 2021]; the Environmental influences on Child Health Outcomes study [Knapp et al., 2023]; the All of Us program [All of Us Research Program Investigators, 2019]) are designed to include biological measures as well as measures of experiences and exposures. Unlike the much smaller genomics and neuroimaging studies that were, until recently, common, these large-scale data collection efforts are better-powered to detect the small gene- and brain-behavior associations that appear to be typical and are better powered to detect gene-by-environment interactions. Thus, the field is shifting rapidly, and one of these shifts involves moving to larger consortium studies. This results in a benefit of larger sample sizes and adequate power to detect associations, as well as public data that may be accessed more broadly be a wider variety of researchers, with the potential for more diversity in viewpoints. At the same time, with fewer (but larger) projects, there is also a danger that this process can concentrate the researchers leading this science into a smaller subset of individuals, which can limit innovation and diversity of ideas and scholars—amplifying a threat identified earlier in this section regarding lack of diversity in researchers.

Measurement Issues For biomarkers to be effectively integrated into prevention science studies, researchers must be able to measure them reliably, they must have predictive validity, and there should be some understanding of the pathway from the biological marker or process to the behavior. This can be challenging if, for example, a prevention trial is focused on an underserved community for whom biomarker research has been rare and less likely to have been validated previously. In genomics and neuroimaging research, researchers are still striving to meet these criteria. For example, the acquisition and processing of neuroimaging data (and branching forking of analysis options) creates concerns about reproducibility (for discussion, see Poldrack et al., 2017). In epigenetics research, expert users debate which tissues to sample (e.g., blood, buccal, saliva, hair) and assays to use (e.g., Southern Blot vs. qPCR; https://trn.tulane.edu/), quite apart from the question of whether epigenetic changes in peripheral tissue (versus brain tissue) play any causal role in affect, behavior, or cognition. Even for DNA biomarkers that can be measured reliably, the mapping between biology and behavior is likely complex (i.e., not 1:1) and moderated by developmental and environmental factors (e.g., Tucker-Drob et al., 2013).

Ethical Considerations

A final set of challenges discussed in this report, which is one that permeates each of the aforementioned challenges, is that biomarker research broadly, but also specifically in a translational context with goals to inform prevention, can raise potential moral and ethical considerations. First, the eugenics movement, which is a scientifically inaccurate theory that humans can be improved through selective breeding of populations, caused widespread harm beginning in the early twentieth century, particularly to marginalized populations. Some researchers involved in this movement provided inaccurate genetic and/or brain-based justification for these horrific beliefs, leading to a long history of concerns about the use of biological and especially genetic and brain-based measures among many scholars and communities. The eugenics movement has understandably impacted perceptions of the utility of any research that incorporates biomarker data, such as genomics or neuroimaging. It contributed to social disparities that continue into the present in education, medicine, and prevention science, impacting participants' interest in and acceptance of biomarker research (Prather et al., 2018; Sanchez-Rivera, 2020; Selden, 2000; Winston et al., 2020).

Second, there are valid concerns about confidentiality with biomarker data, particularly the use of DNA data. Violations of privacy and confidentiality in the use of DNA could, theoretically, impact later insurance coverage and/or access to treatments. Even if such a situation never arises, the sheer possibility of a privacy violation may undermine trust between researchers using biomarkers, prevention scientists, and potential participants in a prevention science study.

Third, the use of biomarkers such as genomics and neuroimaging in prevention research can alienate key community leaders and partners, and, combined with the eugenics movement discussed above, has a history of such alienation. The Syphilis Study at Tuskegee, in which Black male participants with syphilis in the study were not offered medical treatments known to be effective in treating syphilis, is one such example. Historical contexts such as this one may alienate participants and community stakeholders who are skeptical of how the data will be used and/or how it will be interpreted (Ricard et al., 2022). This history may also alienate key potential future collaborators (e.g., sociologists) who have important perspectives to share. This justified skepticism contributes to a vicious cycle in which researchers lack key collaborators and community partners, and thus may lack input to make the research more ethical and equitable, which in turn may further motivate those from marginalized and oppressed groups to avoid engaging in integrated biomarker-prevention science research.

Fourth, given many people's inaccurate intuitions of genes and brain as "immutable," "in-born," and "static" (Dar-Nimrod & Heine, 2011), identifying risk biomarkers may lead to stigma and/or self-fulfilling prophecies. The stigma attached for a "risk" biomarker may undermine its use in informing preventative interventions. For example, in one study, participants were randomly assigned to be told that there was either a very high or very low chance that they had a genetic risk for obesity. When asked to select a meal from a menu of options, participants who were told that they were *not* genetically predisposed to obesity were more likely to select unhealthy foods, indicating that personalized feedback that one's genetic risk is low may increase the likelihood of unhealthy choices (Ahn & Lebowitz, 2018). Fortunately, research has shown that beliefs regarding associations between genes and health outcomes can be changed via brief informational interventions (e.g., Driver et al., 2022).

Fifth, biomarker research may be challenging to interpret, which can lead the public to misinterpret research headlines. For example, a growing number of studies have documented the association between poverty and brain structure and function (e.g., Troller-Renfree et al., 2022). These studies may motivate policy to ameliorate or address the negative impacts of poverty, likely because biological research is viewed as more compelling (e.g., poverty must be "bad" if it impacts children's brains). It may also help motivate researchers to study this topic and see the potential upside of this research (and how it can inform policy to prevent child poverty). However, this same research may be communicated to the public and to relevant communities (e.g., those with lower income) in ways that increase stigma and undermine potential partnerships with communities at risk. For example, this same research could be incorrectly interpreted by youth as meaning that "poor kids have holes in their brains"—leading to self-fulfilling prophecies and stigma (Tolwinski, 2019). Although researchers understand that correlation does not equal causation, the general public may mistakenly make the false assumption that, for example, people with marginalized identities have mental illnesses like schizophrenia at higher rates due to their genetics, when the science is much more complex than this, given the non-random assortment of people to environments. Thus, there is a clear need for science education in society and amongst clinicians to address some outdated and inaccurate views about biology being static and unmalleable.

These are just some of the complex ethical challenges that must be further acknowledged, discussed, and integrated into the design of prevention science research endeavors before prevention-biomarker science can evolve in an equitable and meaningful manner. If these issues are not discussed, up-front, in potential collaborations and projects, key community partners may be alienated, undermining the success of integrating these fields.

Strategies to Promote the Responsible Integration of Biological and Prevention Science

Despite the limitations and challenges noted in the prior section, we believe that there are some approaches that could be implemented in the short term to move the field toward more equitable and responsible integration of biological and prevention science. Building on directions led by others in this area (e.g., Dick et al., 2017; Tindana et al., 2015), we present five such approaches in this section, at the center of which is to apply CBPR approaches.

Adopt a CBPR Approach

As noted in the prior section, racial and ethnic minorities are underrepresented in biomarker research. To increase participation from marginalized communities, prevention science research that involves biomarkers would benefit from leveraging a CBPR approach where community involvement is integrated in all aspects of the research (or even, through the use of some CBPR-consistent approaches to engage with the community). This approach requires the development

of mutual trust and bidirectional communication between biomarker scientists, prevention scientists, and communities (Fregonese, 2018), and we believe that it would ultimately help researchers achieve higher-quality research and benefit our society in a more representative manner.

As described by the National Institute on Minority Health and Health Disparities (NIMHD), CBPR "begins with the involvement of and a research topic of importance to the community and combines knowledge with action to improve health outcomes and eliminate health disparities" (https://www.nimhd.nih.gov/programs/extramural/community-based-participatory.html). It is a partnership that equitably involves community members, organizational representatives, and academic researchers in all aspects of the research process. It enables all partners to contribute their expertise, with shared responsibility and ownership; it enhances the understanding of a given phenomenon; and it integrates the knowledge gained with action to improve the health and well-being of community members, such as through interventions and policy change (Israel et al., 1998).

A CBPR approach requires that the researchers leading the work are committed to systematically involving all partners in the research process, and to recognizing and acknowledging the unique strengths that each partner brings. As such, researchers inform and give a voice to the community affected by the health condition and understand and value that this approach may reduce the autonomy and control of the research team (Fregonese, 2018; Tapp & Dulin, 2010). To achieve effective communication, scientists need to be willing to adapt technical language for the benefit of community leaders and advisory boards who are not familiar with scientific dialects (Fregonese, 2018). They also need to become familiar with methodologies such as focus groups, photo-voice, social network analysis, and ethnographic work (Kanamori et al., 2021a). Specific to genomics and neuroimaging research, this means explaining the methods, the data to be collected, and the ways the data will be used so that community members can easily understand. Models of successful science education efforts include public resources developed by the National Human Genome Research Institute (https://www.genome.gov/about-genomics), audiovisual media science communication disseminated by the Collaborative Studies on the Genetics of Alcoholism (COGA) project (https://cogastudy.org/aud/genes-in-aud/), Brain Awareness Campaign events sponsored by the Society for Neuroscience (https://www.sfn.org/outreach/brain-awareness-campaign), and coursework and activities geared towards high school students on the topics of genetics (https://cadrek12.org/projects/reducing-racially-biased-beliefs-fostering-complex-understanding-human-genetics-research) and neuroscience (Flanagan-Cato, 2019). However, more science education efforts are still needed to engage marginalized communities, such as increasing accessibility for non-English speakers (e.g., Budd et al., 2022) and disseminating these materials more broadly.

