UNIT 1.
CONTEXTUAL FRAMEWORK FOR MOLECULAR EPIDEMIOLOGY

CHAPTER 2.

Ethical issues in molecular epidemiologic research

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Introduction

Contemporary and future molecular epidemiologic research will be conducted against a backdrop of massive biological databases, comprehensive and longitudinal electronic medical records, large medical care expenditures, aging populations, emerging infectious diseases in some countries, and global climate change. These conditions will influence the ethical issues that arise in molecular epidemiologic research. Will these issues differ from epidemiologic or scientific research in general? Some of the issues will be unique to molecular epidemiology, and others will be relevant to all research. If the conduct of molecular epidemiology is to contribute to medical and public health research and have a positive impact, there is a need for investigators to be aware of and adhere to the generally accepted ethical principles discussed in this chapter. Further, it is important to realize that data that will be made available in the future from new genomic technology will continue to pose challenges to the ethical conduct of molecular epidemiologic research. Therefore, researchers will need to be aware of the dynamic nature of guidelines and regulations.

Distinctive ethical issues in molecular epidemiology

Three key features of molecular epidemiology form the basis for the distinctive ethical issues unique to the field. First and foremost is that molecular epidemiology relies on the collection of biologic specimens and the identification and use of biological markers derived from those specimens (1,2). The second feature is that many of the biological markers pertain to inherited genetic information. While similar to other biomedical information, genetic information is often perceived (rightly or wrongly) as being more powerful and sensitive, a perception reflected in the widespread use of the metaphor of genes as the blueprint for what makes us human (3). Moreover, critical in molecular epidemiologic research is the emerging capability to efficiently sequence nearly the entire genome, as well as the availability of information in public databases, most of which are restricted to bona fide researchers who gain formal permission (2,4,5). Lastly, molecular epidemiology continually involves the application of new technologies and methodologies

whose validity and reliability are in the process of being established. Together these three features trigger the need for molecular epidemiologists to consider and address specific ethical issues in addition to the more generic ones typical of epidemiological studies (2,6–13). Epidemiology, as a population science, observes the characteristics of individual research participants to understand disease at the level of the population. As a result, the ethical concerns generated in the field are two-fold: there are those that pertain to interaction with individual study participants, and those that are concerned with populations. This means that molecular epidemiologists need to reflect upon ethical issues beyond those encountered in any particular study. The broader issues to be considered include how to distribute the scientific and social benefits of molecular epidemiologic research, particularly research that involves genomic data and addresses various social, political and scientific questions related to collective, as well as individual, rights (14–16).

Clearly, these are questions not answerable by molecular epidemiologists alone, and require the input and involvement of various other disciplines. Yet, important for molecular epidemiologists to bear in mind is the larger context in which their work is situated, and to build dialogue across disciplines in an effort to contribute to these larger issues. A review of ethical issues follows, primarily as they relate to the molecular epidemiologic research process, and a discussion on how they arise in: 1) the development of the study protocol, 2) obtaining participation and informed consent, 3) maintaining privacy of subjects and confidentiality of data, 4) interpreting and communicating test and study results, and 5) avoiding inappropriate inferences and actions (or lack of appropriate actions) based on study results. Wherever relevant, we point towards the broader population health ethics involved in molecular epidemiology, acknowledging that these discussions are merely introductory and far from exhaustive.

Most of the health research, including molecular epidemiologic research, conducted in the United States is regulated by the Common Rule (45 CFR Part 46, subpart A). The Common Rule pertains to individually identifiable data and does not apply to research conducted on specimens or health records that are not individually identifiable (12). Overlapping some aspects of the Common Rule is the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) (45 CFR Parts 160, 164). They both cover large, academic medical centre institutions, but differ on such issues as reviews preparatory to research, research involving health records of deceased individuals, and revocations of consents and authorizations (17).

The other major regulatory feature of research is the Institutional Review Board (IRB). IRBs review protocols for human subject research as defined by the Common Rule. They also are charged with addressing the ethical aspects of the increasing volume and variation of genetic molecular epidemiologic studies (2,13). These boards face significant challenges, as currently in many cases there is no general agreement on the ethical aspects of issues that arise. Nonetheless, as described in this chapter, there are some established principles and experiences and practices that can fill this gap.

