Emerging Issues in Public Health Genomics

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Abstract

This review highlights emerging areas of interest in public health genomics. First, we describe recent advances in newborn screening (NBS), with a focus on the practice and policy implications of current and future efforts to expand NBS programs (e.g., via next-generation sequencing). Next, we detail research findings from the rapidly progressing field of epigenetics and epigenomics, highlighting ways in which our emerging understanding in these areas could guide future intervention and research efforts in public health. We close by considering various ethical, legal, and social issues posed by recent developments in public health genomics; these include policies to regulate access to personal genomic information, the need to enhance genetic literacy in both health professionals and the public, and challenges in ensuring that the benefits (and burdens) of genomic discoveries and applications are equitably distributed. We also note needs for future genomic research that integrates across basic and social sciences.

INTRODUCTION

Ongoing advances in genomic sciences and technology have important implications for the understanding, prevention, and treatment of human disease. Most often, such developments are considered within the realm of medicine, with applications in pharmacogenomics and, more recently, precision therapy in oncology being commonly cited examples (24, 81, 82, 105). Yet the field of public health is also witnessing important transformations brought about by the advent of new biotechnologies—e.g., next-generation sequencing (NGS)—and the increasing incorporation of genomics into population health sciences. In this review, we highlight what we view as important trends and emerging issues within the changing landscape of public health genomics.

Public health genomics is a broad interdisciplinary enterprise that defies succinct description or definition. It includes within its purview many long-standing disciplines—such as genetic epidemiology, biostatistics, health policy, and health education—as well as state-funded programs focused on the surveillance and prevention of birth defects and heritable disorders (18, 35). Some traditional public health activities have begun to more fully integrate genomics. For example, environmental health studies now feature more intensive consideration of genomics to provide a better understanding of populations that might be particularly vulnerable to toxic environmental exposures (7, 10, 38). The field of statistical genetics has also undergone dramatic changes in recent years, with the development of innovative analytic approaches to harness the "big data" now being generated by whole-genome exploration (26, 72, 78, 95). Given its wide-ranging goals and activities, public health genomics requires complex structures and processes to integrate knowledge from genomics-based research and ultimately translate these findings for improved population health. Burke et al. (13) have developed a useful framework for conceptualizing these functions (shown in **Figure 1**). This framework highlights the importance of engaging a diverse range of stakeholders, both within and outside the scientific and public health communities, to support core activities such as informing public policy, developing and evaluating preventive and clinical health services, promoting communication and stakeholder engagement, and supporting education and training.

Given the vast scope of this enterprise, it should be clear that a comprehensive review of its components is beyond the reach of this article (for a more extensive overview of the field, see 80). Our focus is instead on areas that we view as particularly relevant to present and/or future population-based screening that could incorporate emerging genomic technologies. Population-based screening is a classic public health intervention, yet NGS technologies may not only transform existing interventions in this area but also create new screening opportunities in the future. First, we consider recent advances in newborn screening (NBS). Although NBS is a public health program that has been in effect for half a century, it is now being considered as a platform for population-based whole-genome sequencing, raising new questions about the potential benefits and harms of expanding its mission for both research and practice purposes. Second, we discuss the burgeoning science of epigenetics and epigenomics, considering its potential both for advancing the understanding of complex disease and for providing new avenues for public health intervention and prevention, including population-based screening. Finally, we consider the ethical, legal, and social implications (ELSI) raised by advances in these and related areas of public health genomics. Although we recognize that public health genomics increasingly involves international efforts, our focus is primarily on activities within the United States.

ADVANCES IN NEWBORN SCREENING

Background

Each year, nearly all of the 4 million infants born in the United States are screened by state NBS programs to identify and initiate treatment for rare diseases. During the past 50 years, NBS