It is also important to display cultural humility in the creation of mutually respectful, equal, and dynamic partnerships between academic and underrepresented communities (Wallerstein & Duran, 2006). In other words, to create inclusive research approaches when integrating prevention science and biological science, we need to move the university-driven research agenda towards a mutually defined agenda or even a community-driven agenda (Wallerstein & Duran, 2006). Social network analysis can be used to identify and build a collaborative network of community partners (Kanamori et al., 2021b). Within CBPR approaches, the degree to which researchers and community partners collaborate can fall on a continuum, as illustrated in Fig. 2 (Clinical & Translational Science Awards Consortium, 2011). On the far right of the continuum, the goal is a truly equal partnership between scientists and underrepresented communities, where community members play a central role in

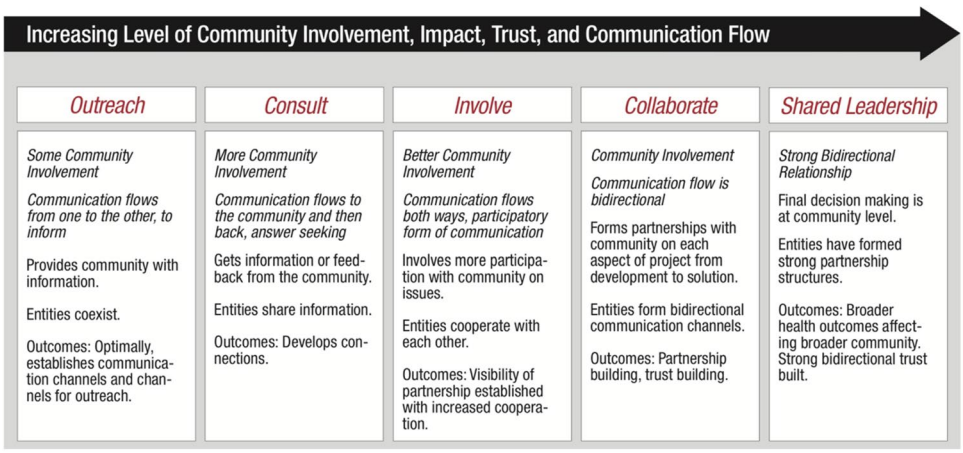

Fig. 2 Researcher-Community Collaboration Continuum. Source: Clinical and Translational Science Awards Consortium. (2011). Principles of community engagement. Rockville, MD: US Gov. Printing Office

decision-making, agenda-setting, and evaluating the appropriateness and priorities of future studies (Fregonese, 2018). By incorporating CBPR or aspects of CBPR approaches, prevention science-biomarker research has greater potential to improve an entire community's health and reduce health disparities (Minkler & Wallerstein, 2003). As such, the unit of analysis expands from focusing on the health of a participant to the health of the community at large.

Establish a Diverse and inclusive Research Team

Establishing an inclusive and diverse workforce (clinicians, translational researchers, and basic science investigators) is a second way to responsibly integrate biological and prevention science (Clark & Hurd, 2020). As noted above, this is also an element of CBPR. Increasing the number of scientists from marginalized communities who are involved in integrated biomarker-prevention science research can increase the number of participants from marginalized communities in this research. Pipeline strategies that increase the number of early career researchers from underrepresented and marginalized groups, who have good qualifications in CBPR, but face challenges when submitting NIH applications as principal investigator because of current considerations as to what constitutes an excellent score for an application (Wallerstein & Duran, 2006), would facilitate this goal. Consistent with the CBPR approach discussed above, inclusive representation in prevention science-biomarker collaborations from marginalized communities is promoted when efforts to improve diversity in researcher leadership, including equal recruitment, retention, and promotion rates with respect to age, sex, gender, race, and ethnicity, are enacted. This type of paradigm shift requires changes in the current funding and academic performance evaluation systems (Fregonese, 2018). For example, there are currently disincentives to incorporating CBPR into biomarker-prevention science projects because of long development times to form true and sustainable partnerships, implement interventions collaboratively, and publish together with community members (Wallerstein & Duran, 2006). Promotion and tenure performance review committees would need to consider the time and efforts involved in implementing a study that incorporated CBPR approaches, due to the impact of the timing of data collection and publications and the inclusion of a combination of peer-reviewed scientific and non-peer-reviewed community-oriented publications (Fregonese, 2018). Early career faculty from marginalized communities also require protected time free from heavy administrative responsibilities, and benefit from mentoring by researchers who have required expertise (Wallerstein & Duran, 2006). When these strategies are incorporated at a systems level, a more diverse scientific field will develop, which will lead to more innovation and collective creativity.

Ensure Robust Collaborations Between Prevention Scientists and Biomarker Experts

Another important CBPR-based element for advancing research that integrates prevention science and biological science is to develop and nurture collaborative partnerships across disciplines. Similar to community partnerships, successful prevention scientist-biological scientist partnerships take years to establish. To earn respect and trust across disciplines, the team members need to establish a common language; understand the respective discipline-specific theories, methods, and analytic approaches; and have an agreed upon approach to collaboration and "who does what." Common within-discipline activities such as writing a manuscript for publication are complicated when the work is multidisciplinary, as journal outlets, formats, lengths, and even authorship conventions may differ.

Once an effective partnership has been established, the team members can begin to discuss potential biological mechanisms and associated biomarkers that may be relevant, impacted, or invoked when a specific intervention is applied. It can be tempting (and certainly easier) to conduct a prevention trial and then measure a wide range of biomarkers to see what may have changed as a result of the intervention (see Fig. 1, Prevention Research Cycle, phase #2). However, atheoretical approaches are subject to Type I error, and do less to advance the field and the progression to the prevention research cycle phase #3 and beyond. Ideally, the team co-develops a theoretically grounded model of how a specific biomarker or system is part of a specific predictive pathway to a specific emotional or behavioral health outcome of interest before the work has been launched (prevention research cycle phases #1–2). Basic and applied research on transdiagnostic targets may be a good example—targeting these and learning about their biological correlates may be more effective than sticking to current diagnostic or preventative targets.

As noted earlier in Fig. 1, successful collaborations can create new knowledge that informs the prevention research cycle in bi-directional ways. For example, collaborative research in prevention research cycle phase #1 may indicate that parental scaffolding plays an etiological protective role on behavioral measures of child executive functioning. This might inform the development of a new study in the prevention research cycle phase #2, to add neuroimaging and a longitudinal element to examine the role of parental scaffolding on a biomarker of child executive functioning over time (e.g., prefrontal brain activity). If associations are identified, the research team may conceptualize an intervention to foster parental scaffolding, and measure whether changes in children's executive functioning were identified as a result. This could be tested in a prevention research cycle phase #3 efficacy trial. The knowledge gained from

this phase #3 trial may prompt the research team to theorize that *parental* executive functioning may also have an etiological role on associations between parental scaffolding and child executive functioning. A prevention research cycle phase #1 basic science study could then be initiated with a new sample, to test a modified theoretical model that tests a biomarker of parental executive functioning as a moderator of the association between parental scaffolding and child executive functioning (which could, in turn, inform future prevention targets in prevention research cycle phases #2–3).

Prioritize Improved Analytic and Multidimensional Modeling

There are a number of analytic and computational steps that can be implemented to help better integrate biological methods into prevention science research and interventions. The first pertains to how we model biomarker data. Historically, structural and functional neuroimaging studies examined brain regions in isolation of each other. There is growing recognition, however, that mental health and illness may be driven more by connections among brain regions than focal brain pathology (Basset et al., 2018; Braun et al., 2018; Menon, 2011). The emerging field of network neuroscience builds on a branch of mathematics called graph theory to model the connections between hundreds to thousands of regions of interests across the cortex and subcortex (Bassett et al., 2018). Similar developments are happening in bioinformatics and computational genomics to better understand the regulatory influence that genes have on each other and the principles of how DNA directs biology and molecular signaling pathways (Civelek & Lusis, 2014; Wei et al., 2014). These data-driven methods may enhance our mechanistic understanding of emotional and behavioral health and illness and provide new targets for both behavioral and pharmacological prevention and intervention efforts.

Next, most research on emotional and behavioral health and illness focuses on group-based statistics, examining how diverse groups differ on some outcome variable, or how one treatment compares to another. But group comparisons do not capture the heterogeneity of biological and psychological characteristics across any given outcome (Etkin et al., 2013; Insel & Cuthbert, 2015). Thus, any integrative approach to prevention science will ultimately need to model the individual at both biological and psychological levels of analysis. An example of this at the biomarker level is the recent development of "precision fMRI" approaches that use extended data acquisition and forward-thinking analyses of the functional connections in the brain to provide reliable and stable individual measures of brain organization (Gordon et al., 2017; Gratton et al., 2019). Early reports indicate that precision fMRI is more sensitive to individual differences and clinical symptoms than standard group-based analyses, and can increase the association between fMRI measures and behavior (Finn et al., 2015; Gordon et al., 2018; Kong et al., 2019). Future research is needed to examine whether precision fMRI techniques generate more individualized prognostic and diagnostic biomarkers, and more personalized targets in the brain for therapeutic interventions such as neuromodulation (e.g., transcranial magnetic stimulation, ultrasound). Paralleling precision fMRI is the development of personalized approaches to emotional and behavioral health that model variation in psychological symptoms and subjective experiences at the individual, rather than group, level of analysis (Wright & Woods, 2020). This development has been aided by advancements in the collection and sampling of longitudinal data (e.g., ambulatory assessment) and new statistical techniques that model dynamic processes of each individual's psychopathology. An important direction for future research will be to integrate person-specific approaches to measuring brain activity (e.g., precision fMRI) with personalized models of emotional and behavioral health into a prevention science framework.