Development of the study protocol

Ethics are an intrinsic aspect of the framing of the research question and in the selection of methods to carry out any study. The decision to use or focus on molecular biomarkers in a study can itself raise ethical issues. A starting point for considering the appropriateness of molecular biomarkers is whether or not the research question being addressed is of public health importance (18). If the answer is no, then the use of scarce resources to develop, validate or apply a biological marker can be wasteful and inefficient, and detract from efforts to address other public health issues of greater urgency. Ethically, molecular epidemiologic research should identify driving scientific and public health questions that cannot be answered by some other more accessible and less costly approach. Given the resource-intensive nature of biobanking and molecular technologies, the use of biomarkers within epidemiologic research should be done judiciously. Like all research, studies that propose to use biomarkers must ground their decisions in the available empirical evidence and sound scientific reasoning. In the genomic era, vast amounts of biological data are generated using technologies that simultaneously process hundreds of genes within hundreds of samples. Even in a small epidemiological study, such as one with 100 cases and 100 controls, investigators can easily obtain genetic and epigenomic data involving millions of variables for each participant (although such studies are likely to be both underpowered and likely to produce large numbers of false-positive findings unless they have replication efforts built into them). Bioinformatic approaches are

needed to sort through such data sets and the literature. Ideally, such approaches are first conducted in iterative processes using existing databases before the initiation of a new study. This detailed preparation provides a rationale for the study design and focuses the scope of the research question.

One set of ethical concerns relevant to protocol development involves whether the investigator has any interests that conflict with the ultimate aim or potential outcomes of the research. Ideally, investigators should be involved in research to seek the prevention of disease through free inquiry and the pursuit of knowledge. Conflicting interests may lead investigators (consciously or not) to make choices about study design that could introduce biases, yielding results that deviate from less biased approaches. To foster a transparent and accountable process through peer review and other mechanisms, it is important that investigators acknowledge and identify their conflict of interest to their collaborators, research participants and other stakeholders. Not only do conflicts of interest jeopardize the validity and utility of any particular study, they also bear on the health research enterprise as a whole, since the ramifications of failing to disclose them can damage the public's trust in and support of science (20). The issue of conflict of interest is particularly acute in research using genetic material, due to the push by academic and research institutions (and commercial collaborators) to seek intellectual property rights, and other avenues of commercialization, of their research (13).

Turning to more methodological issues, the decision on where to conduct a molecular epidemiologic study, and on whom, should also be scrutinized with ethical considerations such as equity, justice and autonomy kept in mind. In light of these principles, many decisions relating to sample design that initially seem of little ethical consequence, gain stature. For example, how well the sample population reflects the target population is a matter that bears on both scientific validity and moral concerns. Within molecular epidemiologic research, an additional issue includes whether it is the responsibility of investigators to attempt to obtain ethnic, racial or social class diversity in studies. This question extends into the avoidance of socio-genetic marginalization, that is, the isolation of social groups and individuals as a consequence of discrimination on the basis of genetic information (22). In a similar vein, should one assess whether various ethnic groups are provided similar opportunities to be in a database? If not, characterization in a database can make one ethnic group appear more or less susceptible than another ethnic group lacking the same opportunity for characterization. Other questions about sample selection that should be taken into account are whether the sample is representative in terms of genetic and ethnic factors, as well as various other host or environmental factors of the study's target population. However, there is a cost associated with representativeness—loss of power and the need to adjust for confounding factors. Small groups included to make samples more representative may be subject to statistical power limitations and, for studies on restricted budgets, may decrease the ability of the study to accomplish its primary aims. At the same time, power issues can be surmounted in part if data are collected in a way that is consistent with previous studies that have included multiple ethnic populations, and if plans for pooling data with other studies are made, preferably early in the study design phase.

