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Chapter 2

ENLARGING THE SOCIAL DEFINITION OF HARM TO INCLUDE GENETICS

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ABSTRACT

Harm can be both physical and social, a function of the health-related ethos that society adopts. Ecological models clarify that harm can result from acts of commission and omission occurring at the genetic, not just gross, level. In this commentary we present examples of harm reduction from the public health genetics literature that touch on positive actions which may be taken to promote primary, secondary, and tertiary disease prevention. The avoidance of neural tube defects through cereal fortification, dietary prevention of newborn metabolic defects, and genetic testing to avoid pernicious spread of hereditary breast and ovarian cancer occupy these categories of harm reduction, each touching on starkly visible harms that could take place without proper public health efforts. Neighborhoods in low income areas in multiple countries present challenging conditions. Poor nutritional food availability and the possibility of environmental contaminants, lead being a widespread example, require attention to avoid exposure in one generation resulting

in harm to the next. Genetic research has uncovered the epigenetic mechanisms behind the gene-environment interactions that may result. The solutions are both biological and social, with community resources playing a part. The unique contribution of public health genetics to the field of harm reduction is the awareness it has raised of the distinction between genotypic and phenotypic prevention, especially in the realm of prenatal genetic testing. This distinction has impacted the United States more so than other countries in terms of the range of services offered by public health authorities, and has helped to avoid labeling and stigmatization that might otherwise occur through the prevention of human characteristics. An educated public health workforce can maximize the benefits of genetic policies for physical harm reduction while minimizing the use of interventions that could otherwise result in social harm.

Keywords: Genetics, harm, public health, prevention, genetic testing, prenatal testing, newborn screening, neural tube defects, lead exposure, diabetes, epigenetics, inborn errors of metabolism, hemoglobinopathies, breast cancer, stigmatization, discrimination, disability rights perspective, health policy

INTRODUCTION – HARM FROM THE OUTSIDE-IN

Harm reduction in the public health context is often thought of in the physical sense, leading to needle exchange and substance abuse prevention programs, avoidance of drunk driving, promotion of safe sex, and attention to workplace hazards. In its broadest sense, harm can entail both physical and psychosocial injury or damage. The effects of repeat discrimination can impact health. Public health authorities have coined the term "John Henryism" for the chronic disease accompanying stress and overexertion experienced by members of marginalized minority groups [1]. The legendary John Henry, for all his efforts at escaping the southern sharecropping system to win freedom, suffered considerable harm from his exertions in the form of early arthritis, peptic ulcer, and the sequelae of high blood pressure.

Harm can result from acts of commission (injurious actions, as experienced in John Henry's time and in occupational settings today, as well as through risky behaviors) and omission (lack of attention to disease and injury as it ensues). Public health's main focus is prevention, adopting a pro-active stance to the avoidance of harm. Preventive action can take place at a number of levels.

The Institute of Medicine has publicized a circular model of the determinants of population health which depicts the biological determinants of health centrally, community factors midway, and broad social policies at the state and national levels outermost [2]. The model is ecological in the sense that it takes into account the surrounding behavioral and social milieu. If attention is devoted to biological factors, then genes and genetic predispositions would be at the center of the circular model [3]. Public health is able to advocate for and implement action at the various levels needed to curtail harm, social and biological, gross and molecular. The field of public health genetics is aimed at the most intimate causative mechanisms underlying harm, with the goal of preventing harm at the earliest stages.

PRIMARY PREVENTION OF HARM

The prenatal period is an especially delicate time for the developing fetus. Physical abnormalities such as placenta previa (low placement of the placenta in the womb), premature separation of the placenta, and prolapse of the umbilical cord may result in fetal hypoxia and short-term neurological deficits in the newborn, but can also result in cerebral palsy and mental retardation [4]. The harm from delayed attention to these occurrences is clear-cut; each of these maladies, further, may be caught in time with appropriate medical attention. Such events happen on an individual basis -- it is the individual family, mother, and child-to-be that benefit from the attention of the health care provider. Outcomes are not entirely predictable; the child is drawn into a family system where resources and care take center stage and provide stability.