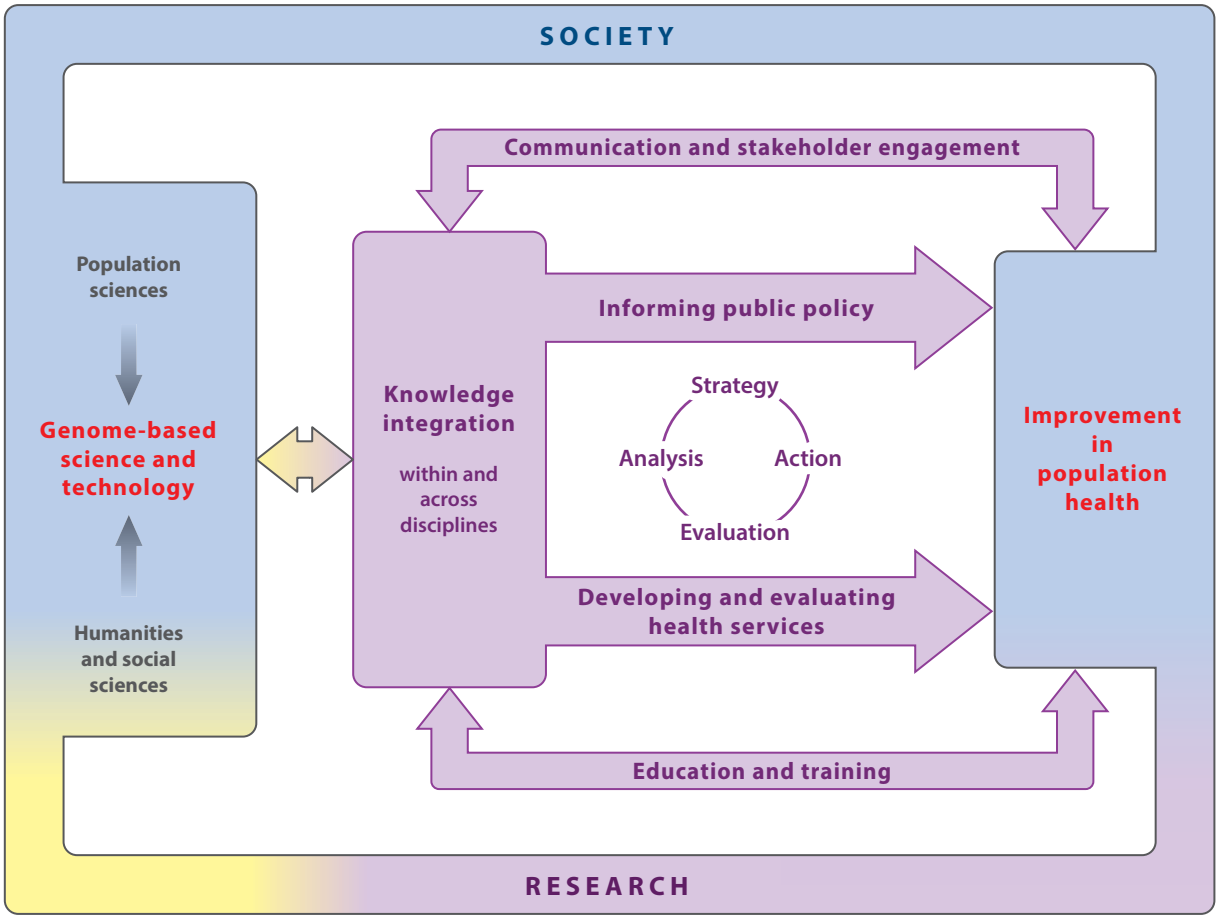

Figure 1

Components of the public health genomics enterprise. Adapted from Reference 13.

has saved thousands of children's lives and prevented disability in many more (88). Population-based NBS first started in Massachusetts in 1963. Now, every US state provides mandatory NBS, usually coordinated through each state's department of health. Programs screen for a variety of disorder types, including inborn errors of metabolism, endocrine disorders, congenital heart disorders, cystic fibrosis, and hearing loss. What these disorders have in common is that nearly all are lifelong conditions without cure. Furthermore, if not tested for immediately after birth, these disorders may progress unnoticed in newborns until they cause irreversible damage, such as cognitive impairment or death. Each year, NBS programs identify more than 12,000 children with rare inherited disorders and connect them with life-saving interventions before irreversible health effects or death occurs (17).

NBS programs function at the intersection of public health, public policy, and clinical care. Although federal guidance is provided by the Maternal and Child Health Bureau of the Health Resources and Services Administration, decisions about implementation are made by each state's NBS program (77, 113). Each NBS program oversees both the laboratory testing and the follow-up of positive results through the coordination of hospitals, state laboratories, and health care providers (primary care and specialty), who assure that NBS results are communicated effectively

to families and that children with positive screens receive appropriate diagnostic evaluations (93). As a result, the process for delivering care in the time period between the identification of an initial positive screening result and subsequent confirmatory testing may vary by state.

There is an ongoing federal effort to minimize variation and maximize quality across state programs. In 2004, the Health Resources and Services Administration funded the organization of seven regional collaboratives. Each state is a member of one of the regional collaboratives, the goal of which is "to promote the identification of shared areas of need, as well as data collection and information sharing among member states" (68, p. S204). In addition, the Secretary of Health and Human Services oversees the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC), which provides policy recommendations to state NBS programs. The most well-recognized responsibility of this committee is the development of a panel of disorders recommended for screening in all states, called the Recommended Uniform Screening Panel (RUSP), which currently comprises more than 50 disorders (49). The committee's decisions are guided by the Wilson & Jungner (133) criteria for population screening, although recent calls have been made for the committee to abandon these in favor of criteria with a broader perspective, including consideration of nonmedical benefits (e.g., parental reproductive decision making, access to early intervention, and avoidance of diagnostic odysseys) for the child and other family members.

It should be noted that the RUSP defines a floor for the content of state NBS panels; states can add (and have added) disorders that either have not been reviewed by the SACHDNC or, after review, have been deemed not appropriate for the RUSP, often because of insufficient existing evidence to justify population-based screening according to the Wilson & Jungner criteria (35). Therefore, despite the influence of the regional collaboratives and the SACHDNC, the process and delivery of services in state NBS programs continue to be strongly influenced by state policies.

The Expansion of Newborn Screening Programs

Historically, the addition of disorders to state NBS panels has been slow and incremental. However, in the past 10 years, advances in technology and the introduction of tandem mass spectrometry into NBS programs have led to a rapid and prodigious increase in the number of disorders screened for. In 1995, before the advent of tandem mass spectrometry, states screened for an average of 5 disorders. By 2005 that number had increased to 19, with some states mandating screening for as many as 52 disorders (115). Given continued advances in the realm of screening technology, the number of disorders screened for will likely continue to increase (83).