Molecular epidemiologic study design and analysis also can affect whether the research contributes to public health. The promise of genome-wide association and other genetic susceptibility studies, in terms of prevention and public health, may not be realized if a study is designed to minimize observing the effect of environment and lifestyle factors. To take full public health advantage of such research, environmental exposures, quantified by state-of-the-art exposure assessment methods when feasible, must be considered in the design, particularly in the selection of study populations and in the analysis (23). Such an approach may involve using analytical techniques that do not require relying on either significant main genetic or environmental effects as a threshold for investigating gene-environment interactions.

A particularly sticky issue relating to study design is the premature use of biological markers as variables in research before they have been validated (10,24); there are many examples of premature use in commerce (25). Validation is not an all-or-none state, but rather a process that is informed by continued research and investigation. Critical in any definition of validation is the extent to which the biomarker actually represents what it is intended to represent (1,26). The use of biomarkers that have not been validated for the purpose for which they are being used can lead to false or misleading findings, which may harm participants, groups or communities. For transitional studies in which the characteristics of a marker are being determined, and for which there are clearly no associated clinical findings, prognostic

significance, or clear meaning, the needs of study participants may be different from those in studies with established biomarkers. In the case where a biomarker has a known association with a disease outcome (or exposure or susceptibility) and holds implications for individual risk, interventions such as medical screening, biological monitoring, or diagnostic evaluation may be appropriate follow-up measures.

Furthermore, ethical issues may arise during the design phase of a study protocol from a researcher's failure to anticipate how to respond to the distributional extremes in biomarker assay results (6). Possible responses may include repeat testing, risk communications counselling or clinical surveillance. With genetic markers of susceptibility, it may be important to consider the impact of the research not only on individual participants, but also on their families, given that knowing something about an individual's genes possibly means knowing something about their past, present and future family's genetic constitution.

Recruiting participants and informed consent

When recruiting potential research participants, a core ethical issue in molecular epidemiologic research is respect for individuals, which is upheld by ensuring their autonomy. This means that potential research subjects should be viewed and treated as self-ruling and able to voluntarily participate in and withdraw from research without coercion or prejudice. Autonomy also implies that those who are not capable of self-determination, such as children, are to be protected from exploitation and harm (27). Potential participants need to be informed of a broad range of information (e.g. purpose of the study, its duration, identity of the investigators and sponsors, ownership and other uses of specimens, the methods and procedures to be used, and all potential risks and benefits of participating in the study), some of which are unique to molecular epidemiology (6,28). The investment in population-based field studies to obtain biologic specimens and covariate information is generally quite large, making it cost-effective to collect and bank DNA and other biological materials for current and future research. Moreover, the number of biological specimen banks is growing, and as a result the nature of future research might not be known at the time of specimen collection (29). Accurately depicting the purpose of a molecular epidemiologic study can be difficult for the investigator, because there may be a multiplicity of purposes, some intended, others not even yet envisioned. At issue is how one should solicit consent for future use of specimens, and what to tell potential participants about this.

Future use of specimens requires additional procedures for obtaining consent (30). Some have proposed that informed consent for future use is best acquired by enabling participants to specify the research areas to which they sanction, or to permit them to give blanket approval, which informs them of the intention of banking specimens and their subsequent use for a wide range of research purposes (31,32). While such procedures clearly allow the maximum scientific benefit and potential public health impact to be obtained from such biobanks, they could be considered to deviate in important ways from the general standards of informed consent. In soliciting blanket consent for future use, investigators are generally unable to provide research participants specific and accurate information as to all the purposes of the study (as they are yet unknown); thus, the attendant potential harms and benefits of participation are not fully fleshed out. The resulting scenario is that the informed consent reflects a "potential" informed consent, not one in which research participants are fully informed and then knowingly choose to be involved (13). This appears to stand in contrast to the principles of informed consent as laid out in ethical codes of medical research, such as the Declaration of Helsinki (33). The evolution of technologies used in molecular epidemiologic research has pushed IRBs to consider how ethical codes apply. This is illustrated in the development of a large number of prospective cohort studies worldwide and the guidelines pertaining to them, such as the United Kingdom Biobank Ethics and Governance Framework and the independent advisory council formed to oversee the Biobank's activities (34–36). After careful consideration and review by IRBs, informed consent procedures have been developed that accomplish the dual purposes of protecting the rights of individual participants while also providing the opportunity for the maximum public health benefit from the substantial resources needed to establish and maintain such prospective studies.

