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Chapter 1

DISTINCTIVE FEATURES OF PUBLIC HEALTH ETHICS IN THE DOMAIN OF EXPANDED GENETIC SCREENING AND POPULATION BIOBANKING

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ABSTRACT

Traditional healthcare ethics has flourished in an environment of ethical principlism, with its focus on patient privacy and autonomy. Clinical genetic testing and tissue banking utilize protocols that rest on a combination of autonomy and beneficence, incorporated into codes of professional practice. Exceptions occur under a case-based rubric, but these departures are the minority. Public health, with its emphasis on the common good and general welfare of the greater population, invokes additional ethical-legal features such as the "*parens patriae*" doctrine and a spectrum of means to assure health that go beyond traditional consent. This protective legal blanket moves solidaristic and communitarian principles to the forefront. In our piece we look at significant new

developments in the genomics field – family risk assessment (using family health history and cascade genetic screening) and population biobanking. We describe new forms of consent that have arisen in response to group-level genetic interventions, as well as the conflicts and compromises that arise with institutional privacy rules. The shift towards a public health ethics calls for a form of synergistic ethics in which benefits to any one individual mutually enhance benefits to all in need. This enlarged ethical perspective aims at a concept of personalized risk assessment and management in the context of public, as opposed to strictly individual, health.

Keywords: Genetics, ethics, public health policy, family health history, cascade screening, biobanks, education, legislation, professional standards, surveillance

INTRODUCTION: CURRENT TRENDS AND PAST PRECEDENTS IN GENETICS AND ETHICS

No sooner had the Human Genome Project (HGP) yielded a complete working draft of the human genome in February 2001 than scientists voiced the need to map out blocks of human genetic variation – haplotypes – dotting the genetic landscape. The new agenda was an admission that the fruits of the painstaking research would not become relevant if the population meaning of genetic discoveries was not taken into account. Further downstream, scientists envisioned employing knowledge of individual genetic variation to predict response to cancer drugs and possible toxicities that might arise. This ambition, known as "personalized medicine," would depend on the pooling of genetic information from many individuals into databases that would store collective data. No matter what phase of the genetic translational enterprise one is referring to, individual results and interventions depend on population-level knowledge. Public health, whether in the United States (the Centers for Disease Control and Prevention Office of Public Health Genomics; CDC-OPHG) or abroad (the European Centre for Public Health Genomics), has long prepared for the spillage of genetic interventions into the medical mainstream affecting large portions of the population. Policy makers are also aware that the widespread use of genetic technology carries with it public health ethical, legal, and social implications ("PHELSI") that require analysis not just at the personal but also at the population level for buy-in and appropriate application of new genetic technologies to occur [1].

Part of the dilemma in focusing on the low-hanging fruit of the HGP is that the earlier genetic discoveries, which mapped out conditions like cystic fibrosis and Duchenne muscular dystrophy, addressed single gene conditions that represent only a small portion of the genetic variations that affect health. The vast majority of human illnesses are either polygenic, involving multiple genetic loci, or multifactorial, resulting from a combination of small inherited variations in genes acting in concert with environmental factors. Examples of the former include familial breast and ovarian cancer (FBOC) and inherited cardiac arrhythmias, and of the latter diabetes, heart disease, and complex cancers. These more common but genetically complex conditions command the attention of public health practitioners. By way of contrast, clinical geneticists often find themselves in the position of utilizing genetic testing and counseling for the rarer single gene conditions requiring immediate attention.

A principlist ethical framework stressing autonomy, beneficence, non-maleficence, and justice has evolved to handle the conduct of genetic testing and counseling. The framework pays heed to the disastrous history of genetics in the first half of the twentieth century in which people placed their trust in a crude form of genetics practice – eugenics – and in forms of medical/public health investigation, such as the U.S. Public Health Service's Syphilis Study at Tuskegee, which lacked an ethical guidance structure [2]. In the United States, the 1979 Belmont Report answered such historic indiscretions with an organized set of ethical principles to underlie biomedical research [3]. As new, legitimate forms of genetic testing arose and genetic medicine struggled to divorce itself from its eugenics past, the patient's decision making capacity also gained ascendency alongside the professional's expertise, again calling for ethical principles that respected individual patients' decisions and values preferences.

Patient judgment and the personal values of health care consumers are also deeply respected by public health practitioners. The American Public Health Association (APHA) Code of Ethics for Public Health has among its principles of ethical practice respect for the rights of individuals in the community as well as respect for the diverse values, beliefs, and cultures in the community [4]. Because of its community outlook, PHELSI stresses the welfare of the collective in conjunction with the autonomy of the individual [1]. Science is used to further the health of the population, of which individuals and families are a part.

In this paper we will explore the distinctive group-oriented emphasis of public health ethics and the modalities health practitioners use to conduct their programs in an ethical manner. The interventions to be considered are a central

focus of public health genetics at this very moment – use of family health histories, a form of expanded genetic screening – cascade screening among relatives, and the harnessing of population biobanks for public health ends. Certain commonalities will appear in the categories of ethical consideration belonging to these major forms of intervention. Part of the task also lies in excavating the ethical contrasts which emerge between clinical and public health practice and between these three interventional baskets. The overall intent is to build an ethical framework for a continuum of technologies. This comprehensive treatment will show that personalized medicine in the genetics arena depends on population-level activities. The application of genetic interventions to groups is not straightforward, however. Dilemmas naturally arise, which a comprehensive ethical framework can be used to address.