Finally, there are well-known concerns about the validity of the two major classification systems for psychiatric disorders currently in use (the ICD and DSM; Etkin et al., 2013; Krueger et al., 2018; Wright & Woods, 2020). These systems are not grounded in current psychological science, neuroscience, or genetics and do not appear to capture the fundamental mechanisms underlying emotional and behavioral health symptoms. This disconnect between diagnostic nosology and biological processes and mechanisms has most certainly contributed to the challenges in integrating biological and prevention sciences. Moving forward, it will be important for prevention science to align itself with forward-thinking and data-driven analytic methods for classifying psychiatric symptoms, including the NIMH's Research Domain Criteria (RDoC; Insel & Cuthbert, 2015) and the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017).

Engage Research Teams in Conversations About Racism, Health Disparities, Language, and Ethical Issues

Given the long history of racism and other structural inequalities that have harmed science, harmed marginalized communities, and impeded progress in our ability to better integrate biomarkers into prevention science, we recommend that researchers who engage in biomarker-prevention science research also embed conversations and professional development activities about these topics into their research activities. Clark and Hurd (2020) recommend the inclusion of more proactive race-conscious or antiracism approaches to provide: (1) cognitive skillsets needed to identify and critically analyze biased assumptions, and (2) psychological tools required for healthy conversations about bias, racism, structural inequalities, and other social conditions that are perpetuating health

disparities in the U.S. Further, we need increased awareness of the language we use in describing participants in biomarker research, with a recent National Academies of Sciences report (2023) recommending that researchers tailor their use of population descriptors based on the type and purpose of their study and explain why and how those descriptors were selected in their work. Their report offers a decision tree to help researchers choose whether race, ethnicity or indigeneity, geography, genetic ancestry, or genetic similarity are most appropriate for the work. By embedding these conversations, trainings, language, and commitment to learning from the field's history and negative impacts (Gordon-Achebe et al., 2019), both established and early career prevention scientists will be better positioned to embark on prevention science-biomarker science with greater humility and respect for all persons, with the goal of improving the well-being of marginalized communities.

Include Relevant Expertise on Grant Review Panels and Journal Editorial Boards

Increasing the quality and quantity of integrated prevention science-biological science research requires that rigorous studies in this area are conducted and shared with scientific and community audiences. Possible solutions to accelerating the pace of translational research includes administrative actions such as ensuring that biologically oriented study sections and journal editorial boards include reviewers with prevention science and CBPR expertise, and vice versa. Similarly, inviting reviewers with interdisciplinary, integrative expertise may help provide relevant expertise to both promote research that is grounded in some of the principles laid out in this report, while also providing constructive critiques on research that may be lacking in one or more core ethical translational priority, to help guide future directions. Without scientists who are well versed across the spectrum—with training in working with marginalized communities and expertise in biological and prevention sciences, challenges will remain for this work to move forward, both because there will not be experts to lead it and because reviewers of papers and grants may not have the requisite expertise to review and appreciate the public health value of such work.

Benefits and Challenges to Integrating Biomarker Science into Prevention Science Research Within a CBPR Context

Building on the strategies to promote the responsible integration of biological and prevention sciences described in the prior section, Table 1 presents an adaptation of the work of Hartwig and colleagues (2006) to describe a set of community benefits, research benefits, and challenges to consider when embarking on research that includes the integration of prevention science and biomarker science. As shown in Table 1, integrated prevention-biomarker collaborative research involves a series of steps, beginning with the assembly of a team of collaborators and progressing sequentially to activities such as defining the research questions and designing the project, conducting the study and intervention, analyzing and interpreting the data, and disseminating the findings. There are both community benefits and research benefits when researchers and the community work together in a collaborative prevention-biomarker study. Yet, there are also challenges in this type of collaborative research. In designing new collaborative studies in prevention-biomarker science, it is helpful to understand the unique benefits and challenges for the specific project early in the collaborative process. Unexpected challenges will likely still arise, but explicit conversations about benefits and challenges can help the team weather such challenges successfully. Table 1 highlights some of the common community benefits, research benefits, and challenges in prevention-biomarker collaborative science. The Table is intended to provide a high-level guide for researchers who wish to engage in integrated prevention science-biomarker research in the context of CBPR principles and approaches. The specific benefits to the community and researchers will necessarily need to be customized to the specific research topic and focal population. However, the challenges described in Table 1 are intended to serve as a guide for the team to consider and customize before embarking on a new project, to ensure the viability of a collaborative endeavor well in advance of asking for significant time, resources, and investment from the community.

Examples of Studies That Have Infused CBPR Components into an Integrated Prevention-Biomarker Study

We have discussed the challenges in integrating prevention-biological science in research and provided some ready-to-implement strategies and frameworks that could move integration forward. In this section, we provide examples of prevention science research that have incorporated at least some of the strategies recommended throughout this article and presented in Table 1. Our examples are not comprehensive, rather, the purpose is to present a few studies that reflect different phases of the prevention research cycle and incorporate biomarker science, with consideration of at least one CBPR value or approach.

We draw specifically from prevention research cycle phases #1–3 (see Fig. 1). Knowledge from phase #1 can provide insights into biological mechanisms in the etiology of a behavior, such as stress response systems, that may be suitable for incorporation into phase #2 research to help identify new targets for prevention or intervention. Further, knowledge from phases #1–2 may lead to insights about

Table 1 Proposed steps to apply a CBPR framework to integrated prevention-biomarker research: benefits and considerations

Assemble a team of collaborators	
Community benefits	• Community and research resources are used efficiently • Community members feel empowered • Representation is also prioritized when forming the research team • Community members may enjoy interacting with an interdisciplinary team
Research benefits	• Better probability of completing the project as planned • Diverse perspectives could generate important and unanticipated new questions
Challenges	• Takes time to identify the right collaborators with expertise in prevention science and/or the specific biomarker(s) of interest • Takes time to convince potential collaborators that they will play an important role in the project • Collaborators without community engagement experience may be less interested in or skilled at engaging in this type of integrated work
Develop the structure for collaboration to guide decision making	
Community benefits	• Trust is built (over time) • All members understand and accept human subject protection procedures
Research benefits	• Each collaborator shares their agenda • Clear roles and responsibilities for all partners in the research can improve teamwork and ultimately enhance the research through consideration of diverse perspectives
Challenges	• Takes time to build skills in group facilitation, consensus building, and group negotiation • Researchers who have not engaged with the community may have trouble sharing decision making or may not understand the value
Define the research question	
Community benefits	• Problems addressed are highly relevant to the community • Community members may enjoy learning about various research approaches (e.g., neuroimaging, genetics)
Research benefits	• Participants are motivated to invest their time in the project because it is viewed as relevant to them/their community • Research questions tailored to the community may be more acceptable to participants
Challenges	• Time consuming, yet sometimes decisions may need to be made with a rapid turn-around • The community may identify different issues than those identified by researchers, or for which funding is available • Community members may not perceive the relevance of measuring biomarkers or may have ethical concerns
Design the project at a high level	
Community benefits	• The community gains health knowledge and learns program design
Research benefits	• The community supports the research process • The community encourages members to participate • Designs that will be less appealing to participants are discarded
Challenges	• Study design may be more expensive and may take longer to implement • Possible threats to scientific rigor • Community may not have interest in some components of the study (e.g., biomarkers)
Seek funding	
Community benefits	• Aims of the grant proposal address issues that are important to the community • Community may gain knowledge of how to seek funding or learn of new funding sources
Research benefits	• Including community members on a steering committee or as co-investigators increases the likelihood of the application being funded • Additional funding opportunities may be available given the community partnership
Challenges	• Seeking input from the community slows the process and may complicate the proposal development, and sometimes funding opportunities have a very short turn-around timeline • Researcher's goals may not align with community goals
Recruit and retain participants	
Community benefits	• Data collection approaches are acceptable to participants
Research benefits	• Participant recruitment and retention is easier and more effective • Participants are more motivated to be part of the project

Table 1 (continued)