NGS is an emerging genomic technology with the potential to transform numerous aspects of NBS programs. The hope is that NGS will improve the quality of screening for current NBS conditions by helping to increase the predictive value of NBS results (76). To this end, the National Institutes of Health has awarded $25 million to explore the benefits and challenges of the use of genomic sequencing in newborn health care (87). Although some platforms, like cystic fibrosis NBS (21), incorporate genomic analysis into their screening test algorithms, it is unlikely that whole-genome sequencing will become the sole testing platform in NBS programs (116) because of a lack of phenotype–genotype correlation for many of the disorders.

In addition, NGS raises several programmatic and ethical issues for NBS programs. For example, NGS could uncover additional, unanticipated information (e.g., incidental findings, including mutations associated with high risk for hereditary cancer syndromes) for infants who may have normal NBS results (112). Parents may not have consented to receive such information about their child, and some of that information, like carrier results, may not be immediately actionable

for the child (112). Moreover, some of the information may be predictive (not diagnostic) and related to the onset of adult conditions. Some information, such as variants of uncertain significance, may not be clearly instructive. Using correct terminology will be crucial so that these variants are distinguished from false positives, a term historically used to identify cases in which the follow-up confirmatory testing is normal. The important distinction will be whether DNA is used as a screening or confirmatory test. The potential harms to children and families of divulging this information need to be examined further (116) before programs incorporate NGS into their testing protocols and algorithms.

An Emerging Life-Course Perspective in Newborn Screening

As the number of disorders detected by NBS increases, the types of disorders screened for and the care provided by NBS programs are also shifting. For much of its existence, NBS has focused on the identification and treatment of inherited disorders in infants and children. The subtle but consistent move toward a life-course perspective in NBS evokes several public health, ethical, and policy challenges. Increasing recognition of the need for lifelong treatment of many of these disorders is one area in which a life-course perspective has emerged.

The first disorder to be screened through NBS programs, phenylketonuria (PKU), is a classic example of this perspective shift. Treatment for PKU requires consumption of a diet that is low in phenylalanine (an amino acid found in protein and other food products, such as aspartame). Because clinicians long believed that the most important impact of this diet was on childhood development, it was initially prescribed only during childhood. Data from international longitudinal studies then revealed that elevated phenylalanine levels in mothers with PKU were associated with increased risk of having a child with birth defects and cognitive impairment (i.e., maternal PKU syndrome) (99). As a result, the recommendation for a phenylalanine-restricted diet expanded to include girls and women of childbearing age (22). Since the initial recommendation was made, evidence has shown improved outcomes in adolescents and adults treated with this diet, and the recommendation now calls for individuals to remain on a phenylalanine-restricted diet for life (69).

The recommendations for lifelong treatment for conditions like PKU are not without ethical and policy challenges. Metabolic conditions like PKU and galactosemia that require special diets are expensive and sometimes lack coverage by third-party payors (9, 16). As a result, many adults who have been diagnosed with an inherited, lifelong disease by a mandatory public health program must forgo treatment because they cannot afford to pay for it out of pocket. In some states, the NBS program pays for the formulas and medical foods that make up this diet. However, this service is becoming increasingly difficult to provide as state public health budgets decrease. The extent to which these challenges will be addressed by the recently established Affordable Care Act remains uncertain.

This shift toward a life-course perspective in NBS raises the additional ethical and policy issue of how long the NBS program is responsible for overseeing the care of individuals diagnosed with NBS disorders. After newborns receive a positive NBS result, they undergo additional testing and evaluation to determine whether they have the disorder in question. If they are subsequently diagnosed with an NBS condition, they go on to receive care in the clinical health care system (although some clinics may be funded, in part, by NBS program funds). Recommendations have been made that these children be followed for a sufficient time after their initial diagnosis to ensure that they receive appropriate and high-quality clinical care that maximizes health outcomes (i.e., long-term follow-up surveillance) (50). However, given the increasing recognition that many of these disorders require treatment into adulthood, it is unclear whether NBS programs have the resources and funds to conduct extensive long-term follow-up surveillance of these children (52).

Screening Beyond Childhood-Onset Disorders

Although some disorders might require treatment that extends into adulthood, others may have limited health implications until adulthood. NBS has screened largely for disorders with symptoms that develop in childhood, but subtle shifts in this paradigm have also been occurring. Perhaps the first shift began with the addition of disorders in which unaffected carriers are identified (e.g., sickle cell disease and cystic fibrosis). The greatest individual benefit to unaffected carriers of knowing their status is for future reproductive planning, which is not an immediate concern for childhood health. In fact, parents receive the most immediate benefit from the identification of newborns as carriers. When a child is diagnosed as a carrier for a disorder, parents may be alerted that at least one of them is also a carrier and that future children may be affected with the disorder. Screening of this type is a departure from the primary mission of NBS, which is to screen for disorders that pose emergent health risks in childhood (43).

An incidental change in mission has occurred recently with the introduction of screening for adult-onset disorders. In September 2013, the SACHDNC recommended adding Pompe disease to the RUSP (49). This lysosomal storage disease is the first disorder recommended for addition to the RUSP that also has a distinct adult-onset form (58). Although the primary motivation for adding the disorder was that enzyme replacement treatment improved health outcomes for infants affected by it, the addition represents a shift in focus from screening for disorders that develop in childhood to screening for disorders that may manifest initial symptoms later in the life course. This situation creates a group of individuals, called "patients in waiting," who are diagnosed with a disorder but are "waiting" for symptoms of their disorder to develop (64, 119). Data on the psychological and emotional effects of living with a looming diagnosis of a disorder discovered by NBS are lacking.