FROM PERSONAL AUTONOMY TO GROUP BENEFIT

Clinical medicine emphasizes the principle of autonomy in dealings with patients and research participants. A patient's approval to undergo a diagnostic or therapeutic procedure is the sine qua non of medical practice. Respect for persons is also a major pillar in biomedical research. It is carried out via an adequate informed consent, which guarantees an informed decision on the part of the research participant. Fulda and Lykens cite a case example of a 55 year-old female dialysis patient identified as a carrier of autosomal dominant polycystic kidney disease (APKD) [5]. As a result of the mother's testing, the four sons also receive genetic testing and are likewise identified as carriers. The sons' being informed of their mother's genetic status allows them each to make their own testing decision.

Genetic testing can sometimes be conducted under extenuating circumstances where patients request information that cannot be accurately known given test limitations, this information being perceived as vital to the individual's future planning. An HGP era example would be a patient's requesting their CAG repeat length from Huntington's disease genetic testing, an approximate reflection of potential longevity which became acceptable for patient disclosure only after genetic counselors gained acquaintance with the test's predictive power. Early on the issuance of repeat length was performed on a case-by-case basis, which falls under the heading of casuistric rather than principle-based ethics.

The upshot of the above APKD case was that each of the sons fully exercised their right to know their genetic status. The 30 year-old son, in order

to save his wife from insurance burdens, sold their home and divorced. The 32 year-old son, father of a six year-old child, committed suicide. The case illustrates the free exercise of individual autonomy, as well as the value of pre- and posttest counseling, especially for late-onset conditions resulting in mortality. Thorough counseling might have enabled family members to exercise their right not-to-know. The condition is an intra-familial one. The mother's test results impacted her children in a major way. One sibling's handling of his own results likely tipped the balance on another's decision making. Additionally, as Fulda and Lykens point out, "... it should not be forgotten that the decision to make dialysis machines available – for example in the case of the 55 year-old mother – is a societal one" [5]. The ethical pertinence of an expansion in scope from the individual to the family and community levels is echoed in an editorial by Thomas et al. on the APHA Code of Ethics in Public Health:

> Interdependence is the complement to autonomy, a dominant principle in medical ethics. Without denying that individuals have a right to some role in decisions that affect them, a recognition of interdependence serves as a correction to an overly individualistic perspective that is inconsistent with public health's concern with whole communities and populations. [4]

The freedoms exercised pertain to the individual as well as the community so long as others are affected either by the individual's decision, as might occur in the family context, or the mode of decision making employed, which can be a societal choice. As Knoppers points out, however, thinking at the level of groups and populations requires a vetting of current ethical and legal principles towards a concept of the public good, or minimally speaking, "common" goods [6].

The idea of public goods has its roots with the 18th century philosopher David Hume, who coined the expression "providing for the 'common good'" in his *Treatise of Human Nature* [6, 7]. In Hume's definition of a "pure" public good, one person's or group's use does not preclude another's, which would seem to preserve the modern day principle of autonomy, and no one can be excluded from benefiting from a public good, which emphasizes the justice principle belonging to both biomedical and public health ethics. In contemporary times, Hannah Arendt noted, "Throughout his life man moves constantly within what is his *own* and he also moves in a sphere that is *common* to him and his fellow men" [8].

The notion of common goods also has an historic legal basis and tie to public health. In the constitutional tradition, the common good refers to individuals' welfare considered as a group, the public, or people generally. The "body politic" and "commonwealth" were the terms used in the early days of the American Republic. The commonwealth doctrine helped shape health and welfare regulatory powers in Massachusetts and throughout the United States. Each year the Massachusetts Medical Society sponsors a Shattuck Lecture on a topic of pressing medical and social significance. The lecture is named after Lemuel Shattuck, an early Massachusetts legislator and author of the 1850 Massachusetts Sanitary Commission *Report* to the state legislature. The *Report* accepted the existence of a public realm deserving of governmental protection to assure public health.

The Commonwealth, while respecting individual property rights, deserved protection for the collective good of its members. Ethical rights, if they are to be enforced, translate into policy in the form of common and statutory law. Massachusetts, with its strong Commonwealth tradition, was the first state to refer to a "police power" (*Gibbons v. Ogden*, 1824) to regulate public health: "Inspection laws, quarantine laws, health laws of every description … are component parts of this mass" [9]. Scholars interpret the case in a double sense: (1) the state has the power to constitutionally restrict private interests; and (2) the state can exercise measures to assure hygiene, seeing to it that communities live in health and safety [10].

In 1905, the United States Supreme Court, in *Jacobson v. Massachusetts*, upheld a Cambridge, Massachusetts ordinance requiring compulsory vaccination in a smallpox outbreak. While the case may be viewed as an instance of the exercise of police power, minors are often the beneficiaries of vaccination, which invokes another legal doctrine – "*parens patriae*." This doctrine refers to the state's role as sovereign and guardian of persons under legal disability, e.g., minors and incompetent persons [10].

