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Evaluating the Continued Integration of Genetics into Medical Sociology

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Abstract

The 2010 special issue of *Journal of Health and Social Behavior*, titled "Fifty Years of Medical Sociology," defined the contours of the medical sociological perspective. We use this as a backdrop to outline and assess the continued integration of genetics into medical sociology research. We contend that the explosion of genetic and epigenetic data in population health data sources has made the medical sociological perspective increasingly relevant to researchers outside of sociology, including public health, epidemiology, and quantitative genetics. We describe vast, underappreciated, and mostly unsolved challenges that limit the scientifically appropriate interest in incorporating genetics into existing paradigms. It is our hope that medical sociologists continue this integration but redouble efforts to maintain the core insights in social science research, such as the importance of environmental and structural (i.e., nonbiological) factors in determining health processes and outcomes and the use of rich, integrated, and rigorous empirical analyses.

Keywords

gene-environment interaction, genetics, medical sociology

The continuing integration of genetics and social science is exciting, mostly useful, consequential, and inevitable. The first law of behavioral genetics states that all human behavioral traits are heritable (Turkheimer 2000). Ignoring or being overly critical of efforts to acknowledge this (Horwitz et al. 2003) is increasingly at odds with current research. Similarly, medical sociologists have their own implicit law that health is shaped by a rich tapestry of environmental, cultural, and historical processes operating at multiple levels and that these processes are fundamental to more proximate determinants, including genetic and epigenetic mechanisms (Link and Phelan 1995). Although seemingly at odds with one another, the truth is that both perspectives are correct, and efforts over the past two decades have greatly enhanced the understanding of health processes by integrating insights from each. Because real-time genome-wide summaries are a reality (Mills and Rahal 2020), a theoretical model that centrally positions the sociological perspective on population health becomes increasingly important.

In 2010, a special issue of *Journal of Health and Social Behavior* (*JHSB*) titled "Fifty Years of Medical Sociology" defined the contours of the medical sociological perspective. We use this framework to illustrate how recent efforts to integrate genetics into medical sociology enhances the centrality of the social environment as a fundamental determinant of health and highlights the increasingly important role of genetics within social scientific research in general (Conley and Fletcher 2017; Harden and Koellinger 2020). The bulk of our review focuses on work in sociology with an explicit emphasis on work that is relevant to medical sociologists. Our goal is to reduce the gap

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between two different audiences: medical sociologists who may integrate genetics into their work and genetic epidemiologists and other health science disciplines who may incorporate elements of the medical sociological framework into their work.

MEDICAL SOCIOLOGY AND GENETICS

Rosich and Hankin (2010) provide a summary of "key findings" of medical sociology described in the 11 articles in the special issue of *JHSB*. In the following, we discuss five areas of their summary in which integration of genetics into medical sociology has enhanced the relevance of the social determinants of health perspective. It is our contention that medical sociology is poised to *lead* this area of research rather than simply *respond* to the work of others.

Health Inequalities Are Deeply Rooted in Society

Research emphasizing the social determinants of health (SDOH) perspective has long been the bedrock of the medical sociology perspective. Importantly, there is an equally large body of work demonstrating that health, health behaviors, and education are all moderately heritable. Can genetics be incorporated into SDOH theoretically and empirically? If so, do these efforts compromise or reinforce the centrality of the SDOH framework for medical sociological research? First, the use of genetically informed designs has provided new insights into some of the key assumptions of the SDOH perspective (Bearman 2013). Recent work published in *JHSB* has utilized measured genotypes to rule out the possibility that some of the association between social contexts such as schools and later life aging is due to previously unobservable genetic factors (Moorman, Greenfield, and Garcia 2019). Some work has specifically examined the possibility that common genetic variants are associated with both education and health (Boardman, Domingue, and Daw 2015). It shows that some of the previously reported correlation between education and two health outcomes (depression and self-rated health) may be due to common genetic factors, but it finds no support that the link between education and body mass index (BMI) is due to genetic correlation. Thus, genetic information can be used to demonstrate when the correlation between social factors and health is entirely due to environmental factors. Likewise, Mendelian randomization techniques are increasingly used by social scientists to identify the causal role of the social environment on health, disease, and mortality (McMartin and Conley 2020).

Genetic studies have also highlighted the SDOH by examining period and cohort effects with respect to genetic effects on health. An article published in *JHSB* (Boardman, Blalock, and Pampel 2010) demonstrates that heritability of smoking was not significantly different from zero during the early 1960s (i.e., smoking was a social phenomenon), but following the 1964 Surgeon General's Report, the composition of those in the smoking population changed considerably such that the relative influence of genetics became stronger. Thus, those for whom entry and exit into the smoking population was due to social, rather than genetic, factors were less likely to enter and more likely to leave the smoking population in light of this information.[1] This creates a new social configuration in which the fundamental aspects of socioeconomic status (SES) and health may still be operating, but the mechanisms in place may now pick up specific genetic polymorphisms. For example, Wedow et al. (2018) show an increasing genetic correlation between low levels of education and smoking across birth cohorts that is linked to selective processes that sort individuals with specific genetic polymorphisms into common social contexts.