Molecular epidemiologic studies have generally used a large number of biological markers analysed in specimens collected directly from research participants enrolled into formal case-control and prospective cohort studies. Increasingly, though, the source of the specimens may not be from participants directly, but from biobanks where specimens were collected before the development of a given study, and possibly even for a different purpose. Given this trend,

it is important that the informed consent process address intellectual property rights and state who maintains ownership of the collected specimens (2). There are various issues that pertain to ownership or custodianship of biospecimens. Generally, however, there do not appear to be laws or regulations that directly address them. Nonetheless, participants have a right to know what future uses their specimens may be considered for. There also could be special concerns about future use of specimens among indigenous people or various 'island' populations that need to be considered (37,38). Overall, molecular epidemiologists involved with biobanks and surveillance efforts should think about both individual and collective rights and interests in creating or assessing such databases for public health research.

While procedures for dealing with biorepositories in the future can be established, what about the millions of human specimens currently in storage collected from a wide variety of formal and less-formal study designs, and obtained from study participants over several decades during which standards of informed consent and IRB review have undergone continuing evolution? These are highly valuable resources but ones where procedures and practices may not necessarily conform to current standards. For example, can a participant whose specimens are in a biorepository decide to discontinue participation and not have their samples continue to be used? General practice and a recent court case ascribe ownership to the institution that maintains the repository. However, this interpretation excludes the input of the research participant. A stewardship model has been described that respects a research participant's request to terminate participation in a DNA biorepository by destroying remaining DNA instead of continuing use of the specimen, as is a common response (28). The American College of Epidemiology has espoused four useful principles regarding the handling of biospecimens: (1) custodianship should encourage openness of scientific inquiry and maximize biospecimen use and sharing so as to exploit the full potential to promote health; (2) the privacy of participants must be protected and informed consent must provide provisions for unanticipated biospecimen use; (3) the intellectual investment of investigators involved in the creation of a biorepository is often substantial and should be respected; and (4) sharing of specimens needs to protect proprietary information and to address the concerns of third-party funders (39). While these principles are a good foundation, they do not specifically address the research participant except in the area of privacy. There also is the need to consider control of human specimens in terms of respect for persons and autonomy (28).

The issue of future use of specimens is more complex with larger studies involving whole-genome analyses. One problem in obtaining consent for future use of specimens is the apparent discrepancies between implementation of the Common Rule (45 CFR Subpart A) and the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). The Common Rule allows patients to consent to unspecified future research, whereas the HIPAA Rule requires that each authorization by a patient for release of protected health information include a specific research purpose (2,40,41). As noted by Vaught *et al.* (2007): "Because support of future research is a major purpose of biospecimen resources, this lack of harmony among federal regulations has had a significant effect on and created a great deal of confusion within the biospecimen community."

Until recently, there was little or no available guidance for addressing informed consent issues in population-based studies of low penetrance gene variants (42,43). Most existing guidance pertains to single genes of high penetrance that are investigated in family studies. Yet the risks and benefits of population-based research involving low penetrance gene variants are substantially different from those associated with family-based genetic epidemiologic research (44). When obtaining informed consent, these differences become particularly meaningful: "Recommendations developed for family-based research are not well suited for most population-based research because they generally fail to distinguish between studies expected to reveal clinically relevant information about participants and studies expected to have meaningful public health implications but involving few physical, psychological, or social risks for individual participants" (42). Further recommendations for obtaining informed consent have been developed by a US Centers for Disease Control and Prevention (CDC) workgroup that considered integrating genetic variation in population-based research (42). The workgroup provided a useful outline of the content, language and considerations for an informed consent document. Much of the language in these consent materials addresses the important distinction between genetic research expected to reveal clinically relevant information about individual participants, and that which is not. It is anticipated that the majority of

population-based genetic research will not identify clinically relevant information. Thus, the workgroup did not recommend informing participants of individual results in these types of studies. However, they did note that the dividing line between low and high penetrance is difficult to define, since there is a spectrum of genetic variants with differing effect sizes. They therefore recommended "…when the risks identified are both valid and associated with proven intervention for risk reduction, disclosure may be appropriate" (42). A broader discussion of communicating test and study results follows in the next section.