Once again, scholars conceive of this doctrine both in the narrow sense – (1) restricting injury to others; and (2) broader sense – limiting liberty in the public realm in order to assure health, fluoridation and protection of the rights of HIV/AIDS victims being the latest examples [9, 10]. Together, these legal doctrines spell-out the province of public health – care for the health of individuals through assuring collective health. The Massachusetts Constitution defined governmental action in terms of a social compact. The whole people covenants with each citizen, and each citizen covenants with the whole people towards the common good.

THE COMMUNITARIAN CHARACTER OF PUBLIC HEALTH

A focus on the common good has prompted authors to elaborate on the distinctive features of the public health enterprise. Leo ten Kate describes clinical genetics as a field concerned with individual persons or couples or families who have or fear a health problem [11]. Public health, he states, tends to prefer a group approach to an individual one. The medical model, while it sometimes takes up the banner of primary (before-the-fact) prevention, usually sets its sights on secondary and tertiary prevention, after disease has manifested. A population approach is most feasibly carried out on the level of prevention in those at risk, before disease has manifested. Public health action tends towards the entire population and its at-risk subgroups, and ideally is anticipatory of disease. These features constitute the first two points of the Public Health Code of Ethics. The first point states: "Public health should address principally the fundamental causes of disease and requirements for health, aiming to prevent adverse health outcomes." The second point, cited earlier, regards the rights of individuals in the community. A genetics explication of the Code of Ethics acknowledges that the starting place for public health is the good of the community. The community must be well informed and public health policies should receive input from community members. But individuals must also continue to exercise their right to informed consent for genetic testing. Further, genetic testing should never be used to "create divisions between people [which] have no biological basis" [12].

The stress on community benefit can be framed by utilitarian theory – the greatest happiness of the greatest number. Indeed, utilitarian theory provides the ethical basis for mass immunization and newborn screening, as well as cost-effectiveness analyses justifying the implementation of many public health programs. Utilitarian theory does tend to clash with a number of ethical principles when a person's freedom to make the most intimate choices is compromised, and when various subgroups do not receive commensurate levels of health services [13]. Such arguments have compelled the creation of pragmatic frameworks for public health ethics where rungs of ethical importance – program goals, benefits, burdens, and fairness – are considered in step-wise fashion [14].

Authors have also suggested a refinement of the carrying out of ethical principles by creating graded options for preserving the individual's values in situations where common good is also being targeted. Chadwick and Berg, for

example, have advocated the introduction of different stages of consent in sample collection for genetic databases [15].

The first step they propose is consent to entry into a sample collection, then to specific research on the samples, and finally more general research. The protocol respects autonomy, but in the background lurks a spirit of solidarity, the desire to lend mutual aid and assistance to others, often on a societal scale. They argue that in a society where one is a beneficiary of medical advancements, a person also has a duty to facilitate research progress and to provide knowledge that could be crucial to others' health:

> Family members share genes, their fates are intertwined and there are moral considerations in favour of sharing information that could benefit the whole group (one's family), even if the people providing information or samples cannot themselves benefit. [15]

Ethical principles are more situation-specific than ethical theories, which can guide the use of ethical principles, weighing and exchanging them as needed. In general, public health legal and ethical literature revolves around a communitarian language [9]. Communitarianism looks to the shared values, ideals, and goals of a community to set social policy [13]. The common good, as opposed to individual welfare, is the objective. The health of the public is one such shared value. Beauchamp and Steinbock go so far as to classify public health as a "species of communitarianism" [9]. While a utilitarian calculus may be used to decide which conditions should be tested for in newborn screening, communitarianism provides the basis for subsidy of the testing and metabolic follow-up. Society's members value the health of their youngest to the extent that they would be willing to support the health of all newborns collectively.

Communitarianism is one pole of an ethical fulcrum that also contains the other extreme of libertarianism. Libertarianism looks to individual values and goals as the arbiters of decisions. Often times it refers to an absence of governmentally-imposed restraint, though people can be guarded as to the actions of other actors, such as researchers and health care systems, as well. A tension, therefore, exists in the actions taken by public health authorities. A similar circumstance exists in the medical arena in clinical equipoise. Researchers begin a clinical trial under the assumption that no difference in efficacy exists between one trial arm and another. The null hypothesis can be dispelled as the trial proceeds, compelling ethical argument about when the trial should be stopped. Public health uses the same kind of logic in comparing

interventions from observational studies. Large scale prospective studies and meta-analyses can be used to provide the decisive justification for one intervention over another. More crucially, though, in the design phase, medical and public health researchers must choose among three options – the standard approach, an alternative approach, or no intervention.

However, in research, often only two options are chosen, based on empirical reasoning and ethical choices. Even in practice, as opposed to research, public health authorities must act in a proportionate way, choosing an intervention or interventions that will improve the collective good while interfering the least with personal prerogative, achieving as much equipoise as possible [10]. The noted tension plays-out in ethical solution seeking to overcome blockades to the implementation and promotion of genetic technologies.

PUBLIC HEALTH ETHICS APPLIED TO THREE GROUP-LEVEL GENETIC INTERVENTIONS

While genetic testing, counseling, and individualized treatment form the bread and butter of genetics in the medical mainstream, public health must concern itself with approaches that are preventive and act at the group level. "Group" here refers to families, communities, and populations. The three group-level interventions to be assessed from an ethical point of view are use of family health history (FHH), cascade screening among family members, and population biobanking. Although education is an integral part of informed consent for each of these three categories, in public health it is a modality that often stands on its own as a way to raise awareness in the community about programs being instituted.