One of the key tenets of the fundamental cause theory (Link and Phelan 1995) is the contextualization of risk factors, which has, to date, focused on the economic, built, and cultural features of the environment. However, recent work has contextualized genetic risk, for example, the sociogenome (Mills and Tropf 2020), comprised of the genomes of one's peers, friends, classmates, workmates, and so on. This has been shown at the grade (Sotoudeh, Harris, and Conley 2019), school (Domingue, Belsky, et al. 2018), and county levels (Domingue, Rehkopf, et al. 2018). We believe that this work adds an additional element to the contextualization of risk whose origins are socially oriented, and it is critical to use the existing frameworks to incorporate how, when, and for whom cumulative-contextual genotype may become an independent influence on population health and health behaviors. For example, Liu and Guo (2015) make it clear that SES is a characteristic of one's life course, rather than simply a measure at one point in time, by showing clear associations between life course SES and BMI. They then show that life course SES moderates genetic influences on BMI such that the genetic associations are weaker among the upwardly mobile, and this gene-by-environment (G×E) association has

become stronger among more recent cohorts. Thus, gene-by-life course-by-environment-by-cohort framing provides new and critical evidence about how the centrality of the current social structure, an individual's location within stratified society, can change over time as paramount to understanding the relative influence of genotype on phenotype.

This perspective is central to work linking genetic expression to socioeconomic position. For instance, the association between early life conditions and later life health, deemed the "long arm of childhood" (Hayward and Gorman 2004), appears to operate in part through the epigenome and transcriptome. Borghol et al. (2012) demonstrate that low SES is linked to hyper-methylation across different promoter regions and that these epigenetic associations are stronger for childhood socioeconomic position compared to current socioeconomic position. Stress exposure is posited as the primary mechanism through which socioeconomic adversity influences epigenetic processes in genes related to inflammation (Needham et al. 2015). And most recently, research has shown that increased levels of inflammation-related diseases among those experiencing poverty during childhood is due, in part, to differences in gene regulation beyond methylation. Carmeli et al. (2021) show that epigenetic processes link early life SES to adult health and that transcriptional activity explains a very large proportion of this association that is above and beyond epigenetic processes. Schmitz et al. (2021) show evidence of a socioeconomic gradient in epigenetic "clocks" that measure biological aging. This work is new and needs to be replicated across different birth cohorts in different social contexts, but it, again, positions SES as fundamental to downstream and more proximate determinants of health.

Stressors Substantially Damage Health

Dohrenwend (2000) summarizes the life-stress process and how social identities, roles, expectations, and resources link both exposure *and* response to proximal life events. His emphasis on the "wider environment" resonates with medical sociologists because it positions social factors as upstream and fundamental to downstream stress appraisal and subsequent response (adaptive or maladaptive). It is important to note that his model places a great deal of import on "personal predispositions," which he states are linked to biology and "especially genetic inheritance" (Dohrenwend 2000:13). Thus, genetic inheritance is positioned as a critical determinant of one's "ongoing situation" (e.g., work, education, relationships, and material resources), one's exposure to stressful life events, and the extent to which one appraises an event as stressful and decides how to cope with stress.

Dohrenwend (2000) correctly points out that genetics and subsequent "predispositions" do not challenge the significance of stress exposure, coping strategies, and subsequent health. In fact, he emphasizes that these factors will reinforce the significance of the social environment in which one is exposed to a stressful life event and how one copes. Gene–environment correlation (rGE) has received a great deal of support in the literature, and it is important to consider that each of the six aspects of stress that Dohrenwend (2000) describes in his article may be influenced by genotype and that the selection mechanism (e.g., passive, active, or evocative) may change across the life course. These aspects include valence, fatefulness, predictability, magnitude, centrality, and physical impact. Shanahan and Boardman (2009) described the opportunity of examining the different forms of rGE across the life course to better understand *for whom* stress exposures happens and *how* stress translates to poor health outcomes. Thus, we encourage researchers to consider the environmental exposures in G×E research and evaluate the possibility that active, evocative, or passive rGE may be at play.

Another article published in *JHSB* (Beam et al. 2017) evaluates the relationship between stress and depression as a function of marital status in which the relationship between stress and depression can be comprised of a genetic component (rG) and an environmental component (rE). They show that common genetic factors partially account for the relationship between perceived stress and depression and that the association is significantly reduced among married women but not among married men. Thus, the environmental moderation of genetic correlation depends on the gender of the individual in the married couple, which, again, highlights the centrality of a sociological interpretation of gendered roles and resources rather than an exclusive focus on biological sex.