Challenges	• Recruitment and retention approaches may be more complex, expensive and time consuming • The original data collection procedures may need to be modified • Larger samples sizes or different recruitment regions or sources may be required • Participants may be hesitant to provide biological samples • Informed consent documents may be more complicated to draft and review with participants
Select study measures	
Community benefits	• Measurement instruments are less likely to be offensive or biased • Measurement instruments are less likely to be confusing or misunderstood by participants
Research benefits	• Measurement instruments may have better reliability and validity for the population being studied • Less missing data if participants view the questions are acceptable, understandable, and appropriate
Challenges	• May be time consuming, particularly if cultural and/or linguistic adaptations or translations/back-translations are incorporated, and measurement invariance testing done • Possible threats to scientific rigor • May be less comparable to other studies if measures were modified or new measures developed for the study • Changes in the specific biomarker(s) collected and/or the collection methods may make them more acceptable, but with less interpretation power • Accommodating community members' requests for modifications to measures or to biomarker collection protocols may make these less comparable to other studies or limit their interpretability
Design and implement the intervention components	
Community benefits	• Community feels the intervention is designed for and by them and offers benefits • Intervention provides resources to the community
Research benefits	• Increased likelihood of having the focal population feel positive about the study • Increased potential for sustainability beyond the initial study
Challenges	• Time consuming process of working together • Hiring community members may be less efficient than hiring staff • May take time to train community members • Universities may have barriers and/or delays in hiring community members, who may have extensive and relevant lived experiences but lack a higher education degree
Analyze and interpret the data	
Community benefits	• Community feels conclusions are accurate and sensitive
Research benefits	• Community supports the conclusions • Researcher less likely to be criticized for limited insight or cultural insensitivity
Challenges	• Interpretation of data by community may differ from that of researchers, calling for negotiation • Biomarker data is often so large/complex, may be difficult to negotiate or co-interpret with the community • Challenges identifying at what point in the analysis process community members should be involved
Disseminate findings	
Community benefits	• Community is proud of project accomplishments • Community gains experience in scientific writing that could facilitate career advancement • Findings are disseminated through outlets other than academic journals, making the science more accessible • Increased potential for project sustainability
Research benefits	• Findings are a more accurate reflection of the experiences of the community
Challenges	• Time consuming; requires extra mutual learning and negotiation • Community may disagree with how biomarkers are interpreted and what it should mean for translation • Challenges if study results indicate less positive outcomes for marginalized communities or people with marginalized identities

Note. Adapted from *Unit 1: Community-Based Participatory Research: Getting Grounded,* by K. Hartwig, D. Calleson, and M. Williams. (2006). In: The Examining Community-Institutional Partnerships for Prevention Research Group (Eds.), *Developing and sustaining community-based participatory research partnerships: A skill-building curriculum.* www.cbprcurriculum.info. Adapted with permission

specific mechanisms of change that could be incorporated into screening criteria in an efficacy study in phase #3, or, could be used to help select a subset of individuals who may be most likely to benefit from a particular intervention in a phase #3 study. Specifically, scores or thresholds of a biological measure may be reliable ways to discern for whom a particular psychosocial intervention may be most effective, using moderation analyses. Biomarkers can also be incorporated into phase #2 to measure the ability of a preventive intervention to serve as a mechanism of change (mediational analysis), and into phase #3 to measure efficacy of an intervention on behavioral or cognitive outcomes, as well as biomarkers. Prevention research phases #4 and #5 involve large-scale community trials and rollout of effective programs. We were unable to locate relevant examples of integrated biomarker-prevention science research that mapped directly onto phases #4–5. Given the additional challenges that are present when integrating biomarkers into the latter phases of the prevention research cycle and the current state of the science, we recommend that human health advances are most likely to occur in prevention research cycle phases #1–2, with application to phase #3 efficacy trials to test the processes and mechanisms identified in earlier stages using prospective designs, within a tightly controlled research study.

Prevention Research Cycle Phase #1: Basic Science Research that Identifies Risk and Protective Factors

As noted in Fig. 1, prevention research cycle phase #1 consists of basic science research that can provide information about biological and environmental risk and protective factors in the etiology of a behavior, that may then be suitable for subsequent incorporation into a prevention research cycle phase #2 or #3 study. One example of research in phase #1 is research from the ABCD study that examined associations between income, brain structure, and mental health, while considering how state-level policies such as anti-poverty programs may impact these associations (Weissman et al., 2023). There is a growing body of work examining the neuroscience of socioeconomic status and proposing that the brain is an entry point or pathway through which poverty and adversity become embedded in biology to generate these disparities (Hyde et al., 2020; Nusslock & Farah, 2022). To address this question, over 10,000 9- to 11-year-old youth from 17 states participated in a neuroimaging assessment, and associations with family income and youth psychopathology were examined (Weissman et al., 2023). Lower family income was associated with smaller hippocampal volume, and this association was stronger in states with a higher cost of living. However, the authors also identified a benefit of policies in some states that provided more income for low-income families (e.g., those that provided more cash benefits via Earned Income Tax Credits and Temporary Assistance for Needy Families). In such instances, the socioeconomic disparities in hippocampal volume were reduced by 34%, such that the association of family income with hippocampal volume in states with more generous benefits resembled that in the lowest cost of living states (with a similar pattern for child depression as an outcome). This study provides one example of how anti-poverty state-wide policies could impact associations between family income and a biomarker (hippocampal volume), in some settings. Also, see work from the Baby's First Years study suggesting that monthly unconditional cash transfers to low-income families may have an impact on infant brain activity (Troller-Renfree et al., 2022). Prevention science researchers interested in examining mechanisms of change related to cash assistance programs and policies in phase #2 or #3 prevention research studies may benefit from including neuroimaging, if they hypothesize biological impacts in specific brain regions of a specific policy or practice.

Prevention Research Cycle Phase #2: Biological Mechanisms of Change Identified via a Prevention Study (Biomarkers as Mediators)

There are several examples from the field of prevention science that document intervention-related changes in a hypothesized biological mechanism. The Bucharest Early Intervention Project (BEIP) serves as one example by leveraging neuroimaging methods to elucidate the effects of psychosocial deprivation on brain development and cognitive functioning. In this study, researchers examined the development of infants and young children residing in institutional care who were randomly assigned to either a high-quality foster care or to care as usual (typically prolonged institutional care; Zeanah et al., 2003). This randomized controlled trial required navigating the complex ethics of conducting rigorous prevention science with vulnerable populations (Zeanah et al., 2012). The experimental design affords greater confidence in examining causal pathways from psychosocial deprivation to a host of negative developmental sequelae thought to be mediated through altered brain development. Structural magnetic resonance imaging (MRI) was initiated at 8 years and additional MRI assessments were conducted at 16 years. Study results indicated that foster care was an effective intervention in mitigating reduced cortical white matter volume associated with early deprivation (Sheridan et al., 2012). Moreover, specific white matter tracts contributed to these improvements, such as those involved in limbic and frontostriatal circuitry (Bick et al., 2015). Longitudinal examinations have shown greater cortical thinning from middle childhood to adolescence for children originally randomized into foster care compared to institutionally reared children, mirroring normative patterns

of neural restructuring that occur across this development transition. Taken together, the BEIP studies highlight how specific biomarkers identified via neuroimaging may serve as mechanisms of action of the intervention "under the skin."

A second example comes from the Strong African American Families study, a family skills training program aimed at mitigating the negative effects of poverty and life stress on rural African American youths through a focus on youths, parents, and their family interactions (Brody, 2016). As young adults (approximately age 25 years old), the same individuals who participated in the original intervention completed fMRI scans. Increased connectivity between the hippocampus and ventromedial prefrontal cortex was noted in the intervention group compared to controls—suggesting a mechanism of action of the adolescent intervention on brain connectivity in young adulthood (Hanson et al., 2019). Furthermore, individual gains in self-regulation, instilled by the intervention, statistically explained this brain difference. These results begin to connect neurobiological and psychosocial markers of risk and resiliency. The Strong African American Families and the BEIP examples both identified a biomarker indicative of a possible mechanism of change appearing years after the original intervention. A new study that proposed to examine these hypothesized biomarkers before and after the intervention in an efficacy trial would represent the progression of this work to the prevention research cycle phase #3.

Prevention Research Cycle Phase #2: Examining Whether Intervention Efficacy Is Predicated on a Biological Variable (Biomarkers as Moderators)

Perhaps the area with the most examples of integrated prevention science-biomarker research falls within this area of prevention research cycle phase #2, where researchers have examined whether the effects of an intervention (either a psychosocial intervention or a policy-level intervention) vary as a function of a specific genetic biomarker. Some of the advantages to this line of research are that: (1) one's inherited DNA sequence does not change, and thus, retroactive collection of DNA in established prevention programs can be a relatively easy way to examine genetic associations across development, regardless of when DNA collection was initiated; (2) retroactive collection allows for participant-investigator rapport to be firmly established, engendering a trust that can facilitate collection of biological data, as described in an earlier section of this manuscript focused on CBPR methods; (3) random assignment to intervention eliminates person-level selection and the confound of gene-environment correlation; (4) random assignment increases statistical power, optimizing the detection of gene-environment interactions; (5) intervention designs are often longitudinal, enabling tests of distal intervention effects.