The focus of public health providers is more population-oriented, yet it is equally concerned with the harms that may arise during the critical time before and after birth. In a review of nineteen state genetics plans, the three most common genetic programs covered birth defects, newborn screening, and childhood and adult genetic conditions such as sickle cell disease [5]. Action to avoid birth defects constitutes primary prevention (before the disease has occurred), while newborn screening and follow-up constitute secondary prevention (early in disease manifestation). It has been estimated that less than 10% of disability is due to birth defects having congenital causes that cannot easily be foreseen or managed [6]. Neural tube defects (NTD) can be prevented, however, by proper maternal folate intake. Meta-analysis suggests that folic acid fortification of food staples could prevent ~46% of NTD incidence and mortality, and ~13% of neonatal deaths due to visible congenital

anomalies in the third world [7]. Public health genetics programs in the United States sponsor on their own and in partnership with the March of Dimes campaigns to promote the use of folate, particularly for women contemplating having a child. State public health programs provide teratogen information services to help pregnant mothers be alert to substances in the home or workplace environments that may pose a risk to fetal growth and development. State health departments also conduct active and passive surveillance systems to monitor birth defects.

Subtler harms with more chronic and less physically overt consequences can also occur prenatally. Diabetes during pregnancy can increase the passage of glucose across the placenta, and result in excess weight gain and metabolic abnormalities in the offspring, posing risk across generations [8]. Lead contamination reaching the fetus may result in cognitive delays in childhood [9]. Maternal diabetes can have purely intrinsic causes, such as gestational diabetes, but it can also pre-exist the period of pregnancy and be perpetuated by neighborhood and cultural dietary practices and local food availability. Diabetes associated with the food deficits in the household and neighboring environment, and lead exposure from paint and automobile proximity from previously lead-laden gasoline are public health concerns in that they can impact the wider community, thus calling for prevention measures. Both have epigenetic effects that can befall socio-economic and racial-ethnic groups differently, and carry an impact across multiple generations.

Epigenetic effects occur when environmentally induced and developmentally regulated variations are transmitted to subsequent generations of cells or organisms. They represent a form of gene-environment interaction that modifies gene operation rather than genes themselves. The literature emphasizes four main types of mechanisms: chromatin marking (e.g., methyl groups that attach to DNA, histone protein wrapping – the scaffolding of DNA), structural inheritance (mostly lower organisms), RNA-mediated inheritance, and feedback loops (gene products acting as regulators). The various measures of lead exposure, methylation of cord blood DNA and maternal tibia lead [9], are proxies for the epigenetic programming taking place in DNA at the neural level from three weeks after conception through juvenile life. Disruption of proteins that bind to methylated DNA sequences and mediate repression of gene expression has been found to alter neuronal survival, differentiation, and synaptic function [10]. DNA methylation also plays a role in downregulating the pluripotency genes in embryonic stem cells during neural induction. Lead's impact starts with maternal exposure, but continues at the cellular, anatomic, and behavioral levels in the child-to-be.

In the case of diabetes, researchers have found that maternal "overnutrition" may lead to metabolic imprinting and alteration of genes involved in the regulation of energy homeostasis. Several such sites can be influenced by DNA methylation and histone modification: leptin, *SOCS3*, and glucose transporter genes [11]. In animal studies, phenotypic (visible) and epigenetic changes can persist for at least two generations [12].

Solutions, because these conditions are so environmentally-attuned, are both biological-physiological and social, touching on community resources. Community leaders can initiate programs that make healthy foods available to neighborhoods. Community groups can decide on the wisdom of environmental hazard abatement versus avoidance policies, and can advocate for environmental justice [13].