Some of the most important scientific advances in the past decade have focused on the molecular processes through which stress "gets under the skin." For example, regulation of genetic expression through the neuroendocrine system is a pathway through which stress upregulates genes involved in inflammation and shows a decreased expression of genes related to antiviral responses (Cole 2013). This conserved transcriptional response to adversity model has been supported in a study of mice (Powell et al. 2013), and an

increasing number of studies involving humans are currently examining the implications of these pathways for population health. Cole et al. (2020) describe the current RNA profiling efforts underway with the National Longitudinal Study of Adolescent to Adult Health and compare the transcriptome profiles for two sets of genes across sociodemographic groups and as a function of health behaviors (smoking, drinking, and BMI). The two gene sets include genes implicated in inflammation and those involved in Type I interferon responses and subsequent immune system well-being. They show that "inflammation-related gene expression showed the most pronounced variation as a function of biobehavioral factors (BMI and smoking) whereas type I IFN-related transcripts varied most strongly as a function of individual demographic characteristics (sex and race-ethnicity)" (Cole et al. 2020:4601). Because these factors are downstream of the broad socioeconomic determinants, these results are, again, in line with the medical sociology approach to understanding population health.

Social Relationships Are Linked to Health Behaviors and Outcomes

Research in this area has produced some of the most important work in medical sociology (Umberson, Crosnoe, and Reczek 2010). One aspect of the social relationships literature is the formation and reinforcement of health-related norms (Mollborn and Lawrence 2018). To further complicate the influence of socially shared understandings of health norms, research has shown that the relative influence of genetics depends on the level and strength of a norm in a particular social context. Boardman et al. (2008) and Daw et al. (2013) both show the genetic influences on smoking to be strongest in schools with prosmoking norms and weakest in schools with antismoking norms. Likewise, selection into social relationships as a function of genotype has been given a lot of attention by social scientists who have reevaluated the findings of genetic homophily among friends reported by Fowler, Settle, and Christakis (2011). Two important findings have emerged from this. First, Domingue, Belsky, et al. (2018) use a different indicator of genetic similarity and report genetically homophilous friendships but conclude that school assignment is the primary reason why genetic similarity is seen among friends in the first place. Second, the probability of genetically homophilous friendships is significantly higher in schools that have the highest level of inequality (Boardman, Domingue, and Fletcher 2012). In both instances, genes are linked to friendship selection, but the mechanisms are social and structural, outside of one's control. That is, genetically similar individuals are not *selecting* into friendships because of observable traits linked to unobservable genotype, but they are *selected into* social environments that increase the likelihood of them interacting with one another in the first place.

One of the most important aspects of the nonrandom selection of genetically similar individuals into similar social contexts involves work in the area of the sociogenome (Mills and Tropf 2020). Akin to neighborhood effects research, in which the poverty rate of one's neighborhood affects an individual's health above and beyond the individual's poverty status, the sociogenome is an indicator of the collective genotype of one's social context in which the average polygenic risk of one's neighbors has a measurable influence on one's health above and beyond the individual's polygenic risk for a specific morbidity. There are two important aspects of this process that are critical for researchers to consider. First, G×E research assumes that broad social environments such as schools, neighborhoods, and even state of residence are independent of genotype, and this is clearly not the case. We believe it is important for researchers to evaluate this possibility empirically and report the results in their analyses. Second, it is essential for social scientists to evaluate the mechanisms for the nonrandom distribution of genotype across social contexts to determine whether the selection process is largely due to active selection into a specific environment on behalf of an individual or selection into specific environments by representatives of institutions (e.g., educators, law enforcement, real estate agents) who are responding to observable behaviors and style (e.g., *habitus*) of the individual that has some genetic origins.

Finally, it is important to use the long-standing emphasis on social relationships and social resources that defines medical sociology (Umberson et al. 2010) to frame research in genetic and epigenetic research. For example, research has shown differential rates of ovarian tumor growth rate to be a function of social resources in which low social support is linked to higher growth rates due to differential regulation of gene expression (Lutgendorf et al. 2009). Those with low social support demonstrate higher rates of beta-adrenoreceptor-linked transcription control pathways across 266 genes that are differentially expressed in ovarian cancer patients. This work is clearly relevant to medical sociological research, but it is equally important that the existing

theory that links social resources to health be included in the motivation of work outside of medical sociology.

Race Is Linked to the Very Large Disparities in Health in the United States

Researchers within medical sociology have made some of the most important contributions to the literature on the social determinants of health and continue to be leaders in the area of health disparities among racial and ethnic groups in the United States (Williams 2012). This work consistently demonstrates the role of institutional (Carr and Friedman 2005) and individual (Finch, Kolody, and Vega 2000) forms of discrimination, health-related factors of the built and social environments in which one lives (Kravitz-Wirtz 2016), and access to quality health care (Kirby and Kaneda 2005) as critical factors related to persistent racial-ethnic differences in health in the United States. These are precisely the environmental factors that Boardman, Daw, and Freese (2013) highlight in their efforts to bring the social epidemiologic research framework to the G×E interaction research area.