The Project Alliance 1 (PAL1) and Early Steps Multisite (ESM) studies, both large, randomized control trials of the Family Check-Up (FCU) intervention (at different developmental periods), are examples of prevention research cycle phase #2 studies that examined whether the intervention's effects differed based on one's genetics. The FCU is a brief psychosocial intervention designed to reduce youth problem behaviors by enhancing family management practices (Dishion & Stormshak, 2007; Dishion et al., 2008; Gill et al., 2008). Both PAL1 and ESM samples are racially/ethnically diverse, with the latter leveraging multi-site recruitment to maximize diversity. Both studies collected DNA well after launch, when participants were 27 and 14 years old, respectively. Using a "gene-by-intervention" analysis approach, each study documented intervention effects that varied as a function of participants' genetic variation. Specifically, the FCU's effects on maladaptive conduct problem trajectories, peer rejection, and substance use problems interacted with an individual's polygenic score that indexed genetic risk for aggression and alcohol dependence (e.g., the intervention attenuated the link between relevant genetic risk and maladaptive outcomes; Elam et al., 2021, 2022; Kuo et al., 2019; Shaw et al., 2019). Moreover, children with greater genetic propensity towards environmental sensitivity showed a greater decrease in internalizing symptoms compared to those assigned to the control group, meaning that this polygenic score may have helped to identify youth who were most receptive to the positive effects of the intervention in preventing internalizing symptoms (Lemery-Chalfant et al., 2018). These emerging findings highlight the promise of genetically informed prevention science. As new and more highly powered GWAS are published and made available, prevention scientists can compute new polygenic scores and test associations with diverse phenotypes a priori, in prevention research cycle phase #2 or #3 studies. Creating a dynamic bank of polygenic scores illustrates another important advantage of integrating genetics into established prevention programs—the ability to generate new variables (assuming proper consent was obtained) without incurring further participant burden. Moreover, this science is evolving rapidly and novel genetic methods that stand to further enhance prevention science are on the horizon. For example, the Joint (Epi)genetics of Parenting and Stress Reactivity in the Development of Youths (JEOPARDY) study will implement a randomized control trial of the FCU and examine intervention effects on gene expression (Overbeek et al., 2020).

Ongoing Barriers, Future Directions, and Recommendations for Researchers

Biological sciences have made significant advances over the past two decades, making technologies such as genomics and neuroimaging increasingly accessible to researchers. This has led to an increase in the uptake of biomarkers into prevention science studies, with multiple examples across prevention research cycle phases #1–2 completed and many more studies currently underway. *Prevention Science* has published a modest number of studies that integrate biomarkers in the last decade, most of which focus on genetics and were included as part of the 2018 special issue, 'Incorporating Genetics in Prevention Science: Considering Methodology and Implications.' Providing channels like this for the publication of burgeoning prevention-biomarker science will be key in advancing this work. Despite this progress, the field of integrated prevention-biomarker science is still quite young, and due both to the relative recency of the field as well as an unanticipated complexity of the science, there are challenges that the field needs to overcome in order to advance an equitable approach to integrated prevention science-biomarker science research. Some of the more prominent challenges discussed in this report include the lack of diversity in participants and researchers who are involved in the research; a lack of community engagement in all stages of the research; data and measurement issues such as small samples and/or small effect sizes, measurement reliability and validity issues; and ethical considerations. Given these challenges and the core value of prevention science of improving the lives of marginalized communities and people with marginalized identities, we recommended more comprehensive integration of CBPR approaches into research aimed at integrating prevention science with biomarker science. In cases where the relevant biomarker data and prevention science-relevant data have already been collected, it is not too late to consider basing the investigation in CBPR principles using some of the approaches discussed in this report.

Ongoing barriers and questions remain that have not been specifically discussed in this report, as we focused primarily on prevention research cycle phases #1–2. But as the work and methods advance to later stages of the prevention research cycle, research teams will need to consider the relevance of this work to policy makers, how to ethically implement large-scale biomarker collections in community settings in the context of effectiveness studies, and whether the investment of time and resources are best spent in biomarker collections or in providing additional direct services to the focal community. Further, it is anticipated that there will be ongoing advances in specific biomarker approaches and methods, and research teams will need to prioritize continued partnerships and training to maximize the likelihood that they will maintain the requisite expertise in the specific biomarker methods. As part of this training and ethical responsibility, it is essential that prevention scientists train and provide opportunities for early career prevention scientists with marginalized identities to become the next leaders in integrated prevention science-biomarker science that is steeped in CBPR approaches.

In closing, engaging in an equitable approach to integrated prevention science-biomarker science can lead to both scientific and community benefits. To maximize these potential benefits and minimize unintended harms, we recommend that prevention science researchers self-reflect on a series of questions before embarking on such endeavors: (1) Is there a theoretical rationale for the inclusion of a biomarker?; (2) Does the team include experts in the specific biomarker science?; Does the team include experts from the community or focal population? (3) Has the study team thoroughly educated themselves about the historical and current context related to their research question and focal population?; (4) Has input and consultation from the community or focal population been collected in the design of the research study? If so, is there support from the community for the research? Can members of the community participate as part of the research process?; (5) If the study is successful and the hypotheses are supported, will the study provide new knowledge that has reasonable potential to directly or indirectly benefit the focal population?; and (6) Is there potential for the community to use the knowledge generated from the research to sustain or apply the work after the research study and any associated funding are concluded? In this self-reflection, if the researchers answer 'no' to any of these questions, we recommend that they pause and revisit their approach and/or research questions until approaches that are more likely to promote health equity can be developed.

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Advancing Translational Research

Lan Murdock, Taylor & Francis and Rose Stephenson, HEPI

Foreword
With a new Labour Government in place, universities have a crucial role in supporting public policy development and enactment. The Prime Minister, Keir Starmer, particularly welcomes evidence-based policy development and evaluation. The higher education sector needs to ensure that it plays its part in providing evidence and support to politicians. This should be seen as a core part of their civic responsibilities. There are excellent examples of researchers engaging with policymakers. Researchers must respond to the needs of public policymakers by showing pragmatism in their approach, embracing problem-solving alongside broader blue-sky thinking and completing their research in a timely manner to meet the pressures politicians face to take decisions. With a mission-driven government focused on growth, opportunities and the green economy, research designed to solve knotty problems will help demonstrate the value of higher education institutions and maximise their civic impact.

The Rt Hon. the Baroness Hodge of Barking DBE, Former Minister of Lifelong Learning, Further and Higher Education

Executive summary

This Policy Note explains the crucial role of translational research in bridging the gap between scientific discovery and real-world application and underscores its potential to enhance interdisciplinary collaboration, foster innovation and commercialisation and translate research into policy, practice and products. While translational research originated in applied medicine, other disciplines can adopt and benefit from its approaches and mindset.

Key findings

- **Definition and importance:** Translational research involves turning basic research knowledge into practical applications to improve human health and well-being or adopting a 'goal-orientated' approach from the initial research design stage to solve specific problems. It encourages cross-disciplinary collaboration and can significantly impact societal challenges.
- **Challenges:** The field faces numerous barriers, including scientific, regulatory, financial, infrastructural and cultural obstacles. These challenges require innovative solutions and collective efforts to overcome.
- **Role of publishers:** Publishers can support translational research by making scientific knowledge more accessible, fostering cross-disciplinary collaboration and promoting the translation of research findings into actionable insights.

Recommendations

For academia and research institutions:

- Develop a comprehensive framework for planning, delivering and assessing translational research.
- Offer training and mentoring opportunities for researchers and staff.
- Incentivise and reward researchers involved in translational research.

For funders and decision-makers:

- Diversify funding support for translational research, especially in early and intermediate stages.
- Align funding strategies and policies among various types of funders.
- Develop funding programmes that are adaptable to the challenges of translational research.

For institutions:

- Improve structures, facilities, and equipment crucial for research translation.
- Foster stakeholder and end-user participation in the research process.
- Recognise team science contributions in academic evaluations.

For publishers:

- Create new formats to engage researchers with different audiences more easily.
- Develop platforms and networks to facilitate interaction across academia, industry and the public.
- Adopt standards and tools to improve the access, visibility and impact of translational research.

Introduction

Translational research is a goal-oriented approach that aims to bridge the gap between scientific discovery and real-world application. It involves change, transdisciplinarity (integrating the natural, social and health sciences beyond their traditional boundaries) and collaboration across multiple domains and stakeholders [1]. Translational research can enhance interdisciplinary collaboration, foster innovation and commercialisation and translate research into policy, practice and products. However, translational research also faces many barriers that hinder its progress and impact. These include scientific, regulatory, financial, infrastructural and cultural challenges that require collective efforts and innovative solutions to overcome.

Publishers can play a crucial role in supporting translational research: by making knowledge more accessible, fostering cross-disciplinary collaboration and promoting the translation of research findings into actionable insights. This Policy Note outlines the challenges and opportunities of translational research. It makes recommendations on how to support research translation effectively. This is based on the findings from a co-convened workshop in Brussels, where we brought together a diverse group of topic experts, research policy influencers, funders and decision-makers. This meeting discussed how translational methods, approaches and mindsets could be leveraged beyond specific research fields to foster interdisciplinary collaboration. The Policy Note also showcases an effective translational research case study from the University of Bath, UK.

What is translational research?

For this paper, we have very simply defined research into two categories:

(1) theory-based, discovery-orientated or basic research; and
(2) translational research.

Translational research can turn basic research knowledge into practical applications to enhance human health and wellbeing [2]. This approach looks at what happens to research in its transition from knowledge to application to provide a real-world solution. Translational research can also adopt a 'goal-orientated' approach at the initial research design stage. The translational model originates in the biomedical sciences and clinical practices but it is not exclusive to these fields.

In both models, translational research utilises transdisciplinarity and collaboration and can lead to a more substantial research impact [3].