SECONDARY PREVENTION OF HARM

Interventions focusing on prevention of harm are the bread and butter of public health. If risk conditions can be attended to before harm occurs, then health can be preserved before it suffers substantial compromise, and the possibility exists that many at-risk people can be reached. In many situations, however, the setting has already begun to exert a health impact. An adolescent has already been exposed to substances of abuse as a result of peer pressure. A youngster has frolicked through neighborhood grounds high in lead before the possibility of lead hazard has entered people's minds. A family health history or thorough maternal history is not taken; a child in the first few days of life is born with a metabolic condition first detected in a newborn blood spot [14]. Since secondary prevention implies that harm has already begun to occur, amelioration of the condition is all the more pressing. The inborn errors of metabolism can have dire mental and physical consequences if not attended to quickly (Table 1).

The vast majority of states also screen newborns for hemoglobinopathies (sickle cell anemia, beta-thalassemia) and cystic fibrosis. These conditions are conceptually distinct from those in Table 1 in that they may have a chronic impact, but current therapies, including for beta-thalassemia, are yielding almost normal life expectancies. Worldwide, carrier and prenatal screening can lead to a reduction in the birth prevalence of thalassemia of over 90% [20], an incredible statistic considering that beta-thalassemia can take the life of children before the age of three.

Table 1. Physical consequences of inborn errors of metabolism

Condition	Sequelae [15]	Interventions
Organic acid metabolism defects, Urea acid defects	life-threatening encephalopathy, coma	dietary restriction, removal of toxic metabolites, enhancement of enzyme activity [16]
Biotinidase deficiency	limb weakness, hearing loss, optic atrophy, seizures and coma	avoidance of egg whites, biotin supplementation [17]
Galactosemia	poor weight gain, liver dysfunction, cataract formation	restriction of galactose intake, lactose-free formulas, calcium and vitamin intake [18]
Mucopolysachharidosis type I	mental retardation, course facial features, cardiomyopathy, hepatosplenomegaly	enzyme replacement therapy, blood stem cell transplantation [19]

Controversy exists in the application of prenatal testing to genetic conditions that leave a relatively normal life expectancy and fairly high quality of life. Sickle cell anemia, cystic fibrosis, Down syndrome, and congenital deafness fall in this territory. Juengst and Khoury draw a distinction between "phenotypic prevention," which emphasizes efforts to prevent clinical manifestations of a genetic condition, and "genotypic prevention," bent on preventing transmission of particular genotypes to the next generation [21, 22]. The perspective of the disability community lies heavily against prenatal testing, with its abortion option [23]. States Adrienne Asch, "Autobiographical writings and family narratives testify eloquently to the rich lives and the even richer futures that are possible for people with disabilities today" [24]. The additional option of preimplantation genetic diagnosis (PGD), prenatal testing at the four- to eight-cell stage post-conception, only complicates the matter, especially considering the technology may be used to select heterozygote embryos that have only one affected gene, not two. Ethical relativism plays a part in the judgment of the technologic alternatives. The prevalence of hemoglobinopathies in diverse ethnic communities will have a different moral weight in the United Kingdom than in Germany, where eugenics remains a stark memory.

Concerns over stigmatization and discrimination persist for prospective partners who test positive for having a future at-risk child, parents who opt to give birth to a child affected with a genetic condition in the face of positive carrier and/or prenatal testing, and the child as he or she matures and applies for health insurance and employment. For example, identified carriers in a sickle cell screening program in Ochemenos, Greece were socially ostracized as being undesirable marriage partners [25]. The possibility of stigmatization in a variety of settings represents a distinct form of harm – social, not physical – and can be equally paralyzing. When an individual is discriminated against in the community or in the workplace, the harm inflicted is of a psychosocial kind, but it can compare to physical harm and have lasting repercussions. Dor Yeshorim was started in Brooklyn to protect genetic privacy, and the Americans with Disabilities Act and Genetic Information Nondiscrimination Act were legislated to guard against genetic discrimination.