The array of ethical concerns for public health interventions stretch from education and informed consent to stigmatization and discrimination. Table 1. lists the primary ethical considerations common to each of the three types of intervention. In keeping with recent developments, a row has also been added for the ethics of electronic means of information storage and communication.

Table 1. Ethical considerations for three public health genetics interventions

	Use of family health history	**Cascade genetic screening**	**Population biobanking**
Educational strategies	Annual Surgeon General's "My Family Health Portrait" campaign [16]	Healthy People 2020 [17], Advocacy organization awareness raising [18]	Multimedia public education campaigns [19], Public consultation [20]
Consent	3rd Party consent [21]	Direct and Indirect contact, Right Not-to-Know vs. Right-to-Know [18,22]	Broad and Blanket consent [19], Community values advisory committees [23], Public consultation [24]
Privacy & confidentiality	Controlled by family members and research team	Controlled by proband and relatives, and research team [22]	Anonymization and double-coding [19]
Stigmatization & discrimination	Attention to sensitivity of information [25]	Life insurance institutional policies [22], Health insurance - GINA	Regulatory policy for non-health-related uses [26]
Computer-based considerations	Surveillance system incorporation [27], Electronic health records policies [28]	Database use; index case identification versus relative contact [29,30]	Selective control of information use [31], Decentralized databanks and firewalls [32]

Example 1: Use of Family Health History

Family health history (FHH) is a simple yet powerful tool to assess risk for single gene diseases as well as more genetically complex common, chronic disorders in family members. Family history has come to be viewed as an independent variable in disease genesis, offering a global reflection of both genetic and environmental factors. Significant reviews have been compiled both for the effectiveness of family history [33] and its use in public health practice [34]. Williams and Hunt in the Health Family Tree Study at the University of Utah estimated FHH's cost to be about $10 per proband, making it considerably less expensive than genetic testing, and earning it the title of "first genetic test" [35]. FHH can be used to triage family members into low, medium, and high risk categories, the latter meriting referral for genetic counseling and possible genetic testing [36].

Turoldo writes about a noncoercive level of public health intervention, this category contrasting with the more concerted "soft coercive" and "highly coercive" varieties:

> Noncoercive interventions are those interventions that simply monitor the situation, that provide information, that enable individuals to change their behaviors by offering psychological or material support, or that guide choice through changing the default policy. [37]

The major public educational effort to promote the use of FHH is the Surgeon General's "My Family Health Portrait" campaign, which provides an online tool for family members to download, fill-out, and take to their healthcare provider [16]. Announcement of the Portrait and web site occurs annually around Thanksgiving; it is suggested that the holiday provides the perfect opportunity, while family members are gathered, to complete the form together. The Portrait is a good example of a dual family- and population-oriented tool to assess risk in a noncoercive way. The use of family history has also been promoted in school high schools [35], community, and church events [38] to raise health awareness and promote the taking of family history, all in a way that also maximizes individual autonomy.

It must be remembered that autonomy refers not only to the proband – to the person sent the research letter or starting the chain of family inquiry – but also to his or her relatives. Classically, the federal Common Rule 45 CFR 46.102(f) did not explicitly contemplate the extent of consent and privacy rights in "secondary" or "indirect" subjects. Awareness of the need for greater protections came about as the result of the Virginia Commonwealth University case [21]. In this case, the father of a woman being recruited for a twin study contacted federal regulators over breach of privacy. The survey instrument she had received asked questions of a private nature concerning the health behavior of family members. The federal decision was in favor of the father's position. Professional organizations such as the American Society of Human Genetics (ASHG) and the American Society of Clinical Oncology (ASCO) made adjustments in their policies concerning third parties, such as family members, after the case. The proposed revisions to the Common Rule issued in 2011 include a single informed consent process that can be applied uniformly to different types of research participants. Some criticism has been levied against the possibility of developing a single process for disparate specialized populations, which include children, groups of family members, and disaster victims [39]. Until a uniform consent policy is established, the ASHG policy,

that investigators should pay close attention to the information being obtained on family members, serves as a model to other organizations.

In the non-research setting, privacy and confidentiality are controlled by: (1) those family members who assemble to fill-out a family history; and (2) the family member and health professional who together discuss the family history. Online FHH instruments keep inputed information private or within the province of the research team. In a cohort study of Health Heritage, an 89-condition web-based family history tool, 75 percent of participants said they were willing to share their risk assessment with family members, but only 39.6 percent, upon questioning, had actually done so (39.6% also responded that they were "somewhat satisfied" with the confidentiality provided by Health Heritage) [40]. Family members have a great deal of autonomy in what information they release, and sometimes do exercise their privacy. In the orbit beyond the family circle, the federal Health Insurance Portability and Accountability Act (HIPAA) governs release and exchange of family history information, just as it does the personal medical history.

Authors have commented on the type of health information that can be gathered on family members [21,25]. Information on physical conditions, such as cancer and diabetes, tends to be viewed as having less sensitivity than behavioral characteristics, such as sexual history; smoking, alcohol, and drug use; and mental health history. A family member can also be stigmatized by information that impacts their job performance (e.g., a family history of Huntington disease or heart disease in critical occupational settings). Standards of practice cover disclosure of information in situations of potential harm. Family history information containing identifiers is the property of the family itself and the family's contact(s) within the health system.