Maintaining privacy of subjects and confidentiality of data

Molecular epidemiologic research participants explicitly agree to cooperate in a specified study when they consent to provide specimens and corollary demographic and risk factor information. Such participation generally does not include or imply consent to the distribution of the data in any way that identifies them individually to any other party, such as government agencies, employers, unions, insurers, credit agencies or lawyers. Such confidentiality and anonymity is premised on the ethical concept of respect for persons. Dissemination or revelation of results beyond the explicit purposes for which specimens were collected intrudes on subjects' privacy. Inadvertent labelling of a subject as "abnormal" or as "in the extremes of a distribution of biomarker assay results" could have a potentially deleterious impact on the person's ability to obtain insurance, a job, or credit, and can also affect the person socially or psychologically. Thus, as Nelkin and Tancredi noted, some union representatives are concerned that workers who participate in genetic research or screening will bear a genetic "scarlet letter" and that they will become "lepers" or genetic untouchables (45). The psychological impact of such stigmatization is virtually unknown.

Molecular epidemiology investigators must maintain the confidentiality of biomarker data because of the potential for misuse or abuse leading to discrimination, labelling and stigmatization (3,6,7). This can be increasingly difficult because ownership of stored specimens may be in question, and various investigators may request the use of them for research, litigation or commercial enterprise. In some cases, where specimens are identifiable or are capable of being linked to databases where identification is possible, it may be difficult to assure confidentiality. Informatics and the ability to link disparate databases are progressing at a rapid pace. In some countries, there may be a need for further legislation to prohibit unauthorized access to, or use of, specimen results. The Genetic Information Nondiscrimination Act (GINA) of 2008 was enacted to prohibit the use of genetic information in hiring or providing insurance. Nonetheless, the challenge to investigators will be to assure the rights of study participants while providing for a broad range of research opportunities.

As noted earlier, the regulation of privacy issues in the United States is addressed by the Federal Rule on the Protection of Human Subjects (the Common Rule), and, since 2003, the Privacy Rule of HIPAA. The lack of harmonization of these rules has been reported to "…create confusion, frustration, and misunderstanding by researchers, research subjects, and institutional review boards … [Nonetheless] both rules seek to strike a reasonable balance between individuals' interests in privacy, autonomy, and well-being with the societal interest in promoting ethical scientific research" (17). The investigators concluded that the two rules should be revised to promote consistency and maximize privacy protections while minimizing the burdens on researchers.