Screening for disorders with an adult onset of symptoms also raises the issue of long-term follow-up responsibilities. After being diagnosed with a condition that may arise in adulthood, infants must be consistently followed to identify signs and symptoms of disease as soon as they occur so that treatment can be initiated. It will be a challenge to track these infants as they move into adulthood to ensure that they have appropriate clinical follow-up. Although some NBS programs engage in long-term follow-up activities (51), such a systematic, long-term surveillance of an asymptomatic group of infants diagnosed through NBS has little precedent.

Against these emerging developments, one should not lose sight of the fact that NBS is a mandatory program. This means that state programs require that infants be screened and do not require parental consent or notification (70). The legal framework for mandatory screening is *parens patriae*, whereby the state steps in to make decisions in the best interests of a child (40). It should also be noted that screening is not mandatory in all countries. Few non-US programs mandate NBS for genetic disease. For example, NBS in the Netherlands has always been voluntary, but before the recent expansion of screening, parents were provided with limited information about the tests and did not know about the option to decline screening. In France, written consent is required before any specimen is collected for DNA analysis (44). Given the movement toward screening for adult-onset conditions and disorders that do not meet traditional screening criteria (1), the President's Council on Bioethics (100) has suggested a two-tiered approach to screening that would involve mandatory screening for conditions that fulfill the traditional public health criteria and a voluntary pilot screening program for selected conditions that do not yet meet these criteria. However, this poses the theoretical risk that tiered screening (i.e., voluntary and mandatory) would confuse parents and cause them to seek exemption from NBS altogether.

It should be clear that state NBS programs, a long-standing public health enterprise, are undergoing significant transformation, with numerous implications for practice and policy. A

focus on genetic alterations present in the newborn period, however, does not capture the complex processes of gene–environment interaction involved in most disorders of public health significance. These processes are under investigation in another rapidly evolving area of research in public health genomics: epigenetics and epigenomics. Although public health screening programs based on this emerging science have not yet been undertaken, the field holds significant promise for better understanding, and intervening in, population health risks.

EPIGENETICS AND PUBLIC HEALTH

Epigenetic Modifications Comprise the Epigenome

The term epigenetics was popularized in the 1940s by developmental biologist Conrad Hal Waddington (123) to explain "the interactions of genes with their environment, which bring the phenotype into being." In the 1970s, Holliday & Pugh (53) first proposed covalent DNA modifications, such as methylation of cytosine-guanine (CpG) dinucleotides, as the molecular mechanism to explain Waddington's hypothesis. In the 1990s and beyond, the Human Genome Project inspired the investigation of genome-wide rather than local gene analyses, and the term epigenomics was coined to describe all of the chemical modifications that are added to the genome to regulate gene expression and activity (84). *Epi-* is Greek for "above," and thus the epigenome is defined as the entirety of the modifications to the genome, including modifications directly to DNA as well as modifications that attach to nucleosomes, the proteins around which DNA is wrapped. Although all cells in the body share the same DNA sequence (the genome), the epigenome controls whether they become, e.g., liver, lung, skin, or heart cells.

External Influences on the Epigenome

Environmental factors, including social, chemical, and nutritional exposures, are viewed as influential predictors of subsequent phenotypes and disease risk in later life. In particular, the "developmental origins of health and disease" hypothesis posits that gene–environment interactions during early life result in long-lasting effects and points to epigenetic inheritance as a prime underlying mechanism (6). Epigenetics is the study of changes in gene expression that are heritable from cell to cell and hence through cell lineage development or, in rarer cases, transgenerationally from parent to child to grandchild (136). Because epigenetic changes are dynamic and (unlike genetic changes) potentially reversible, they hold promise for public health as targets for preventive and therapeutic interventions. For example, in a mouse model, epigenetic alterations associated with perinatal chemical exposure can be counteracted by maternal nutritional supplementation with methyl donors (e.g., folic acid) or components of soy (28). Similarly, in rats, in utero choline supplementation negated alcohol-induced alterations in epigenetic modification (8). Although it is unclear whether and (if so) how these animal model findings may generalize to humans, they nevertheless suggest great potential for identifying at-risk populations and strategies for epigenetic intervention.

Increasingly, we are recognizing that environmental influences on the epigenome are diverse and include dietary (total caloric intake, specific micro- and macronutrient levels, phytochemicals), physical (temperature, species density), social (stress, behavior, socioeconomic factors), chemical (toxins, endocrine disruptors, drugs), and unknown (stochastic, random) effects. Extensive reviews on environmental epigenetics have recently been published (5, 20, 33); here, we wish to highlight a few seminal studies relating to life-course epigenetic effects.

Because diet-derived methyl donors and cofactors are necessary for the synthesis of *S*-adenosylmethionine (the methyl group donor responsible for DNA methylation), environmental

factors that alter early nutrition and/or *S*-adenosylmethionine synthesis can potentially influence life-course phenotype. For example, persistent epigenetic adaptations occur early in development in response to maternal nutritional factors, like the intake of folic acid (125) or genistein (29), and are associated with increased disease susceptibility later in life among genetically identical mice. Consequently, aberrant epigenetic gene regulation has been proposed as a mechanism of action for the discordance of disease susceptibility in monozygotic twins (97). Esteller and colleagues (34) compared epigenetic profiles from sets of monozygotic twins at different ages as well as from those raised in different environments. The profiles exhibited greater divergence in older twins as well as in twins who had spent more than 50% of their lives apart, implicating lifestyle choices and/or environmental exposures as contributing factors to divergent epigenomes.