From an early stage of the research process, translational research design must consider: future dissemination; accessibility; exploitation; safety monitoring; and the potential reuse of results. In the biomedical field, this would mean planning a project's regulatory strategy at a very early stage, ensuring that requirements for commercialisation (for example, compliance with regulations and standards) are met from the outset. Society is the starting point of the investigation for the humanities and social sciences, and translational research means the direct involvement of those affected by a study to create a 'social license to operate' among the stakeholders. In other words, a deep understanding of citizens' needs and for companies operating in an environment of mutual trust within a community. The social licence is built over time and foresees the engagement of those impacted by the research outputs, such as the patients directly impacted by medical trials or communities affected by green energy pilots. A participatory approach to development or public policies is critical for successful outcomes. Translational research also requires a 'team science' mindset, entailing collaborative efforts across disciplinary boundaries, extending across multiple research projects and involving various stakeholders over time.

This 'team science' mindset typically fits with biomedical sciences, where there are clear pathways from scientific breakthroughs, trials, regulatory approval and streamlining to market access [4]. The journey of translating discoveries into treatments, spanning many years and diverse research expertise, offers a set of foreseeable stages and timelines. This helps guide the planning of steps needed to advance early-stage scientific breakthroughs into practical treatments and their real-world application. However, the same process does not often apply to many other disciplines undertaking basic research as the research does not necessarily have a clear target user, audience or beneficiary.

Why is translational research important?

Translational research can accelerate scientific discovery and address pressing societal challenges. Big science requires large multidisciplinary teams, which differs from the approach a single researcher running a subject-based research project might take. The key benefits of adopting a translational research mindset include:

- **Promoting cross-disciplinary collaboration:** Translational research encourages researchers from different disciplines, sectors and institutions to work together. By combining diverse views and skills, translational research can tackle complex and multidimensional problems with interdisciplinary solutions. Translational research is goal-oriented, involving all the subjects needed to solve a problem.
- **Fostering innovation and commercialisation:** Translational research can enable knowledge and

technology transfer between academia and industry. By matching research goals and outputs with market demands and opportunities, translational research can speed up the creation and uptake of new products, services and methods to enhance health, wellbeing and quality of life. Translational research can also foster entrepreneurship and economic development by creating new markets and industries, generating jobs and incomes and improving growth and productivity.

- **Solving complex and pressing health and societal challenges:** Large multidisciplinary translational research teams can set more ambitious goals to solve some of our most complex health and societal challenges. These may include a cure for cancer, ending neurodegenerative disease, new approaches to diabetes mellitus care and even new approaches to health equity.
- **Making research useful for policy and practice:** Translational research can connect research, policy and practice. By working with policymakers, practitioners and end-users from the beginning of the research process, translational research can ensure that research findings are useful and digestible for decision-making and implementation. Translational research can also shape and inform policy priorities as well as policy evaluation. In addition, translational research can increase the impact of research by providing evidence-based solutions and recommendations for solving societal challenges and needs.

Challenges for translational research

Translational research has many possibilities, but it also faces difficulties that hinder its development and influence. These include scientific, infrastructural, financial, cultural and regulatory aspects, from the difficulties of complying with regulatory requirements to obtaining funding support. To overcome these challenges requires collaborative actions and creative approaches [5]. Challenges to successful translational research include:

- **Lack of education and training:** Translational research involves various stages and phases that require different expertise, methods and structures. The combination and organisation of these elements can create difficulties for translational research, such as ensuring the quality, accuracy and reliability of research outcomes, solving ethical and legal problems and managing data and information. This lack of education and training can lead to a lack of capabilities among scientists to translate scientific research into applicable insights, as well as a lack of trained staff to organise and manage the complex transitional research cycle [6]. Institutions can also develop a role for facilitators of translational research, who manage the process alongside scientists.
- **Lack of career incentives to perform translational research:** Individual research output, such as high-impact publications, is still the primary criterion (as required by the Research Excellence Framework) for career progression [7]. Researchers involved in translational research may not be able to produce an adequate publication record to meet the requirements of career promotion since translational projects generally take longer to complete. Researchers are also more likely to be part of a cross-disciplinary team, which could make it challenging to evaluate their contribution to the research outcome since they may be working outside their recognised disciplines.
- **Lack of sufficient infrastructural support:** Translational research requires effective and efficient management and coordination of the various resources, activities and stakeholders involved in the translational process, which can encounter practical issues, such as the lack of adequate and accessible facilities and equipment and the difficulty of recruiting trained interdisciplinary staff to support investigations throughout the translational research cycle. Better established research workflows across the translational process would help to counter this challenge.
- **Lack of financial resources:** Translational research needs significant and long-term funding to enable the lengthy and expensive process of turning scientific findings into real-world solutions. However, translational research often lacks funding, especially in the initial and middle stages of the research pipeline, where the chance of failure is high, and the investment outcome is unclear. Furthermore, due to a lack of collaboration among funders and their different standards and requirements, translational research may face challenges in obtaining various types of funding, such as public, private and philanthropic funds. For example, in social sciences and humanities, translational research is rarely considered an option, as the translational approach is rooted in medical research. While funders encourage the narrative around the impact of research, they fail to identify the potential of translational research at the design stage (for example, the need for a multidisciplinary team or the clear involvement of interest groups). There is a lack of funding dedicated to these disciplines because it is only sometimes obvious who the target audience is.
- **Regulatory barriers:** Translational research must follow different rules and norms that control how new products, services and processes are developed, tested, approved and sold. These may cover many complex elements, such as ethics involved in human research, tissue banking and material transfer regulations, intellectual property rights and agreements and toxicology and manufacturing regulations. Similarly in the

humanities, for example, there are privacy issues on the exchange of artefacts, or intellectual rights for performance and images, and social sciences in data collections. These rules and norms can change depending on the country or region, so translational research needs to adapt and match the changing requirements of regulators and stakeholders.

The role of the publisher in translational research

Publishers can boost translational research by making scientific knowledge more accessible, encouraging interdisciplinary cooperation and supporting the translation of research findings into actionable insights. By providing platforms for peer-reviewed research, scholarly journals serve as an intermediary for knowledge exchange and dialogue among researchers, societies, funders, policymakers, industry stakeholders and the broader public. Steps that publishers can take to support translational research include:

- **Making knowledge easier to access:** Publishers can make translational research more accessible, visible and impactful by using open research models, which let people freely access and reuse research outputs [8]. By following standards and tools for data sharing, metadata and linking, publishers can also make translational research easier to find and use. This can include using:
  - the FAIR principles (guidelines to improve the Findability, Accessibility, Interoperability and Reuse of digital assets);
  - the DOI (Digital Identifier of any Object) system; and
  - the ORCID (Open Researcher and Contributor ID) registry [9–11].

Assisted by AI tools (guided by policies and best practices), publishers can create new forms of content such as visualisations, translations and annotations to reach more diverse audiences with translational research [12].

- **Encouraging cross-disciplinary collaboration:** Publishers can curate interdisciplinary journals, special issues and collections highlighting the broad and deep range of research that connects different fields to promote and help researchers from various disciplines and institutions work together [13]. Publishers may also help review and assess interdisciplinary research by using new standards and measures, such as how relevant and impactful the research is for society. Publishers also have a better sense of the 'consumption' of research and can target citizens' needs and demand for knowledge from both public and private audiences.
- **Publishing well-designed studies with negative results:** Negative data and refutations form a crucial part of the scientific process [14]. Publishers should provide avenues and clear policies for researchers to publish negative results, which inform the scientific community about what does not work and prevent costly and time-consuming repetitive negative studies.
- **Supporting the translation of research findings into actionable insights:** Publishers can help turn research findings into practical solutions by bringing together researchers and the people who use and benefit from their work, such as policymakers, practitioners and other end-users, from the beginning of the research process. Publishers can also offer ways to create and share research jointly, such as stakeholder workshops, key policy highlights and plain language summaries, encouraging communication and collaboration among researchers and the beneficiaries of research [15].

Effective translational research – a case study

The following case study illustrates how translational research can address complex and multifaceted problems, generating significant benefits for health, society and the economy.

Delivering affordable reductions in CO_2 from vehicles sold in high volumes in the UK and abroad

- Researchers: Professor Sam Akehurst, Dr Colin Copeland, Professor Chris Brace, Professor Jamie Turner

How do you link academia with industry?

Researchers at IAAPS (a world-leading centre of excellence supporting the transport industry in the transition to net zero) at the University of Bath have a long-standing relationship with the advanced engineering and research team at Ford's research centre in Dunton, Essex. Like many enduring relationships, the initial connection was through the presentation of work at conferences and subsequently grew through sponsorship of student and postgraduate projects. This led to industry and government-funded research collaborations spanning several decades. Throughout the relationship, our task was to understand the key challenges our industry colleagues face, identify how we could contribute our research capabilities to solving these issues and jointly develop a research programme. In this way, the impact of our research is baked in from the start; this is the key aim of our collaboration. This process was repeated throughout the relationship and the work described here is a typical case study.

What was the goal of the research?

While electrified propulsion will eventually replace internal combustion engines, it will take decades to work through the fleet. Therefore, every engine built must be as efficient as it can be. Ford wanted to make its best-selling petrol engine more efficient by introducing an advanced control strategy, including the use of a larger turbocharger which can drive more air into the engine when needed. However, if launched without sufficient research, these new technologies can introduce unwanted interactions that can degrade their benefits and reduce consumer acceptance. To understand and carefully control such complexities, Ford needed a laboratory-based approach.

What research did your team undertake?