This understanding is important because many genetic associations reported in health research are significantly reduced in magnitude among black compared to white adults, and this is particularly the case among research relying on polygenic scores (PGS). To date, researchers in genetics attribute these differences to purported *genetic* differences across socially defined racial and ethnic groups. Leaders in this area (Martin et al. 2017:635) state that "[t]he vast majority of genome-wide association studies (GWAS) are performed in Europeans, and their transferability to other populations is dependent on many factors (e.g., linkage disequilibrium, allele frequencies, genetic architecture)." The most important part of this statement is not what is said but what is *not* said about environmental factors responsible for this variation. In our view, the G×E interaction perspective is essential to properly understand observed differences in genetic associations across racial and ethnic groups in the United States.

As an example, consider the work on school-based social norms and genetic associations for smoking described previously. The authors (Boardman et al. 2008) point out that school-level smoking norms covary with school-level racial composition in which there are weaker prosmoking norms in schools with a larger proportion of non-Hispanic and white students. They also show that the heritability of smoking is lower in schools that are largely comprised of non-Hispanic and black students. Absent the information about differences in social norms regarding smoking behaviors, one may interpret differences in heritability in line with the limited biological explanations provided previously. Likewise, Boardman, Barnes, et al. (2012) find that the relationship between the presence of the e4 allele in the APOE gene and cognitive decline is significantly weaker among black compared to white adults but show the differences are explained, in large part, by variation in social disorder that are evident in neighborhoods in the city of Chicago. This information, in conjunction with clear evidence of PGS association differences within ancestry groups (Mostafavi et al. 2020), again prioritizes the *sociological* orientation to the social construction and maintenance of racial group "boundaries."

One way that these group boundaries are reinforced in current research practices is the use of principal components (PCs) to characterize genetic ancestry (Price et al. 2010). Although the top two PCs rarely explain more than 2% to 3% of genetic variation in the sample, they align nearly perfectly with racial or ethnic identification (Guo, Fu, Lee, Cai, Harris, and Li 2014; Guo, Fu, Lee, Cai, Li, and Harris 2014), and controlling for the top 5 to 10 PCs has eliminated most concerns about this possible source of bias ("population stratification") in genetic studies. These are important statistical controls for certain purposes, but they come with an important cost of attaching undue meaning of characterizing race in terms of genetic ancestry. We encourage researchers to consider *why* they are adjusting for these principal components, *how* these PCs are calculated (e.g., within or between ancestry PCs), and *what* it means to consider racial identification as independent from controls for PCs (Guo, Fu, Lee, Cai, Li, and Harris 2014).

Health Care, Health Research, and Health Knowledge Have Changed Dramatically over Time and Are Critical Components to the Sociological Perspectives on Health

Access to and utilization of health care services are both influenced by genotype. Wehby and Shane (2019) estimate that one half of the variation in health coverage among the population under the age of 65 in the United States is due to genetic variation.

Importantly, they demonstrate that this broad characterization of genetic influences is largely due to employment industry, employment status, income, and education but *not* factors more proximately associated with the individual, such as risk preferences or even health. Thus, again, describing the role of genetic factors in terms of active, passive, or evocative selection into broad sociogenomic contexts such as employment sector is critical to enhance understanding how and why genotype may be related to different outcomes of interest to medical sociologists. Consider this finding in light of Boyer and Luftey's (2010:S89) description of the increasing role of individual-level characteristics and identities with respect to the patient role in one's health. Whereas the patient role in the 1950s is described as the "sick role," in which patients are "passive and deferential," the role of the patient in 2009 is "active," in which "self-management" has a "long-term orientation."

The key to the medical sociological perspective is that these active and passive roles are linked to broad socioeconomic and historical processes that both structure and maintain social inequalities and are central to the understanding(s) of the extent to which genes are relevant. Understanding this is important when one considers factors such as reduced heritability estimates for a wide range of different outcomes among those with the most limited access to economic resources (Turkheimer et al. 2003). Although genotype is not part of Wright and Perry's (2010) article, their summary regarding health services in the United States is incredibly relevant to this discussion. Their article highlights the following three critical issues:

> (1) health services in the U.S. are unequally distributed, contributing to health inequalities across status groups; (2) social institutions reproduce health care inequalities by constraining and enabling the actions of health service organizations, health care providers, and consumers; and (3) the structure and dynamics of health care organizations shape the quality, effectiveness, and outcomes of health services for different groups and communities. (Wright and Perry 2010:S107)

These statements make it clear that the medical sociology approach to health disparities is more than just a consideration for genetic epidemiological studies reporting race differences in the magnitude of genetic associations. Instead, it should be the starting point. This work is also relevant to medical sociology because of the increasing use of PGS. Babb de Villiers, Kroese, and Moorthie (2020) describe how this research is influencing the way in which providers assess the health, health behaviors, and overall fitness of their patients as well as patients' understanding of their overall health. The use of PGS is appealing because it is a relatively simple summary statistic of an individual's risk for a specific morbidity.