In the past, authors have dealt with security concerns for FHH information from the standpoint of conventional research studies. The "leakiness" of private telephone surveys as opposed to letter surveys, proper training of research personnel in confidentiality, and security coding are among the techniques that have been recommended to avoid breach of confidentiality [25]. The security landscape has become somewhat complicated by the existence of online risk assessment tools (e.g., Family Health*Link*, Your Disease Risk, Health Heritage in process), but these resources are university-based, and lack a commercial purpose for retaining information.

Currently FHH information is in the process of being incorporated into more massive information systems on a state and national scale. At least seven states have included questions about family history of chronic disease in their Behavioral Risk Factor Surveillance System (BRFSS) surveys. Health

departments in Michigan, Minnesota, and Utah have analyzed existing clinical data on cancer family health history by accessing doctor's office chart reviews, electronic medical records, and information from local public health encounters [27]. Such data are appropriately anonymized, the ideal being for removal of identifiers at the earliest stage following collection while still allowing analysis and production of aggregate results. The U.S. Department of Health and Human Services (HHS) Personalized Health Care Initiative is also leading, via efforts of the American Health Information Community's Family Health History Multi-Stakeholder Workgroup, to the formulation of policy anticipating widespread incorporation of personal health records, including FHH, into electronic health records systems [28]. One goal is for patients, authorized family members, and their providers to receive updated pedigree and FHH information, so anonymization is out of the question. Safeguards for privacy, confidentiality, and security acceptable to all stakeholders are part of the acknowledged consensus building that needs to take place for such developments to enhance rather than detract from the common good.

Example 2: Cascade Genetic Screening

The third step in the HHS Personalized Health Care Initiative, return of newly constructed pedigree and family health history information, leads to a logical next step that these blueprints together with other information retrieved from genomic repositories will lead to the selection of genetic tests [28]. Family-based screening can often start with taking a family history of the proband and end in genetic testing of relatives [22]. Cascade genetic testing, or more properly, screening, involves communicating an individual's health information, typically their genetic test status, to their relatives so they become knowledgeable about a shared familial risk [41]. This trajectory is mirrored by the U.S. Centers for Disease Control and Prevention's Office of Public Health Genomics' vision of making cascade screening a widespread possibility [42]. The information transmission pattern resembles a snowball, where the results from an initial proband are passed to a first-degree relative. That relative's results are transmitted to another close first-or second-degree relative, who then gets tested, and so on. Those tested occupy an expanding circle of relatives – cascade screening can be quite an efficient process. Ethics enters into the decisions made since it is personal genetic information that is being transmitted from one relative to another, often in the context of a community program.

Significant progress has been made with cascade screening in Europe. In 2008 the United Kingdom's National Institute for Health and Clinical Excellence (NICE) recommended cascade screening in relatives of individuals with familial hypercholesterolemia (FH), a condition associated with premature heart attacks. Numerous articles on the practicalities and ethics of FH cascade screening have emerged from Europe [43]. Tier 1 conditions are those disease entities for which genetic testing has been strongly validated on grounds of analytical and clinical validity and utility [44]. Other Tier 1 conditions – FBOC and hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) – have received considerable attention from professional organizations within the United States, with recommendations in favor of cascade screening [43], yet concerted screening programs are lacking. Bowen et al. observe: "... implementation will be complex in the US because it must occur within a health care system that, unlike many European countries and Canada, is not interconnected or centrally coordinated, and in which exists widely varying coverage depending on individual insurance plans and resources" [42]. FBOC is on the list of preventive services covered under the Patient Protection and Affordable Care Act, but aside from popular recognition by Healthy People 2020 for family referral, is not being promoted as an entity for cascade genetic screening [17]. It is possible to call on disease advocacy organizations to increase awareness of the importance of screening family members for such conditions (FH has a prevalence of 1 in 500 persons in most Western countries), an approach taken in the Netherlands [18].

The informed consent process always starts with testing of a single individual, who is then asked for their permission to inform relatives [41]. When permission is granted, relatives are then either informed directly by health professionals, or indirectly through their family member [22,41]. Newson and Humphries argue that the values concerned may differ between the clinical investigation team, the proband, relatives, and broader society, which can cause tensions along ethical lines [22]. Society has an interest in reducing morbidity and mortality and thereby keeping healthcare costs down. The simple relaying of unexpected risk information, even just the index case's, may violate a relative's right not-to-know, however, and lead to psychological harm. Counters to this argument are that circumstances differ from other forms of pre-symptomatic screening lacking an effective treatment for a potentially fatal condition, and that the degree of harm caused is minimal and temporary. Additional ethical arguments for contacting relatives cited in the literature are that relatives' right-to-know about a serious, preventible condition should not be abrogated [18]; that contacting relatives in the case of Tier 1 conditions

constitutes a moral duty and an ethical imperative [18,22]; and that "the patient is the family," i.e., the family members' right to informed consent in cascade screening should be respected just like the proband's [18]. The third argument shows the expansive nature of the ethical rights being considered. Simplistic as it may be, the very fact that relatives in cascade screening as opposed to the filling-out of a family history will be asked to contribute a blood sample compels contact for the purpose of informed consent.