To test and improve the new turbocharger, Ford collaborated with the Bath research team. The Bath team developed a new experimental approach that could precisely emulate the real-world behaviour of the engine and the turbocharger across all operating conditions. The results of the experiments helped Ford to improve the design of the turbocharger and control system, leading to lower CO_2 emissions and better customer satisfaction.

How did this research translate into real-world use?
The insights gained through the research were incorporated into the engine design and control system by Ford engineers. The new engine allowed the CO_2 emissions of the most popular engine variant of the latest generation Fiesta (at the time, the UK's biggest selling passenger car) to be reduced by 9%. Engines have been fitted to the Fiesta, the Focus (the UK's second best-selling vehicle) and seven other Ford models.
What was the impact of this translational research?
Around 1.4 million new Ford vehicles each year emit less CO_2 and pollutants because of this work, delivering an annual cumulative CO_2 saving equivalent to taking 109,000 average cars off the road every year. The impact will continue to accrue for a combined design life and in-service life estimated at a total of approximately 20 years, with the benefits continuing into next-generation engines through the incorporation of the knowledge into future designs.

Why translational research?
Translational research is business as usual at IAAPS. Much of the funding for our work comes through The Advance Propulsion Centre and Innovate UK and specifically targets the application of research into real world problems. In the Automotive industry, this means reducing fuel consumption and emissions. This provides research and development funding to 'accelerate the transition to a net-zero automotive industry'. Funding like this can only be won in collaboration with industry and is therefore driving more translation research.
What challenges do you face when undertaking translational research?
There can be a tension between discovery-orientated research and translational research. If your work aims to solve a problem, you can sometimes solve this problem (and meet your goal) without fully discovering new knowledge. If you are no longer pursuing new knowledge, you are arguably not undertaking research. This can be problematic when getting translational research published in the highest-impact journals and achieving four-star papers for REF submissions. However, translation research underpins great impact case studies for the REF.
How are you building translational research capabilities at IAAPS?
The goal-orientated approach of translational research is evolving, with researchers now having to identify clear goals that may have previously been straightforward. For IAAPS this is a direct result of the technological uncertainty that exists within the automotive and propulsion industries. The internal combustion engine is now just one option among many technologies to provide mobility, while the merits of a society built on individual car ownership are also being fundamentally questioned. Instead of simply selling petrol or diesel cars, the industry is grappling with a complex set of energy options, infrastructure obstacles and the broader challenges of sustainability. Researchers need to work in a less siloed, more agile manner to identify and solve these complex issues. The translational approach requires and embraces these skill sets.

In 2019, recognising this shift, IAAPS created an EPSRC Centre for Doctoral Training [16]. The centre is training 70 PhD students in cohorts that include engineers, behavioural scientists, mathematicians, chemists and business and management researchers. The students are being taught to undertake a systematic approach and to seek in collaboration with the research goals that sit on the boundaries between conventional disciplines. This approach combines transdisciplinarity with the industry-focused translational approach.

Recommendations

Based on the findings from the co-convened workshop in Brussels and the example of effective translational research, the following recommendations are proposed for different stakeholders on how to better support translational research:

1. **For academia and research institutions:**
   - Develop and implement a common and comprehensive definition and framework (for instance, a translational map) that sets clear and coherent standards for training, planning, delivery and assessment of translational research. The framework should recognise and encompass the diversity and complexity of translational research across different disciplines and domains of research [17,18].
   - Create active centres for in-house translational research.
2. **For funders and decision-makers:**
   - Diversify the funding and support for translational research, especially in the early and intermediate stages of the research pipeline. This may include ring-fenced funding from within existing funding sources.
   - Align the funding strategies and policies of different funders, such as public, private and philanthropic funders.
   - Develop funding programmes and tools that are customised and adaptable to the challenges of translational research.
   - Create opportunities to regularly share academic findings to inform policymakers and / or interested parties.
3. **For institutions:**
   - Improve the structures, facilities and equipment that are crucial for research translation, such as clinical trial units and data repositories.
   - Offer training and mentoring opportunities for researchers and staff, such as translational research courses, workshops and fellowships.
   - Incentivise and reward researchers involved in translational research, for example by recognising this work in promotion or recruitment criteria.
   - Work with stakeholders and end-users, such as patients, consumers and communities, through approaches and methods that let them participate, co-design and co-create.
   - Incentives should recognise team science contributions in all aspects of academic life, including technology transfer. Team science contributions should be included in promotion and recruitment criteria as well as the REF.
4. **For publishers:**
   - Focus on translational capability by creating new formats to enable different audiences to engage with research more easily. More accessible formats could include short summaries in plain English and syntheses of large bodies of research.

- Provide venues to facilitate more significant interaction and coordination across academia, industry and the public. This can be done by developing and supporting platforms and networks that foster the exchange and dialogue among various actors and sectors involved in translational research, such as interdisciplinary journals, special issues and collections, stakeholder workshops and policy highlights. These venues should enable the communication of research outcomes that cross disciplinary boundaries to non-academic audiences and make research outcomes applicable in real-world contexts [19].
- Adopt standards and tools that improve the access, visibility and impact of translational research, such as open research models, data-sharing principles and indexing systems.
- Assemble articles or translated research output as a portfolio of different disciplines addressing single policy issues for non-academic audiences, including international organisations, think tanks and policymakers.

Conclusion

The translational research process is a relay race that requires different roles at different phases. The translational approach and mindset can be applied to other disciplines to enhance the relevance of research to society and the public. We can realise the full benefits of translational research for improving lives and creating a positive impact by recognising its difficulties and possibilities, systemising and rewarding it and using different actors' contributions to support collaboration and knowledge exchange.

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MINI REVIEW

Research translation: A pathway for health inequity

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Abstract

In a context of social inequity, research translation naturally furthers health inequity. As Fundamental Cause Theory (FCT) explains—and an associated empirical literature illustrates—those with more resources benefit earlier and more from scientific innovation than those with fewer resources. Therefore, research translation of its own course creates and widens health disparities based on socioeconomic status and race/ethnicity. Yet, the conversation about research translation has yet to center this critical reality, undermining our efforts to address heath inequity. Moving toward sustainable health equity requires that we build the evidence base for, prioritize, and institutionalize translation approaches that center the needs and assets of low-resource populations (with community engagement helping toward that end). However, even the impact of that approach will be limited if we as a society do not mobilize knowledge to address social inequity and the many ways in which it shapes health. The health research community should engage the FCT paradigm to think critically about resource allocation among different kinds of research and action. Moreover, in our contributions to discussions about the road to health equity, we must be forthcoming about the reality FCT describes and the limitations it indicates for achieving health equity through translation of biomedical, clinical, health services, and health behavior research alone.

Over the last 20 years, there has been an increased emphasis on the "translation" of research into actions to improve population health. More recently, scholars have broadened the goal of translation to include reducing health inequity while improving health overall. However, we have not focused on an essential point: the fact that research translation is itself a pathway for the creation and widening of health inequities.

In 2005, Elias Zerhouni, then director of the National Institutes of Health, announced the Clinical and Translational Science Awards Program to create infrastructure to promote the spectrum of translation—from basic science into preclinical research (T1), preclinical research into clinical, behavioral and health services research (T2), and translation of the latter into clinical practice (T3) and public health improvement (T4).[1] Recognition of the importance of research translation is also reflected in the growing interest in creating "learning healthcare systems" that can quickly adopt effective innovations[2] and in developing and applying implementation science to the spread of innovation in health care.[3]

More recently, disparities in the prevalence and outcomes of coronavirus disease 2019 (COVID-19), together with the increased visibility of murders of Black Americans by police, have brought greater attention to the problem of health disparities.[4] Accordingly, the literature on research

translation has broadened to encompass translation as a means of promoting health equity. This incipient literature has brought attention to a number of issues, such as the value of community engagement, non-traditional approaches to translation, and tailoring of interventions[5]; the need to diversify study teams and study participants, and conduct more research on health equity[5]; the reality of global inequities in research translation[6]; and the utility of health equity impact research assessments.[7] However, the discourse has not centered what is arguably the most important point about the relationship between translation and health equity—the fact that the natural course of translation is to create and widen inequity.

FUNDAMENTAL CAUSE THEORY

Why does research translation contribute to health inequity? The answer lies in the Fundamental Cause Theory of health disparities. Fundamental Cause Theory or FCT was developed by sociologists 25 years ago to explain the persistent association between socioeconomic status (SES) and health across different diseases, historical time periods, and country contexts. What explains this striking pattern, according to FCT, is the fact that people of higher SES, both individually and collectively, have the resources to avail themselves of the protective factors associated with better health—*whatever* the health condition in question. The theory has been summarized in this way:

> "People of higher SES use flexible resources—knowledge, money, power, prestige, and beneficial social connections—to garner health advantages irrespective of which diseases are prevalent or which modifiable risk and protective factors have been identified at a particular place and time (p.132)."[8]

Moreover, because of systemic dynamics such as "spillover" (the ways in which our social networks affect our health), the health of highly resourced individuals can benefit from their circumstances even if they do not themselves directly and proactively take advantage of specific opportunities to leverage their resources.[8] Other systems of social stratification operate similarly to SES. In the United States, because race and ethnicity (as a result of racism) affect access to "flexible resources," they are associated with health—both through their association with SES *and* independently of that association. Figure 1 offers a visual representation of FCT, indicating that the "fundamental cause" (social stratification and its relationship to resources) continually shapes the distribution of changing proximal mechanisms associated with specific health conditions.