The shift from the scientific community to private industry has been very clear because different groups are competing for the best approach to summarize an individual's genetic risk and characterize their likelihood of contracting a particular disease without any consultation with a physician. As Casper and Morrison (2010) point out, this is precisely the type of dangerous diagnostic anticipated by Nelkin and Tancredi (1989), and absent a sociological framing and contextualization of risk, these common practices are, again, doing the work anticipated by Duster (1990) three decades ago. Here, we argue that the same biobanks that are criticized by some as instrumental in this process can also be used to shatter this narrow and problematic classification system. The medical sociological perspective provides the theoretical, methodological, and empirical tools to do this work, and we can think of no more important task for the next decade. This is particularly important when you consider the "dialogue" between patients and physicians that is structured around a sense of trust (Mechanic and McAlpine 2010). If that trust is eroded by an increasing role of technology in the determination of health and illness based on measured genotype, then it will likely enhance long-standing disparities in health as a function of race, class, and gender.

In sum, the goal of this section of the article was to take the main pillars of the medical sociology framework, as articulated by leaders in our field a decade ago, and rethink if, how, when, and why the incorporation of genetics as a causal or confounding factor in a model may enhance or compromise the key assumptions among medical sociologists. As we described, regardless of the method (twin study, candidate gene, genetic similarity, or polygenic approaches), in most cases, the inclusion of genetically informative or molecular genetic data has the capacity to enhance the centrality of social identities, contexts, and resources as fundamental determinants of health of individuals and communities.

MOVING FORWARD

The work described previously has made important inroads into the long process of integrating genetics into medical sociological research. The following

section reviews the four most important opportunities for continued progress in this area. First, the bulk of the research described previously has been exploratory and somewhat descriptive in terms of genetic confounding and G×E interactions. We strongly encourage researchers to have clear, a priori, and hypothesized pathways through which genotype may be relevant to their overarching research question. We feel that this is very important with respect to G×E interaction studies in which more care is needed in the interpretation of the main genetic effects, the main environmental effects, and the direction and magnitude of the interaction. Focusing on a *p* value does little to advance medical sociological research because it is not properly anticipated by *theory*. For whom should the genetic associations be the strongest? If there are purported mediating pathways, evaluate those pathways empirically or think creatively about approaches you can use to rule out different explanations. Do you expect the same G×E associations regardless of age, gender, class, or racialized experience? If not, why?

We stress that this *why* is in desperate need of an overarching theory, which is lacking in some G×E research. This is particularly relevant to G×E work that relies on PGS estimates because these scores are derived from the summary statistics from GWAS and are conventionally weighted by the single nucleotide polymorphisms (SNPs) that have the largest effect sizes and are thus the least likely to interact with the environment. Hence, failure to identify G×E associations using PGS as the indicator of G may have more to do with the method rather than the utility of the G×E framework. Instead, it might be more useful to construct genetic measures that are trained to predict the variance in outcomes rather than the levels. So-called variance-PGS have begun to be explored (Conley et al. 2018; Miao et al. 2021) as an alternative measure, which harken back to the conceptual models discovered previously of differential susceptibility.

Second, work needs to be both interdisciplinary *and* collaborative in the sense that all participating researchers have sufficient input into the initial research questions, analytic plan, and interpretation of the results. This takes time and energy, but in our experience, these are the types of collaborations that lead to the most interesting and important research findings. We encourage the National Institutes of Health (NIH) and other funding agencies to continue to invest into the training of the next generation of population health scientists that prioritizes an interdisciplinary pedagogy as the norm rather than the exception. We encourage PhD-granting institutions to consider the development of new interdisciplinary training programs with commensurate certifications that will attract new candidates to traditional social science PhD programs and provide formal recognition of those candidates who have received specialized training in this area.

Third, research in this this area has unique data needs. In addition to the requirement of genome-wide data, the measurement of the sociogenome, environmental moderation of genome-wide heritability estimates, measures of genetic correlation, and other techniques needed to evaluate some of the most important questions in this area, this work requires very large and representative samples. The UK Biobank has proven to be a go-to resource for many social scientists because of its size given that it currently contains genome-wide data, including imputed data containing over 90 million SNPs, for roughly 500,000 individuals. Unfortunately, the response rate for this resource is less than 6%, and there are important concerns regarding the extent to which the parameter estimates are generalizable to the UK population (Keyes and Westreich 2019). We encourage the NIH and the National Science Foundation to consider a comparable U.S. Biobank study that takes representativeness as a requirement rather than an afterthought. As described previously, this is singularly important for G×E, rGE, and rG×E research because the ability to describe the presence and magnitude of these effects requires representation from the *full range of environments*. This point cannot be stressed enough.