The ethical grounding of privacy and confidentiality differs slightly for the proband versus their relatives. Historically, cascade screening programs have depended largely on indirect contact [41]. Only a small percentage of index cases decline to inform their relatives [41]. Initial family member contact by the proband allows them to judge the readiness of the relative to engage in genetic testing and receive information about his or her self, but it can also result in the proband's disclosure of their own testing status. A compromise approach respecting the proband's right to privacy, which also increases the relative's decisional autonomy, is for them to be provided a general leaflet for distribution to family members prior to further contact [22]. Several countries – the United States, France, Greece, and Denmark – have adopted policies that prohibit or do not support direct contact by investigators [41].

Information diffusion within the family can be more nuanced than expected. A qualitative study of family communication about HNPCC genetic testing revealed proband readiness to share news of a genetic mutation with spouse, children, and siblings, but reluctance to do so with nieces, nephews, and cousins [45]. Direct contact of relatives by the professional team can help by maximizing privacy of the proband's genetic information. From a public health standpoint, it also maximizes the chances of being able to contact additional at-risk relatives, a methodology that has been likened to contact tracing [22]. Direct contact by the investigative team is, therefore, the preferred method in the United Kingdom and the Netherlands [41]. Relatives, however, may be less willing to share news of a mutation than the proband. A compromise procedure has been suggested for direct contact whereby relatives' names and addresses are not *recorded* in the cascade screening register until they have themselves consented [22].

It could be argued that communication of genetic risk status between family members, either before or after direct contact, carries with it the potential for stigma. Unlike the stigmatization noted in premarital genetic testing, though, all family members are at risk. In cascade screening the family is an integral unit. Regarding societal discrimination, in many countries life insurance premiums for life expectancy curtailing conditions such as FH can

be raised or lowered depending on whether the condition is well-treated [22]. The ethics of life insurance are different from the ethics of health insurance, with actuarial fairness playing a much larger role in the former, and communitarian concerns having a more prominent place in the latter. It is important that countries have health insurance-related legislative protections for genetic testing in place, analogous to the Genetic Information Nondiscrimination Act (GINA) in the United States, before major population screening is implemented.

O'Kane et al. have argued that an effective, large-scale cascade screening program cannot be undertaken without a suitable database to allow full documentation of family trees, screening status, and screening results in family members [46]. Checks have been made on the feasibility of electronically identifying index cases of Tier 1 conditions from primary care clinical records. Gray et al. identified 12 definite and 8 probable cases of FH from computer and notes searches of 402 patients in a South London practice, 9 of whom were not previously known to have FH [29]. However, one study of computerized Duchenne muscular dystrophy registry use and letter send-out in West of Scotland and South East Thames, United Kingdom failed to demonstrate increased levels of carrier testing compared to more informal, non-computer-based registries [30]. Cascade screening in the community setting is only as effective as the means used to contact at-risk family members.

Example 3: Population Biobanking

At a certain size threshold, health information needs to be stored in a centralized repository making it more manageable and accessible. Hospitals have a longstanding history of storing pathology samples in paraffin blocks, accessing them when the derived information will be helpful for patient treatment and related disease research. Population biobanks expand the concept to a population-wide level. On the international front, population biobanks now exist in myriad countries, including the United Kingdom, Iceland, Canada, Sweden, Estonia, Japan, Latvia, and Singapore. The United States Department of Health and Human Services has undertaken activities evaluating the possibility of a large-scale (1 million person strong) cohort study of genes, environment, and disease, a project which is yet to occur. Nevertheless, major healthcare systems in the United States – the Mayo Health Clinic in Minnesota, Marshfield Clinic in Wisconsin, Kaiser Permanente in

California, and Veterans Health Administration in Washington, D.C. – have established biobanks that mirror on a regional level what has transpired nationally in other countries. While these efforts have many applications in pharmacogenomics and personalized medicine, health departments in a number of states, Michigan, Connecticut, and California, have either planned or established repositories that can be used for public health purposes. Denmark as well has a newborn screening register and biobank. These biobanks require special ethical attention because their continuity rests on individual willingness and public need, two forces that do not always intersect.

Of all the interventions discussed in this paper, biobanks depend the most on an atmosphere of transparency and an effort at public education. The Icelandic Biobank partnering with deCODE Genetics was preceded by a public campaign involving 700 newspaper articles, more than 100 radio and television programs, and several town hall meetings spread across Iceland [19]. The UK Biobank hosted 8 consultations with various public groups before it was established [20]. A web site was constructed listing the results of public and stakeholder consultations, committee members' names and biographies, and reviewers' reports on scientific protocol. Lay members were also on the committee developing the ethics and governance framework. The consequences of ignoring the public are dire. The Tongan Biobank was abandoned after awarding an exclusive licensing agreement between the Tongan government and a private biotechnology company without a public forum for discussion. Numerous advocacy groups expressed vehement criticism of the project [19]. In Minnesota, lack of public understanding of the utility and ethical use of newborn dried blood spots prompted a statewide campaign against their use by the Citizen's Council for Health Freedom. In Texas, a federal law suit prompted the Department of State Health Services to destroy ~4.5 million stored blood spots [24]. These two sets of examples show the immense value of public education and consultation, which ultimately address ethical issues, such as parental consent and sharing of benefits, of great interest to the public.