The proponents of FCT note that stratified access to resources is not the only force affecting the distribution of health in a society. For example, some health behavior, such as smoking among young people, may be conditioned by cultural realities not associated with social stratification. Nonetheless, FCT explains *dominant* patterns of health distribution across a wide range of contexts and the past 25 years have seen the emergence of an impressive body of literature that has tested and confirmed hypotheses rooted in this theory.[8]

One of the approaches to empirically testing FCT has been to study the relationship between health care innovation and health disparities. If FCT is correct, then new innovations in health care and health promotion should first improve the health of those with the greatest access to the "critical resources" of health, thereby creating or widening health disparities. Research supports this hypothesis. For example, Phelan has found a stronger association between SES and mortality for causes of death that are preventable than for those that are not preventable.[9] Phelan and Link also demonstrate that as our capacity to prevent disease-specific mortality improves over time, SES/race-based disparities for these deaths increase.[9] Conversely, for diseases on which we have not made progress, disparities have not changed.

In a more granular example, Chang and Lauderdale studied income gradients for cholesterol in nationally representative data from 1976 to 2004.[10] They found that at the beginning of this time period higher income was associated with higher cholesterol levels, presumably reflecting dietary patterns. However, once statins were determined to be impactful in lowering cholesterol and "translated" into clinical practice, the relationship between SES and cholesterol levels reversed, with higher income associated with lower cholesterol levels. In a study of receipt of the adolescent human papillomavirus (HPV) vaccine, Polonijo and Carpiano traced how FCT worked

FIGURE 1 Fundamental Cause Theory Adapted from Diez Roux.[23]

at each step toward uptake, demonstrating the association of race/ethnicity and SES with parental awareness of the vaccine, likelihood of receiving a recommendation for the vaccine from a healthcare professional, and initiation and completion of the vaccine series.[11]

As diffusion of innovation increases over time, disparities associated with research translation lessen. However, translation of the next advance in health research will widen inequities again.[12] Moreover, as Chang and Lauderdale note, in some situations, the disparities associated with earlier access to innovation are compounded by the cumulative benefits of longer treatment.[10]

WHAT SHOULD WE DO?

What should be done about the relationship between research translation and health inequity? Quashing new discovery—which, in any event, is not feasible—is certainly not desirable. Indeed, as David Mechanic notes, even innovations that widen disparities can improve the health of those with the fewest resources.[13] In other words, disparities can widen even as health improves among all social groups.

Nonetheless, it is incumbent upon those who have dedicated themselves to health improvement to mitigate the inequities associated with research translation. Health inequities represent a missed opportunity for health improvement. If better health outcomes are possible, then we can realize those health outcomes for all. Moreover, although we may not all agree on what societies should do about the social inequities that underlie health disparities, we can agree that the roots of many of those inequities—such as racism, sexism, and exploitive labor practices—are unfair and must be addressed. Finally, research indicates that economic inequality tends to be self-reinforcing, with current inequality shaping a politics of future inequality—either because government is more responsive to the interests of the wealthy or because (in many scenarios) growing income inequality increases the number of those who would "lose" from income redistribution and therefore oppose it.[3,14] The same logic may hold for health inequity—with widening gaps in the health-related political and policy interests of differently-resourced people reinforcing and even widening inequity.

The ethical imperative to confront the relationship between research translation and health inequity is brought home by the translational impact of inequitable health care access—one of the multiple resources that links social and health inequity. The late Senator Ted Kennedy explained that his passion for universal health care began with his son's participation in a clinical trial to treat bone cancer. Speaking of the parents of children in the trial, he wrote:

> We all hoped that our child's life would be saved by this experimental treatment. Because we were part of a clinical trial, none of us paid for it. Then the trial was declared a success and terminated before some patients had completed their treatments. That meant families had to have insurance to cover the rest or pay for them out of pocket. Our family had the necessary resources as well as excellent insurance coverage. But other heartbroken parents pleaded with the doctors.[15]

As Kennedy's searing reflection makes clear, it is a contradiction to talk about addressing health inequity through research translation when even some research participants cannot access the treatments they help create. We must address the link between research translation and health inequity. But how can we do so?

WHAT CAN WE DO?

The variables that link social inequity to health inequity—differences in knowledge, money, power, social standing, and social connections—may not always be transparent or fully understood, but they are not mysterious and they are not ineffable. They can be identified and researchers can address some of them through proactive translation strategies.

Research has shown that population-specific messaging, culturally tailored outreach, asset-based translation strategies, and dissemination through select community locations—such as faith-based organizations and barbershops—can support health behavior changes in low income and racial/ethnic minority communities.[16–18] However, if this approach is to have a significant impact on health equity, it cannot be used by individual research teams working on individual projects. Given the intrinsic relationship between research translation and health inequity, every innovation translated *without* special attention to equity sets us back. Evidence-based approaches to equitable translation need to become standard practice. In order for that to happen, research funders and research institutions must require researchers to utilize translation strategies that center the needs and assets of marginalized populations, and must design funding opportunities that provide the time, staffing, and material resources required to carry out these strategies. Furthermore, the research community will need to develop, sustain, and systematically deploy an infrastructure that supports widespread and consistent use of these new translation strategies (e.g., institutionalized channels of communication, and relationships with decision-makers). Additionally, we must make equitable translation strategies a critical subject of

research and translation themselves. If translational science—or the study of research translation—is to promote health equity, it must be rooted in a recognition of the naturally inequitable course of translation.

Partnership among researchers and the communities affected by the issues they are studying—or community engaged research—is one way to facilitate research translation in general and translation for low-resource communities in particular.[19] Engagement improves community trust and buy-in to research and helps research teams to identify and prioritize research topics, methods, and translation strategies that are appropriate for specific communities. In fact, some practitioners of community-engaged research argue that the language of "research translation" is inappropriate, as it suggests that improved health will result from researchers unidirectionally transferring what they know to health professionals and affected communities.[19] In actuality, they argue, communities and practitioners have a great deal of knowledge to share about turning research into action and the greatest impact is achieved when they work with researchers to co-create and "mobilize" knowledge. Whatever language is used, the critical point is that community engagement—if widely institutionalized and institutionally supported—can help build our capacity for more equitable action.

Changing our approach to research translation can address inequities in knowledge of new innovations and counter some of the systemic effects of social inequity (e.g., by enhancing the health supporting capacity of networks, clinical sites, and social institutions serving under-resourced populations). However, changing translation strategies will *not* affect the inequitable access to medications described by Ted Kennedy or myriad other ways in which the unequal distribution of power, prestige, money, and other resources affect the distribution of health risks and protections.

Rather, health inequity will be most impacted by the application of research—and other forms of knowledge—to: (1) reducing the ways in which social inequity affects access to resources and (2) reducing social inequity itself. As noted by former Centers for Disease Control and Prevention (CDC) director Tom Frieden, changes in social conditions have a bigger impact on population health than do changes in clinical care and health education.[20] Social stratification is among the most important of those social conditions. There is even a body of literature indicating that the relationship between social expenditures and health outcomes is stronger than that between health expenditures and health outcomes.[21]

What does this mean for health research funders and institutions? Some might argue that the implications are minimal. Policy researchers and social scientists already conduct research on social drivers of health. Moreover, what should be done with our knowledge of social drivers of health is not straightforward, raising many legitimate (and arguably some unsubstantiated) debates over facts and values. Additionally, academic medical centers are already beginning to recognize the importance of social drivers of health, with some in the early stages of implementing and studying integration of social services and clinical care.

However, I would argue that the implications are significant. As Paula Lantz has noted, and as FCT would indicate, it is unrealistic to think that we can improve the health of patients with complex, chronic, long-standing needs facing structural obstacles merely through referrals to individual social services,[22] indicating that this approach to addressing social drivers of health in medical centers will have limited impact. Given all that FCT indicates about the natural contribution of research translation to health inequity and the limits of what can be done through modifying translation strategies, the health research community should think critically about the allocation of our resources and societal resources to different kinds of research and different kinds of action. In addition, in our contributions to deliberations about the road to health equity we must be forthcoming about what that road entails and the limits of what translation of biomedical, clinical, health services, and behavioral research alone can do.

Determining how to do this requires debate around facts and values (the nature of a good society, the role of researchers, etc.) that will not be answered here. However, these discussions need to happen and they need to center the realities explained by FCT.

CONCLUSION

Without understanding and significant redress of the ways in which research translation creates and widens health inequities, efforts to address those inequities will falter; indeed, as FCT explains–and the associated empirical literature illustrates, scientific innovation will widen disparities again and again. At a minimum, the health research community needs to recognize and be forthcoming about the ways in which translation contributes to inequity. If we wish to counter that dynamic, we must build the evidence base for, prioritize, and institutionalize translation approaches that center the needs and assets of low-resource populations. We must also recognize the limitations of any approach to translation—even the most intentional—if we as a society do not address social inequity. The health research community should engage the FCT paradigm to think critically about resource allocation among different kinds of research and action. Moreover, in our contributions to deliberations about the road to health equity, we must be forthcoming about the reality FCT describes and the limitations it indicates for achieving health equity

through translation of biomedical, clinical, health services, and health behavior research alone.

CONFLICT OF INTEREST

The author declares no competing interests for this work.

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