Novel situations arise which move into vaster policy domains, while resurrecting memories of past discrimination. Following the 2006 death of Bennie Abram, a Rice University student-athlete, the National Collegiate Athletic Association instituted a policy of mandatory screening (can utilize former newborn screening records) to establish the sickle cell status of college athletes. The policy has stirred controversy, as its impact can be both protective and labeling – for athlete and family [26]. The American Society of Hematology has called for universal preventive interventions instead of genetic screening, a move that would avoid labeling of individuals and groups. According to a 2010 American Public Health Association policy statement on genetic and genomic literacy, these qualities are to be viewed as a capacity to see the individual at-risk not in isolation, but in the context of a social environment that provides effective resources, rights, and freedoms [27]. Public health practitioners need to be educated not just in the technical aspects of assessing potential for harm, but also the socio-ethical risks posed by various measures. Balancing must occur so that future genetic policies protect against physical harm while not inflicting social harm.

TERTIARY PREVENTION OF HARM

The bar for implementing multi-pronged strategies to avoid harm from hereditary conditions and genetic interventions should be set high when those efforts are directed at entire populations. Caution is called for when the interventions themselves carry the possibility of harm.

Mortality from breast cancer is about 21 persons per 100,000 individuals per year. Cohort studies and clinical trials have estimated a 90% reduction in risk for hereditary breast cancer from prophylactic mastectomy, and a 49% reduction in breast cancer risk with tamoxifen treatment [28]. Oophorectomy results in comparable (80-90%) reductions in risk for ovarian cancer. Harm can be gauged in terms of the disfigurement and mortality risk from advanced breast cancer versus the psychosocial impact and disfigurement of breast removal in the case of mastectomy.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group has moved cautiously on the relative prognostic capabilities of two tumor gene expression profiling assays that predict outcome, *MammaPrint* and *Oncotype Dx*, until further clinical trials are completed [29]. The United States Centers for Disease Control and Prevention places gene expression profiling for breast cancer in the Tier-2 category for levels of evidence [30]. Tier-1 genetic applications include those with sufficient evidence of validity and clinical utility for the test to be implemented into practice; tier-2 include those with sufficient evidence of validity and promising evidence of utility, but as yet insufficient to support a consistent recommendation for use [31]. The public health perspective is that family history of hereditary breast and ovarian cancer has sufficient evidence for referral for BRCA genetic counseling and testing (primary prevention) [32], but that secondary and tertiary prevention (where disease has already occurred) using genetic assays as prognostic indicators requires further evidence [30]. A strong level of evidence is required when moving genetic technologies to the population level for tertiary prevention.

CONCLUSION – HARM IN THE GENETIC DOMAIN CAN BE BOTH PHYSICAL AND SOCIAL

Public health has a natural tendency to view early prevention of harm as preferable to prevention of harm that has already begun. This orientation is just as true in the realm of genetics as it is in other areas such as harm from drug abuse and injury. Because genetic identity is so tied-up with personal identity, harm from labeling individuals and groups is also a foremost consideration. Disease conditions can harm, but so can health technologies. The eugenics of the earlier part of the 20th Century, sickle cell screening of the 1970s, and recent encounters with pharmacotherapies targeting specific racial-

ethnic groups make it paramount that the definition of harm including genetics be extrapolated through a lens of physical and social harm. Public health genetics has developed a code of evidence – Tier 1 through Tier 3 applications – that assists in deciphering when a genetic technology will cause the least harm while offering the greatest benefit. This system respects the *primum non nocere* – "first, do no harm" – principle as primary in the health field.

As Pernick has stated, the degree of advancement in genetics is no antidote to the possibility that the use of a given technology will not have socially untoward effects [33]. Transparency is required so that a stiff view is taken before policies are solidified and the technology becomes mainstream. Given proper cautions, we hope to have established that public health has much to say and recommend about interventions applied to the most central level of harm, that occurring at the molecular genetic level. Overarching conceptual frameworks dealing with levels of prevention and degrees of evidence have just as much applicability in the field of genetics as they do in other public health arenas that forecast and avoid harm. In this light, much can be done to secure the safety of the youngest among us, born into the world in such a fragile state, as well as those of us who have been weathered by time, with our disease susceptibilities exposed. Harm, like one's genetic fate, is not written in stone. The health practitioner and consumer have the power to prevent harm in an equitable way, allowing the effect to transcend the single individual and spread to the wider population.

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