Fourth, our review focuses on environmental moderations of genetic associations and global indicators of heritability but only partially describes work in the area of the epigenome (Landecker and Panofsky 2013), which may provide incredible opportunities to further demonstrate the centrality of the social environment with respect to physical and mental health, and each provides detailed biological evidence for the imprint of environmental exposures throughout the life course on the basic functioning of genetic polymorphisms. This is particularly important with respect to the disparities in polygenic associations across socially defined racial and ethnic groups described previously. Although our review focuses on the environmental confounds and triggers for observed differences in genetic associations by racial identity, it is also quite possible that the intergenerational transmission of the epigenome is an important mechanism that dampens genetic associations among non-Hispanic and black adults in the

United States because of generations of experience with institutional and individual discrimination (Kuzawa and Sweet 2009). Likewise, medical sociologists have had a long interest in the social determinants of aging. Recent work in the area of epigenetics has made it clear that differential rates of aging have clear epigenetic markers that can be used to characterize biological aging in a way that was previously not possible (Schmitz et al. 2021; Zhang et al. 2020). We encourage readers to consider these indicators of overall health that are derived from genomic material in future research on the social determinants of health.

Fifth, the success of integrating medical sociology and genetic research should not be dependent on the method. We stress the need for continued development of theoretical frameworks that go beyond description and to articulate how and why life course pathways to healthy aging may or may not include genetic influences and how genetic factors may limit the range of life course pathways available. Here, we stress that this effort should not be limited by methodological debates regarding "method x versus method y" to determine the relevance of genetics for medical sociological research. Computational capabilities, new insights into the human genome, increased understandings of the coevolution of the genome and environment, and other important changes will quickly make both "method x" and "method y" outdated. The clearest example is the case of candidate gene–environment interaction (cG×E) research that has been highly criticized by many (Dick et al. 2015). The criticisms of the cG×E approach include limited power, publication bias, measurement issues related to the environment, and poor replication history as the leading concerns of the cG×E approach.

The Emergence of Polygenic Scores in Medical Sociology

Although we have detailed here five major directions in continuing the progress of integrating genetic/biological measures with medical sociology, it is also necessary to provide a more in-depth discussion of one of the major emerging conventions in this field—using PGS. A first important point in considering PGS is to juxtapose the paradigm of tiny genetic effects spread throughout the genome with the previous paradigm of candidate gene of "big effect." Indeed, the candidate gene approach—hypothesis driven and deductive with an aim of finding large effects from single genes—has been replaced with the inductive approach of GWAS for genetic discovery. This change has been consequential because, among other reasons, social scientists generally do not rely on hypothesis-free methods and have little use for genetic variants of tiny effect; this has led to two changes in the interchanges between social and genetic scientists. First, social scientists have begun to extend genetic analysis for their own genetic discovery for traits like educational attainment (Rietveld et al. 2013). Second, social scientists coalesced around the use of PGS to transform millions of tiny effects into a single measure of "genetics" to use in medical sociology and other fields.[2]

We believe that increasing use of PGS is important, but there are limitations to the measurement, interpretation, and use of PGS that need to be highlighted. From a social scientific perspective, we allege that the fact of fixed from conception genetic variation is the source of its greatest analytical strength as well as its weakness. The strength is multifaceted, often deployed to argue convincingly against a key challenge in empirical social science by sorting out issues of causal direction and reverse causality. The typical argument made is that genetics predate other influences and cannot be shaped by these influences (i.e., no feedback effects), which provides a substantial, and relatively unique, strength for social science inquiry. But this comes at a large and partially hidden cost, which is that genetic variation is then, essentially, no longer a source of variation able to be manipulated by policy or natural experiment. We argue that this feature, in fact, substantially reduces our ability to separate genetic effects from environmental confounding. A key issue here is that genetics *is* family background and related social contexts; genetic measures inherit many of the issues of confounding that standard social science analysis attempts to resolve in understanding impacts of, for example, income, education, SES, and neighborhoods on health behaviors and outcomes. Although health behaviors do not affect genetics, assuring no reverse causality, SES can be manipulated to estimate causal effects on health; genetics cannot.

Importantly, these issues affect upstream analysis, well before social scientists encounter "genetic measures" to use in their own work. Specifically, current practice in estimating effects of genotype on health outcomes is to make assumptions similar to selection-on-observables. This occurs at the discovery stage (GWAS), where "effects" of genetic variants on health outcomes are first estimated, and then is baked into downstream applications of these GWAS (e.g., PGS). This practice and the underlying unsolved

difficulty of separating causal genetic effects from confounding then has substantial implications for downstream medical sociological uses of genetic data. These issues are only partly understood and rarely sufficiently discussed and addressed by most researchers currently integrating genetics and social science.

In addition, PGS have been difficult to interpret for at least three reasons. First, even if each of the genetic variant effects that are added together were causal effects, the resulting summary measure would not have a clear interpretation. Many researchers have used vague terms, such as *genetic endowment*, *genetic risk*, or *genetic predisposition*, in labeling these constructs. Second, the fact that many of the genetic variant effects are not causal further challenges the interpretation—so much so that it is not clear that they can be called "genetic" effects at all, especially in cases where the explicit goal of the analysis is to separate PGS effects from family background leading to the idea of "genetic nurture" (Domingue and Fletcher 2020; Kong et al. 2018; Wu et al. 2020). Third, the integration of PGS into medical sociology has varied by use. Many articles have sought to examine the direct effects of PGS on socioeconomic and health outcomes. Others have used it to measure G within a G×E interaction framework. Both are challenged if PGS are not G. It may be that this second wave, with the near universal use of PGS, is a dead end for some of the primary goals of social science inquiry.[3]