Because of the vast number of participants involved, biobanks are most appropriately couched in several layers of consent. Methodologies such as community review and community consultation have been used with community-based research. Consultation in the form of public forums, town hall meetings, and focus groups is of value because it allows public input before biobank design is completed and during the early stages of operation [23,24]. Inclusion in biobank ethics or community values advisory committees represents a second level of active, vocal participation, one that extends

through time [23]. Ideally the participation involves lay inclusion on the committee or board itself. Individual consent is the third level of autonomy. Consent must take into account policy for samples and records existing prior to and after establishment of the biobank. For the Michigan Neonatal Biobank, the Michigan Department of Community Health Institutional Review Board (IRB) granted a waiver of consent for the 4 million dried blood spots that had been stored before May 1, 2010 [23]. Opt-out is available for persons who do not want their pre-2010 blood spots to be available for research, but community meetings have suggested that many residents are unaware of the very existence of the Biobank [24]. Parent or legal guardian signed consent is required for research on newborn blood spots taken after the May 2010 date. Sensitivity is required in this state-run biobank and others to achieve consents that are genuinely informed. Secondary use of samples beyond the originally stated use creates a standing dilemma for many varieties of biobank, with solutions varying from opt-out for particular uses, to broad consent, to blanket consent for all purposes [19]. Public health biobanks generally operate under blanket consent since they are not created to address just one genre of research, yet the research areas they do address must apply to the standard of serving the public good. Those charged with oversight must not assume that the public nature of state-run biobanks removes the need for public education about them.

Three main methods are used to protect the confidentiality of biobank donors: (1) full anonymization of samples and removal of identifiers from the start; (2) initial anonymization of samples with removal of identifiers after accomplishment of the originally intended use; and (3) double-coding, involving maintenance of a secure code linking samples given project identification numbers with personally identifying information [19]. The ethical equation is more complicated with public health biobanks which are built around biological samples, e.g., newborn dried blood spots, which may have immediate or more remote preventive purposes involving familial disease.

The concept of confidentiality is eroded from two different quarters by genetic biobanks. First, maverick research has shown that it is easier than expected to re-identify persons participating in public sequencing and personalized genomics projects [47]. Research organizations are moving in the direction of establishing professional sanctions for such occurrences [48]. Sanction mechanisms are already in place in the United Kingdom in case any violation of UK Biobank confidentiality policies occurs. Secondly, should possibly beneficial discoveries be made, the participating public may not want

total removal of identifiers [19]. Corresponding input during public consultation caused the Canadian CARTaGENE project to shift its policy from anonymization of samples to double-coding. This approach also has advantages for longitudinal research in which participant medical or health information is periodically updated [49].

For the most part, findings generated by biobanks are reported in aggregate form, making it very difficult to use them for discriminatory purposes. GINA was passed to outlaw genetic discrimination on the part of health insurers and employers. Biobank participants may still have concerns about untoward uses of their samples or personal health information. For example, in a paternity suit in 1999, the High Court in New Zealand was asked for release of a recently deceased child's blood sample for DNA analysis, which it granted [26]. Several forensic uses of biobank tissue samples exist which people would view as intrusive. These uses are not health-related. Kharaboyan et al. suggest, "Introducing regulatory policies and security measures to regulate the length of sample retention and access to identifiable samples will help insure that [dried blood spots] do not automatically end up as part of law enforcement or government DNA databases, or in the hands of other third parties ..." [26]. Although in the past electronic systems provoked fears of loss of privacy and violation of security, in the present they are providing solutions to several of the above ethical dilemmas. For distributed samples and data from different biobanks, cohort or associational studies that are being combined, methods have been developed to pool and analyze the *calculations* from harmonized individual-level data at the various centers, rather than the individualized data itself [32]. This approach keeps individual data behind multi-center firewalls, inaccessible to outside parties. Other systems allow biobank contributors to selectively prespecify what type of personal identifying or health information they want to make available downstream, and for what types of research organizations and health researchers [31]. Electronic systems can be used not only for informational purposes but to assure ethical use of the information as well.

SUMMARY OF COMMON THEMES ALONG A POPULATION TRAJECTORY

The interventions described move markedly beyond a strictly individualistic orientation, and of necessity arc back to public health ethics. In

the clinical setting information provision and explanations offered by the healthcare provider are sufficient openers before an examination. In the three examples given, some degree of public education is needed as well. Family health history offers an example of education rallying around a unifying national campaign; population biobanking an example of multiple campaigns, one tailored for each biobank. The consequences of foregoing public transparency and education are dire when society is the program participant.

The consent process billows out over the three categories of intervention like an unfolding umbrella. The filling-out of FHH always starts out with one willing person, though family members can end-up helping. Consent in cascade screening is offered by each family member contacted. Autonomy in population biobanking is exercised at three levels – two group-oriented, and one individual. Confidentiality in the use of FHH and cascade screening is between the index person and their family members, with responsibility for ethical handling of familial information on the part of the provider. With biobanks larger policy formulations – professional regulations and legislation – are needed. The leakiness of information is spread across society.

The greater concern with stigmatization from inadvertant disclosure of FHH information is occupational, whereas with cascade screening, since it relies on system-level coordination, it is insurance-related. The more than ten years it took to pass GINA were well worth it given the volume of genetic testing and data collection that can occur with cascade screening and population biobanking. Biobank information, like that obtained by direct-to-consumer genetic testing companies, would seem to perfectly fit with many non-health-related uses, which is exactly why it is in need of cross-the-board policies – professional, legal, and regulatory – that would restrict its use to constructive health purposes. Nondiscrimination policies for all three categories of intervention go beyond the province of traditional medical institutions.