Studies have also associated pharmaceutical exposures with an altered epigenome and increased disease risk. For example, an increased incidence of uncommon disorders was observed in the granddaughters and grandsons of pregnant women prescribed diethylstilbestrol, suggesting epigenetic multigenerational inheritance (reviewed in 92). Taken together, these findings across animal models and human populations implicate epigenetic modifications as mechanisms by which stressful environments and toxic exposures can have single and multigenerational adverse health effects.

Critical Periods and Vulnerable Populations

Understanding the effects of environmental factors on plasticity through epigenetic mechanisms requires considering both exposure timing and epigenetic drift across time. DNA methylation and other epigenetic patterns are prone to change throughout the life course, but they are especially vulnerable during reprogramming events associated with embryogenesis and early development. This is because the epigenome undergoes extensive reprogramming during two key time points in early gestation for the purpose of establishing cell- and tissue-specific gene expression (48). In male primordial germ cells, which eventually become sperm, methylation is initiated during gestation, whereas in female primordial germ cells, which eventually become eggs, methylation occurs after birth in mature oocytes. A second period of epigenetic reprogramming occurs at fertilization, which helps to establish individual cell-specific methylation patterns (57). As individuals age, DNA methylation is gradually lost genome-wide at the same time that it is increasing in specific genes, with these two processes leading to genome instability and gene-specific suppression, respectively. Whether early or life-course environmental exposures influence the rate of epigenetic drift with time is an active area of interest (33, 118).

Because the epigenome is most vulnerable to external factors during development, women and men of childbearing age, pregnant women, and fetuses represent vulnerable populations for epigenetic reprogramming that is associated with life-course health outcomes (131). Exposure levels, in addition to the absorption, distribution, metabolism, and elimination of exposed factors, may vary across individuals owing to several factors, including genetics, occupation, dietary practices, and health status. Additionally, fetuses are more susceptible to chemical, physical, and biological exposures owing to the ability of the exposure to cross the placental barrier into the uterine environment (56, 59, 63, 94). Fetuses and pregnant women also exhibit altered metabolizing machinery and biotransformation capacity for chemical exposures as compared with nonpregnant adults (74, 85, 121), thereby potentially increasing the risk of abnormal epigenetic reprogramming resulting from environmental exposures. These findings suggest a need to enhance maternal and child public health programs to protect the developing and potentially fragile fetuses against harmful exposures.

Emerging Technologies and Analytic Approaches

Akin to the increased use of genome-wide association studies in genetics research, the field of epigenomics has recently experienced a rapid advancement in technology, in this case allowing for the characterization of multiple epigenetic marks across the genome. Until recently, most attempts to elucidate the effects on the epigenome following environmental exposures were either driven by candidate genes or based on epigenetic techniques with limited genome coverage/sensitivity. Rapid advancements in technology, methodology, and data acquisition are now enabling scientists to identify constellations of genomic loci with altered epigenetic status (23, 65, 109).

To fully succeed in identifying the role of epigenetic mechanisms across the life course, scientists must integrate animal model, human clinical, and human population approaches while paying close attention to windows of vulnerability, environmental and nutritional assessments, and cell-specific epigenetic patterns (27). Animal models, in which exposures are well controlled and characterized, will continue to inform the evaluation of dose–response effects on the epigenome as well as vulnerable time periods, including gestation and multi- or transgenerational effects (71, 96, 111). Further, animal models and clinical samples are often useful for proteomic and chromatin structure evaluation (30), which may be limited in human population approaches owing to sample storage and processing limitations. Finally, subjecting the epigenome (in contrast to the genome) to animal model and human clinical studies, in which cell-type specificity is more readily evaluated, could provide important proof-of-principle approaches for evaluating the use of peripheral tissue (e.g., blood and saliva) in human epigenetic epidemiology studies.

Implications for Public Health Intervention and Areas for Future Research

The evaluation of the epigenome in humans has important implications for reducing health risks by identifying potentially modifiable risk factors. First, environmental exposures are good candidates for modifiable risk factors because they can be effectively regulated at both the personal behavioral and regulatory policy levels. Second, epigenomic profiling can facilitate the identification of biomarkers of exposure, enabling clinicians to identify at-risk individuals prior to disease onset. Unlike genetic mutations, which are static and nonmodifiable, epigenetic marks are dynamic and potentially modifiable. Therefore, if environmental exposures are affecting health outcomes via epigenetics, nutritional and/or pharmacological approaches could potentially be used to counteract adverse effects, along with broader policy approaches to reduce the prevalence of toxic exposures in a given state or municipality. Once epigenetic biomarkers of exposure associated with health outcomes have been established, the future of epigenomics holds tremendous potential not only for individualized reproductive health care but also for population-wide disease diagnostic, screening, and prevention strategies.