Some have argued that the use of sibling-based studies allows researchers to compare differences in PGS with differences in the outcome to, researchers hope, mimic the "genetic lottery" that occurs for biological siblings (Fletcher and Lehrer 2011). Although conceptually sensible, recall that the PGS are downstream of GWAS estimates and thus have confounding baked in. It is unclear (and has yet to be demonstrated) that sibling differences will somehow remove this confounding. Researchers are working on efforts to generate large enough data sets of family members to use family designs in large-scale GWAS to remove the initial step of confounding.[4] Stay tuned. Regardless of this innovation in GWAS, it will remain unclear whether sibling differences in PGS will eventually allow causal interpretations for the same standard reasons known to social scientists who use sibling models without genetic data. Sibling fixed effects are not a panacea—they can be used to remove specific concerns about confounding from shared family background but retain issues of interference (Boardman and Fletcher 2015).

Reviewing the previous methodological approaches used by medical sociological researchers who are working on G×E research is important to ensure that problems evident in previous research are not repeated in the future. However, we are also concerned that this criticism with respect to a specific method (e.g., cG×E) may lead to a general concern about the G×E endeavor in general. This same concern is evident in research that has attempted to test G×E models using highly inductive genome-wide G×E models (Boardman et al. 2014). In both cases, conclusions regarding the relevance of the G×E approach for medical sociological research may be portrayed as futile or irrelevant when in fact the limitation was unique to the method rather than the theory or substance. This is particularly relevant because much of the methodological limitations have been focused on efforts to detect true causal genetic effects when, in fact, the counterfactual of genotype in absence of environment simply has no utility in medical sociological research. That is, genetic associations always take place in a specific historical time; in a specific social, economic, and institutional context; for individuals who differ with respect to social identities, all of which have bearing on the relevance for health-related genotype–phenotype associations. Likewise, new evidence suggests that parents compensate for differential PGS of children (Fletcher et al. 2020), which complicates the causal interpretation of PGS as a "genetic effect" even within the ideal sibling fixed effects setup. In sum, there are instances in which the identification of causal genetic effects is important, and there are a range of different methods that can be used if this is the goal (Conley and Fletcher 2017), but we encourage researchers to think of this identification strategy as just one methodological approach to address a very specific research hypothesis rather than the gold standard for genetic research in medical sociology.

CONCLUSION

In 2005, Peggy Thoits, the incoming editor of *JHSB*, made the following statement regarding the integration of genetics into medical sociology and how this integration affected her vision of the journal:

> [T]here is a genetics revolution underway in the biological sciences that is likely to change our own (and the public's) understanding of disease causality and medical treatment and that has already raised several troubling new ethical and public policy questions. This is a shift deserving

> of sociological attention in its own right, and the revolution might also compel health and medicine researchers to think creatively about the interplay between social and biological factors in health and illness. Given the interdisciplinary reach of *JHSB*, papers that deal with some of the ramifications of the genetics revolution could be particularly influential. (Thoits 2005:2)

As described in our review, articles published in *JHSB* since 2005 have accomplished and surpassed in some ways Thoits's (2005) expectations of the journal, serving as an influential outlet for work bridging the biological and social sciences with respect to health and health behaviors. These articles have collectively demonstrated that genetic associations have little meaning outside of the built, social, and cultural environments in which they are identified. The nature versus nurture dichotomy is not relevant to most of the phenomena of interest to the readers of *JHSB*, in which nature and nurture are almost always involved *and* interacting with one another to define the contours of population health. The "troubling new ethical and public policy questions" that Thoits (2005) anticipated are far less troubling in absence of the overly simplified and incorrect nature–nurture framing. As an indication of this perspective, consider the comments made by Amy Burdette when she took over the role of editor of *JHSB* 15 years later in 2020:

> I will prioritize biological applications. Due to advances in the study of physiological stress, cellular aging, epigenetics, and gene–environment interactions, biological scientists have moved beyond exclusive models of biological determinism to acknowledge that biological processes and socio-environmental conditions often depend on each other. For the most part, sociologists have ignored developments in the biological sciences and have sustained a "nurture fortress" to defend against essentialist (now) obsolete notions of biological determinism. The obvious biological links to health-related processes suggest that *JHSB* should lead the way. (Burdette 2020:2)

Burdette's (2020) statement is similar to the statement of Thoits (2005), but it reflects the changes in the larger scientific community with respect to the "(now) obsolete notions of biological determinism" and takes an additional step and calls out social scientists to limit or eliminate our collective knee-jerk reaction to be critical or skeptical of any efforts to describe complex human behaviors by referencing biological mechanisms. And more importantly, just as we started this article, she urges the medical sociology community to *lead* these efforts rather than simply *respond* to published work that may challenge some of the shared understandings of determinants among social scientists. As we describe in this article, the integration of genetics into medical sociology over the past decades has experienced several phases, has substantially broadened measurement and the possibility of testing new hypotheses central to the social sciences, and is ever changing. Our assessment is therefore enthusiastic and mixed—we see the substantial advances along with the setbacks and current open questions.