When Georgetown University's Laurence Gostin wrote of an emergent “health information infrastructure” in 1996, it was a multi-tentacled beast that connected one's healthcare records with workplace screens and criminal justice records, a very dangerous creature, indeed [50]. In a sign of progress, the electronic face of this infrastructure is allowing family history information to find population relevance in public health surveillance systems and electronic health records systems. It is actually offering a solution to several ethical dilemmas that face biobanks, a result of the biobank ideal to help everyone without harming anyone.

ETHICAL CONCERNS DISTINCTIVE TO PUBLIC HEALTH

While Thomas et al. contend that interdependence is the complement to autonomy, Turoldo takes the position that "responsibility" occupies this spot [37]. The two perspectives do not necessarily contradict each other since one is centered on ethics from a relational standpoint; the other from a view of the agents involved. It has been stated that public health, because it employs coercive measures for the good of others and the whole, continues to be paternalistic. Medicine has been shifting away from paternalism. In actuality the types of paternalistic influence exerted by public health programs can be noncoercive – educational campaigns; softly coercive – legislation; and highly coercive – compulsory programs and population or group monitoring [37]. Much of the national legislation mentioned in this paper, such as HIPAA and GINA, affects both medical and public health activities. On the state level, public health departments have been involved with legislation that prohibits the use of genetic information in Medicare-related services, enforces access to and reporting of cancer and birth defects case information to disease registries, and enacts and molds newborn screening programs.

The paternalism being engaged in is not the usual sort because compulsion is not being levied on the patient. Assisting the patient with their decisions is the duty of the doctor or genetic counselor. Rather, as demonstrated in the three interventions covered, public health is acting on their significant others. Expanding the circle of preventive influence is the goal of family health histories and cascade screening. The ultimate outcome of biobanks is that all will benefit, even those not immediately contributing to them. Looking more closely at exactly what FHH, cascade screening, and biobanks are used for, the aim is prevention of future disease that has not yet manifested. Turoldo contrasts public health responsibility with the after-the-fact imputability for actions that have already taken place, typical of civil and penal law.

Public health is very much concerned with health for all. Point 4. of the Code of Ethics for Public Health states: "Public health should advocate for, or work for the empowerment of, disenfranchised community members, ensuring that the basic resources and conditions necessary for health are accessible to all people in the community" [12]. The egalitarian spirit is precisely why members of the public health community have engaged with members of diverse racial-ethnic groups in community dialogues to sound out their hopes and concerns with genetic technologies, and to avoid policies that only favor the health of the majority [51]. It is also why members of the academic and practicing public health communities are so eager to ensure that the Patient

Protection and Affordable Care Act's covered services impact as many groups as possible. Work is yet to be done to make sure the services are "ethically" covered. Different family members of extended families typically have different levels of healthcare coverage. BRCA1/2 breast and ovarian cancer genetic testing should be available to the array of family members; cascade screening should be covered and use of FHH should be more than a suggestion.

The flip-side of fair allocation is unfair attention to particular groups, thus resulting in discrimination. Stigmatization and discrimination are critical ethical components to any measuring up of genetic technologies. Successful dialoguing on community concerns over population-wide interventions, such as biobanking, will assess for discrimination concerns and suggestions right alongside standard ethical issues such as consent [24].

CONCLUSION: A POPULATION-BASED PERSONALIZED ETHOS

Technical and ethical comparisons of genetic technologies often follow a life course progression – from carrier and prenatal screening to newborn screening to adult predictive and diagnostic genetic testing. All of these modalities stay within the skin of the individual. The earliest public health collaboration was built around between-person disease transmission, though. In this conception, risk is spread across and moves through multiple parties, even the whole population or parts of the population. The requisite ethics is necessarily distinct from a single-person ethics.

Shared territory exists between medicine and public health when it comes to the three interventions discussed. The areas of expertise point in different directions, though. A Mayo or Marshfield Clinic will use its biobank to discover new genetic variants for more effectively treating the individual patient. Traditional autonomy, confidentiality, and beneficence are operative in this realm. A public health biobank, containing cord blood or newborn blood spots, will be used for research that will touch the larger population. Genetic variants and gene-environment interactions discovered can be used for screening which draws from and helps large numbers of people in a preventive fashion. The ethics will focus more on solidarity, sharing, and the common good. Societal benefit is the end; multiparty ethical criteria are the means.

When discussing the good of a certain intervention to society, the philosophy being employed is an "ethos," a collective framework and a new outlook. The difference between "PHELSI" and "ELSI" is more than one letter deep. The vector of attention points outwards rather than inwards. When people attend to one another from a communitarian stance, they consider a synergy of action and not just protection of the self's rights. Think how such an attitude would change the world of disease detection, information collection, and health information utilization. Genetic interventions such as personalized risk assessment would be applied to individuals, but the data underlying the interventions would derive from a maximum number of willing contributors, and the policies employed would enable many people to participate and benefit, often at the same time. Population-based knowledge, when sharing is the goal, yields the most precise and just personalized medicine.

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