Although the investigation of epigenetics as a mechanism of the developmental origins of health and disease has made substantial progress over the past decade, there remains a distinct need for more studies that (*a*) begin exposure prior to conception to ensure coverage of the initial epigenetic reprogramming events; (*b*) characterize exposures and health outcomes over time, with corresponding measures of potential epigenetic drift; (*c*) investigate tissue- and cell-specific differences in epigenetic responses to environmental exposures; and (*d*) examine exposure mixtures that more closely approximate real-world exposures that people face. Regarding these four areas, epigenetic studies may be particularly successful in identifying mechanisms associated with exposures and disease risk by incorporating neonatal blood spots (sometimes accessible at the population level from state NBS programs described above), which are important resources both for exposure assessment in utero and for DNA and gene expression studies (12, 126). In addition

to the general needs noted above, the realization that many chemical exposures act as endocrine-disrupting compounds necessitates the evaluation of multiple doses in toxicological studies as well as advance exposure modeling and statistical methods in human studies. Investigation of sex/gender differences in epigenetic alterations and their downstream health effects is also critical.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

The expansion of NBS programs and the potential future application of findings from epigenetics and epigenomics studies—among other emerging trends in public health genomics—raise numerous ELSI issues that need to be addressed. As noted above, expanded NBS efforts raise delicate issues around informed consent, and insights from epigenetics studies may suggest a more urgent ethical duty to enhance public health interventions early in the life course. In this section, we consider a variety of ELSI issues relevant for current and future efforts in public health genomics, including health policies that determine access to genomic information, challenges in providing health education and understanding behavioral responses to genetic test results, and procedural and distributive issues in public health genomics.

Health Policies Regarding Access to Personal Genomic Information

Many prominent health policy challenges in public health genomics involve the regulation of access to genomic information generated by emerging technologies. Such access can occur across various contexts, including clinical practice, research, consumer genomics services, and public health. For example, as discussed above, the integration of NGS into NBS programs could generate incidental findings of uncertain value to parents, children, and clinicians. Typically, policies regarding access to genetic information with health implications have conformed to a medical model, with clinical experts as the gatekeepers of new information. In this approach, most genomic information would currently be deemed unsuitable for disclosure given the limitations in predictive value and clinical utility (i.e., available treatment options), difficulties in conveying information in accurate and easily understood terms, and possible psychological and social harms to individuals receiving such information. However, many individuals, particularly those with family histories of certain diseases, are curious about their genetic profiles. Both national surveys and clinical research suggest that individuals are generally interested in genetic risk information (even for severe, incurable conditions like Alzheimer's disease), with the benefits of testing seen as outweighing its limitations and risks because of its perceived value in informing advance planning, monitoring treatment developments, and coping with uncertain risk status (91, 102). Survey respondents have claimed that they would be willing to pay significant out-of-pocket costs for genetic risk information, even if it is of modest predictive value (61, 90). Reflecting a broader trend toward patients asserting their right to know personal health information, many believe they should have access to their own genomic information if desired, even if it is secondary to the initial indication for testing.

The issue of incidental findings in the clinical use of whole-genome and whole-exome sequencing has received much recent attention, in large part because of controversial guidelines issued by the American College of Medical Genetics (42). These recommendations assert a more expansive duty to disclose genetic findings of potential clinical utility, even if they are not the intended focus of testing. Some commentators (14) have argued that the guidelines are contrary to standard practice in that they mandate disclosure regardless of patient preferences [a recommendation that has since been modified to include a patient opt-out provision (3a)] and endorse the provision of risk information for adult-onset conditions regardless of patient age. The latter recommendation would have particular relevance if, as discussed above, NBS programs begin to

incorporate whole-genome sequencing approaches into their efforts (39). Leading professional organizations in clinical genetics have issued policy statements that genetic testing should be deferred until adulthood unless the determination of carrier status results in medical benefit in childhood (4, 31). A main ethical justification for withholding this information is that there are no immediate clinical benefits to outweigh the potential harms of receiving distressing and potentially stigmatic information. Some also note the value of preserving autonomy, suggesting that genetic risk information could infringe on the child's right to an "open future" and the corresponding opportunity to make testing decisions as a consenting adult (25). Yet other commentators have argued for a more flexible stance against testing minors for adult-onset conditions, noting that, in the absence of proven (versus speculative) harms from genetic risk disclosure, parental authority in such decision making should be respected (132).

Within genomic research, some commentators (101, 108) have argued that the principle of respect for study participants means that greater access to such information should generally be provided to individuals involved in genomic research. This could prove a daunting challenge, particularly for investigators using data from NBS research repositories and other large population-based data sets. Wolf et al. (134) have developed guidelines for large biobank research systems to discharge potential responsibilities to disclose individual genomic research results to participants. Recommendations include the proactive identification of results warranting disclosure, incorporation of participant preferences regarding return of results into initial consent processes, and development of processes and procedures whereby primary and secondary researchers communicate about the potential need to return individual research results. Still, given the increasing use of techniques to interrogate the whole genome, researchers could easily be overwhelmed by the need to sift through incidental findings and guard against the possibility of disclosing false-positive results (60).

Another area of controversy concerns direct access to personal genomic information via commercially available services. Multiplex genetic testing can now be conducted at a fraction of its prior cost, using saliva samples that can be shipped from one's home. Test results for scores of conditions can be delivered simultaneously via sophisticated web-based user interfaces that provide relevant and tailored education. Direct-to-consumer genetic testing (DTC-GT) has raised ELSI concerns ever since its inception. Commentators have noted that many company websites claim exaggerated benefits of testing and may not fully disclose the risks (particularly privacy and familial implications). For example, a content analysis of 23 DTC-GT websites found six times as many statements about test benefits as about risks and limitations (110). DTC-GT services typically do not screen out psychologically vulnerable consumers or collect detailed family history information, and most do not provide genetic counseling, which could increase the potential for inadequate understanding of the meaning and/or implications of test results.