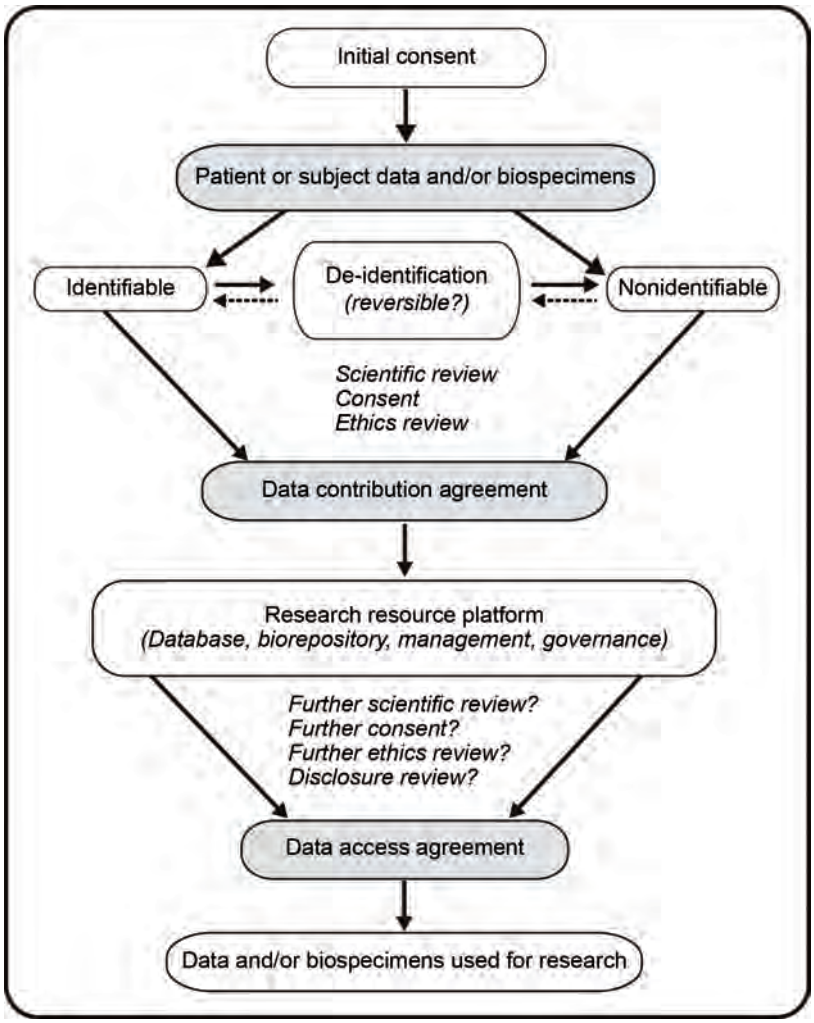
The issue of identifiability of biological specimens (i.e. the linking of a specimen with its originator's identity) that arises with the advent of large-scale research platforms that assemble, organize, and store data and sometimes specimens, and make them available to researchers, has been thoughtfully addressed (46). At issue is the ease with which individuals can be identified from DNA or genomic data. Individual identifiability from a database "…should not be overstated, as it takes competence, perhaps a laboratory equipped for the purpose, computational power perhaps linking to other data, and determined efforts." (46). Nonetheless, identification is increasingly possible as the collection of biospecimens that can be used for matching grows and becomes more widely accessible. It has been demonstrated that an individual can be uniquely identified with high certainty with access to several hundred single-nucleotide polymorphisms (SNP) from that person (4,47).

The advent of the genome-wide association studies (GWAS), which genotype thousands of SNPs in large populations, have generated a series of questions concerning the practice of making summary data publicly available. This is due to the development of methods that use genotype frequencies and

an individual's genotype profile generated elsewhere to infer whether the individual or a close relative participated in the study set (48,49). For published GWAS, the probability of inferring membership in a study is substantially decreased when less than 5000 SNPs are examined. Consequently, it is important for researchers to protect subject participation while making data available to bona fide researchers who provide sufficient and binding institutional support for protecting the confidentiality of IRB-approved research.

There is a need for proper balance between encouraging molecular epidemiologic research on genomic specimens and protecting the privacy and confidentiality of research participants. Figure 2.1 illustrates the flow of data that arises from these platforms. Among the design and governance issues are whether, and how, to de-identify the data, and at what stage to conduct scientific and ethical reviews (46). The ultimate question is whether a completely open-access model is defensible when different amounts of genomic data are present and potentially unique to an individual to allow for identification. Clearly, in the spirit of medical research and privacy laws and ethics, there is a need for controlled access models for these types of data sets, or else consent documents need to make clear the lack of complete confidentiality that may arise from publicly accessible databases.

Figure 2.1. Steps in the protection of the identity of research subjects in large-scale databases and projects (46). Reprinted with permission from AAAS.



Interpreting and communicating test and study results

Molecular epidemiology research yields both individual test (assay) results and study results, and research participants may want or have a right to both (6,50). However, increasingly, the bioethics literature also has recognized a counter-right of informational privacy, that is, the right not to know about certain information about oneself (12,51). Providing test or study results, genetic or otherwise, requires more than merely sending results to participants, it also involves interpreting the results (52); this responsibility ultimately rests with the investigator. Some IRBs require investigators to provide individual test results to subjects as well as overall study results, while others may advise or forbid them not to communicate results of assays that have no clinical relevance (27,42). Even though participants are told that tests may be purely for research purposes and have no clinical value, they may still ultimately want to know if they are "all right." Investigators face difficult ethical issues in interpreting test and study results, and in deciding when biomarkers indicate an early warning where preventive steps should be taken.