One unforeseen, critical, and we believe surmountable issue in this second wave of integration and an area in critical need of *leadership* from the medical sociological community has been that of representation with respect to racial and ethnic diversity. It is the (hopefully temporary) requirement of many research outlets of focusing only on non-Hispanic white respondents in most work that uses PGS. The sources of this requirement are both simple to explain and understand from a statistical perspective but also murky because they align so well with the history of exclusion of marginalized groups and, as we discussed previously, providing lubrication to the revolving door of eugenics. Briefly, the key issue is that efforts of genetic discovery of tiny effects sprinkled across the genome require enormous genotyped samples. Better still, from a statistical point of view, is that these samples be genetically homogeneous. This is one of many shortcuts pursued in genetics to try to separate genetic effects from environmental variation. Because many genotypes are stronger markers for familial migratory and settlement histories than of health outcomes, per se, narrowing the data so that these migratory and settlement histories (which also align with notions of "ancestry") are accounted for is scientifically and statistically important. These statistical conveniences along with incredible differences in data availability have led to a near exclusive focus on analysis of respondents with European ancestry. There are large, ongoing efforts at overcoming this current issue—we believe these efforts will be successful but will also open new issues that are not yet solved.

Apart from the issue of representation, we believe there are standard yet important issues that continue to stall progress in the more complete integration of genetics into medical sociology. Broadly,

it is time to proactively insist that work that integrates genetics with social science abide by the conventions of sound social science. The initial claims that genetic measures are fixed, determined at birth, and unresponsive to the environment have been overextended in interpreting PGS "effects" in social science applications. Social scientists need to be conversant enough in genetics to recognize when important (and often implicit) assumptions are being made about our ability to measure "genetic effects" that are able to be distinguished from the environment and structural factors in which social scientists are most interested. Social scientists cannot wait for geneticists to lead this charge, and we have the specific training and experience to improve both the integration of genetics and social science but also genetics itself. In many ways, our collective efforts to identity true causal genetic effects without quotes have led to a situation in which the initiation of our inquiry prioritizes the statistical methods available to researchers rather than existing theory. Theories that anticipate *why* genetic variation may matter, for *whom* small genetic associations may be the strongest or weakest, *when* genetic associations are likely to be the strongest with respect to historical time and within an individual's life course, and *what* health outcomes and health behaviors are the most likely to evidence the social modification of genetic associations. The methods and parameter estimates will give clues about these complex and highly interactive processes that cannot be structured in an overly simplified causal framework.

There is no holy grail of explanation and understanding of important health and social processes that leaves genetics entirely outside of the analysis. But it also is becoming clear that genetics has features of a Trojan horse. Many researchers are promising more and making stronger interpretations than are warranted given the current limits to data and methods. As medical sociologists know, this endangers further elevation of genetic determinism. Perhaps social scientists will need to learn again what we learn every time there is a new measure that purports to be game changing. Like models, we use simplifications to interpret measures. Test scores both have problems, can be misinterpreted and misused, and also often provide needed information for a more complete understanding—the same is true with PGS. Each has risks and rewards. However, not all new measures are necessarily Trojan horses, and this is where the risks of PGS and also the rewards may be quite high and not yet absorbed and understood. Social science has so far been protected from some of the worst risks of PGS because nearly all uses of them have (correctly) been applied only to whites. We do need to anticipate that this will change as larger scale GWAS are conducted on nonwhite populations and consider what preemptive steps we might take. It is time now to reconsider and reaffirm what *JHSB* editors have outlined in the past—that the integration of genetics in medical sociology is necessary, which requires social scientists to take an active role in this ongoing and increasingly important research area.

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NOTES

1. Similar results are reported by Domingue et al. (2016) and Boardman et al. (2011).
2. This second changed is based, in part, on a new law of behavioral genetics: "A typical human behavioral trait is associated with very many genetic variants,

each of which accounts for a very small percentage of the behavioral variability" (Chabris et al. 2015:305). But we also know the first law of behavioral genetics: All behavioral traits are heritable. Combining the laws leaves social science in a predicament—we need to acknowledge that genetics matters for nearly every outcome we are interested in understanding, but genetic analysis regularly demonstrates that no single piece (or in fact no set of pieces) of genetic data explains any outcome.

3. There are some notable exceptions. One key purported benefit of polygenic scores (PGS) has been as a control variable, serving the purpose of reducing variance and, potentially, in controlling for otherwise unmeasured "genetics" but without interpreting the estimates of PGS themselves. A second direction is to impute variables not typically collected in social surveys but with high heritability. PGS for eye color, baldness, and height are a few examples that could contribute to analysis of social outcomes related to physical appearance.
4. One ongoing irony to this research direction is that for most of the history of genome-wide association studies, related individuals were purposely eliminated from the study to purify the samples.

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