Leading professional organizations representing health professionals and genetics researchers have expressed concerns regarding DTC-GT and its potential harms (3, 54), and others have suggested that risk information gained from DTC-GT services will lead to more, and potentially unnecessary, health care utilization and screening (79). Yet many proponents of consumer genomics view direct access to one's genome as an individual right, noting the potential benefits of learning more about one's predisposition to disease and likelihood of response to specific medications. Findings to date suggest that neither the health benefits promoted by DTC-GT proponents (e.g., improvements in positive health behaviors) nor the worst-case scenarios envisioned by its critics (e.g., catastrophic psychological distress and misunderstanding of test results, undue burden on the health care system) have materialized (103). However, research on the benefits and harms of DTC-GT is in its early stages and has numerous key limitations (e.g., lack of comparison groups, use of nonrepresentative convenience samples). In the meantime, some countries (e.g.,

Germany) have banned DTC-GT entirely, and in the United States, regulators have recently issued cease-and-desist-style warnings to leading personal genome service companies like 23andMe (46).

Another concern about the provision of genetic susceptibility test results involves potential discrimination by insurers and employers. Although proven cases of genetic discrimination are relatively rare, a US survey of individuals at risk for Huntington's disease suggested numerous examples of perceived discrimination in insurance, employment, health care, and social settings (11). In the United States, the federal Genetic Information Nondiscrimination Act (GINA) was passed in 2008, prohibiting health insurers and employers from using genetic information (including family history) to inform decisions about coverage, premiums, or hiring (62). However, GINA does not cover life, disability, or long-term care insurance, which is important to note given the availability of genetic susceptibility testing for disorders like Alzheimer's disease in DTC-GT and other formats. In a series of randomized clinical trials, the disclosure of genetic susceptibility test results (in this case, *APOE* genotype) to individuals at risk for Alzheimer's disease appeared to prompt changes to participants' long-term care insurance plans (137). Given that Alzheimer's disease accounts for a significant proportion of long-term care costs, insurers may be within their legal rights to address potential adverse selection by consumers who know they are at increased risk for Alzheimer's disease (117). Should insurers increase premiums or deny coverage based on *APOE* or other genetic test results, an expansion of GINA protections could be warranted in order to address potential genetic discrimination in long-term care and other insurance domains. It is unclear, however, whether current GINA protections would cover results from epigenomic analyses such as those considered above (104). The legislation was drafted before the emergence of this area of public health genomics and thus does not specifically include epigenetics in its definition of genetic information.

Health Education in Public Health Genomics

Educating the public about genomic information poses numerous challenges, not least of which is that scientists are still determining its meaning across various contexts relevant for human health. Take, for example, genetic risk assessment for health conditions. The complexity of most medical disorders makes it difficult to integrate genetic information with the multiple other factors that influence disease expression, such as health behaviors, environmental exposures, comorbid conditions, and social determinants of health. Within the realm of genetics, factors such as penetrance, variable expressivity, and genotype–phenotype correlations can impact the expression of gene mutations, and we are still relatively ignorant about the role of gene–gene and gene–environment interactions in human diseases. Even when data are available on these factors, sampling biases may limit the generalizability of results. For example, allele frequencies in genes associated with various diseases are known to differ by racial and ethnic groups, but the populations enrolled in studies of disease risk often lack diversity on this dimension (15). Furthermore, extrapolating from aggregate data to make inferences at the individual level can be problematic.

Health education challenges are faced not only in the interpretation of genomic information but also in its disclosure. Effectively conveying genetic information requires an ability to translate complicated findings to individuals who often lack the advanced skills in health literacy, genetic literacy, and numeracy that would be required to fully appreciate the meaning and implications of results (55). Further complicating matters is that tendencies toward genetic exceptionalism and essentialism may mean that recipients treat information differently merely by virtue of its being labeled "genetic." These biases could result in information being misconstrued in either fatalistic or falsely reassuring terms. As discussed above, NBS is a context in which parents often receive

information about disorders they have never heard of, resulting from a test that they may not have consented to or been educated about. This raises the important issue of expectations regarding health information; bad health news is much more likely to pose psychological harms when it is unanticipated. Even in the best of circumstances, the postpartum period can be an overwhelming time for parents. When parents receive the news of a positive NBS result, they are often in a vulnerable state in terms of both their prior knowledge of NBS (which is typically suboptimal) and their emotional status. Studies have shown that the prevalence of postpartum anxiety disorders may be higher than that of postpartum depression (127–129). Thus, during the postpartum period, parents may not be emotionally prepared for the stressful news that a potentially serious illness has been detected in their newborn (120).

When parents are unprepared to hear potentially stressful news, they may fail to understand the significance of the positive initial screening result, the process of evaluation, and the ultimate designation of the positive screening result as true or false. Failure to understand the implications of a positive screening result, regardless of whether it is later confirmed to be true or determined to be false, has been associated with increased utilization of health care that is unrelated to the NBS disorder tested, as well as with dysfunctional parent–child relationships (124). The extent of parental misunderstanding is significant. In one study, only one-third of parents were able to correctly report the reason for repeat screening that occurred (45). Against the backdrop of expanded NBS for unfamiliar disorders, it is essential to deliver information to parents about NBS results in a way that optimizes both parental understanding of the child's health status and parental health care–seeking behavior for the child.

Given these nuances and sensitivities, genomic information would ideally be delivered by a trained genetic counselor with expertise in human genetics, health education, and interpersonal practice. Yet the traditional genetic counseling model—as developed for heritable, high-penetrance, adult-onset disorders—poses feasibility challenges, given the need for extensive case preparation, comprehensive review of family and medical history information, and pre- and posttest education and counseling. This model may not be practical from a public health perspective, especially as greater numbers of people require genetic services. There are more than 3,100 board-certified genetic counselors in the United States (2), with most of these professionals geographically concentrated in urban areas and working in prenatal, pediatrics, and cancer genetics (89). To meet anticipated increased future demands for genetic counseling, leaders in the field have called for the development of alternative models of genetic service delivery and recognized the need for increased involvement of nongenetics health care professionals, use of educational media, and briefer protocols (47). These efforts should draw upon what has been learned in recent years about effective strategies for health risk communication. These strategies include (*a*) using natural frequencies (i.e., not only percentages) to communicate risk estimates (37), (*b*) supplementing verbal disclosure of risk information with graphical representations (e.g., pictographs) (67), (*c*) using printed take-home educational materials to reinforce information presented in person (135), and (*d*) provisioning strategies for coping with risk, such as possible options for risk reduction and resources for additional information and support.

Health Behavior Responses to Genomic Information

From a public health perspective, the value of genomic information lies primarily in its potential to spur disease prevention efforts. Proponents of genetic susceptibility testing, for example, view it as a means to promote healthy behaviors among high-risk subpopulations to reduce chances of disease onset. However, genetic risk assessment has not generally added value when the behaviors in question are complex and difficult to change, as is the case with quitting smoking and improving

diet and exercise habits (75). A few studies have suggested that genetic susceptibility testing may enhance preferences for biological interventions (e.g., medications) over health behavior changes (e.g., lifestyle change) when both are viable options (73, 98, 107). Such a phenomenon was observed in studies of genetic susceptibility testing for Alzheimer's disease, where the most common health behavior change reported by participants receiving high-risk results was the addition of vitamins or nutritional supplements (often vitamin E), even though educational materials noted that this is not a proven means of reducing risk for Alzheimer's disease (19, 122).

Genomics and Social Justice

Public health ethics has long placed an emphasis on issues of justice, with a concern that health benefits and burdens be distributed fairly across the population (41). Yet many current genomic technologies used in health care are available only via specialty medical centers and are not always covered by health insurers, limiting their access to significant proportions of the population, even in wealthy countries. Although the financial costs of whole-genome sequencing have dropped dramatically over time (130), its application requires intensive resources in terms of both sequence analysis and clinical interpretation—not to mention the above-mentioned long-term follow-up costs implicated in expanded approaches to NBS programs. ELSI scholars have further reflected justice concerns by noting how applications of genomic technologies could exacerbate, rather than ameliorate, health disparities between racial and ethnic groups (106) by focusing on biological causes of disease instead of more compelling social and environmental risk factors. Emerging findings from epigenetics could help bridge the gap here, by suggesting potential underlying mechanisms by which differential exposures to extreme environmental stressors translate into adverse health outcomes.

Public health ethics can also be viewed through the lens of procedural justice, where notions of responsible stewardship would require transparency to the general public regarding policy changes and research initiatives. From this standpoint, recent efforts in certain US states to repurpose NBS samples for research without notification or consent of families would be problematic (66, 114). The resulting legal actions taken in Texas and Minnesota to halt ongoing research and even destroy research repositories, although extreme to some, have hopefully resulted in a greater appreciation for the openness and public engagement necessary to maintain trust in the public health genomics enterprise. Public trust may also be at stake when forecasts are made about the potential future benefits of applying genomic discoveries in medicine and public health. Many predictions about the ways in which personalized medicine would transform health care, for example, look wildly optimistic in hindsight, threatening to undermine the credibility of its proponents. Some leaders in the field (32) have called for more realistic promises and responsible claims about the "revolutionary" potential of genomics for medicine and public health.

CONCLUSION

These are exciting times in public health genomics, as witnessed by the potential to integrate powerful new technologies like NGS into public health efforts and the promise of rapidly advancing scientific disciplines like epigenomics. Clearly, however, much research is needed to harness the potential of genomic discoveries to improve human health and secure public trust in ongoing public health genomic initiatives. To have impact beyond the specialty clinic, at more of a population health level, we may also need to think in broader and more creative terms about transdisciplinary approaches to research. We are intrigued by Geronimus's (36) call for a "deep integration" of epigenetic science with social sciences focused on the ways in which socially structured, repeated

activation of stress processes enhances disease vulnerability in marginalized groups. Such integration would seemingly allow public health genomics a larger stake in addressing the chronic disease burdens that account for an increasing proportion of public health costs. Another research development we would advocate is the increased integration of ELSI research within clinical and basic sciences investigations. This approach has been championed by the National Human Genome Research Institute in several of its recent grant programs, including the Clinical Sequencing Exploratory Research consortium (86).

In this review, we have highlighted some areas that we believe to be of emerging importance in the diverse, dynamic field of public health genomics. We anticipate that this enterprise will continue to evolve rapidly, with the implications and challenges for clinical, research, and public policy activities continuing to expand in turn.

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