Prevention actions may include efforts to control exposures (in occupational or environmental settings), the need for subsequent testing, ongoing monitoring, or simply, and often most importantly, counselling and a demonstration of caring (6). Reporting molecular epidemiologic test results to study participants, particularly those involving genetic information, involves among other issues, defining the concept of clinical utility. Clinical utility is generally based on three criteria: (1) clinical validity (the association between the test result and a health condition or risk); (2) the likelihood of a clinical effective outcome; and (3) the value of the outcome to the individual (26,53).

The interpretation of biomarker data is a complex matter. For example, in cross-sectional studies of populations with occupational or environmental exposure and biomarkers of early biological effect, biomarkers will not be indicators of risk *per se*, but of exposure, susceptibility given exposure, or biological changes that could be homeostatic responses to an exposure (6,54). The investigator needs to sort out these changes against a background of extensive intraindividual and interindividual variability in biomarkers. It is also important to note that such studies are not usually those designed for the purpose of identifying risk and should not be construed as such. Current technological capabilities offer investigators and practitioners the opportunity to utilize techniques with heightened sensitivity for detecting changes at cellular and molecular levels and for detecting exposures to minute amounts of a xenobiotic (12). Yet at the same time, at these levels, inherited and acquired host factors and other confounding factors can be strong causes of wide variability in biomarker results unrelated to the exposure or risk factor of interest. Moreover, when multiple biomarkers are to be assessed, researchers have a responsibility to consider whether issues of multiple comparisons can lead to inappropriate selection of significance levels (6). Associations with biomarkers not included in original hypotheses should be evaluated at more rigorous levels of statistical significance with built-in replication strategies, and subsequent interpretations should be considered in that light. This is particularly the case with the development of "omic" platforms that have facilitated the use of critically important agnostic approaches that produce thousands to now millions of biomarker variables.

In general, the accurate interpretation and communication of genetic information is quite challenging due to its probabilistic character and the pleiotropic nature of genes. Moreover, the potential impact of genetic information on family relationships, reproduction, and personal integrity can further complicate its interpretation (53,55).

Using genetic and epigenetic information for public health purposes requires that variation in the population be accurately described and categorized, and that the concept of "abnormal" be thought of more in terms of susceptibility than deterministically; hence, the appropriate interpretation of biomarkers is one, which is probabilistic (56). Lloyd (1998) concluded that "…public and scientific misconceptions of susceptibility are probably one of the most prominent problems facing those interested in the development of genetic medicine." The same can be said for molecular epidemiology as well. For public health purposes, there is a need to define concepts (e.g. susceptibility) on a population level (18).

Another area of interpretation that is problematic is what is called individual risk assessment. Generally speaking, epidemiological studies (with or without biomarkers) yield group results. The disease risk pertains to the group as a whole and not necessarily to individual members of the group, although it is possible to compute an individualistic risk using a risk function equation (57). However, if the marker being used has not been validated for disease, the calculation of an individual's risk will be meaningless. Thus far, for the current generation of biomarkers used in chronic disease research, there are a small number of markers (such as a few genetic mutations linked to high risk of disease in cancer family syndromes) for which an individual probabilistic risk can be estimated based on the biomarker.

These vagaries of biomarker data may lead an investigator to conclude that a particular biomarker is of uncertain meaning with regard to risk. Nonetheless, investigators have an obligation to accurately portray the degree of uncertainty in test and study results. There is a range of opinions about communicating results of biomarker tests on individuals or groups if there is no clinical meaning, such as usually occurs in transitional studies to validate markers and in population-based genetic research. Some believe that autonomy of participants is not honoured if they do not receive results, while others believe that the information communicated by results has no meaning for participants and indeed could be detrimental (52). While the latter view has the appearance of being paternalistic, as it decides what is good for the participant without seeking the opinion or decision of the participant, it may also be viewed as "doing no harm" (6). Such

an interpretation is premised on the notion that providing results lacking any clinical, prognostic, or other use may elevate the risk of harm to participants by creating opportunities for undue anxiety, stress, alarm and unnecessary medical testing. However, recent evidence suggests that most research participants want results provided to them, and that the risk of anxiety may be less than originally estimated (58,59). Nonetheless, individuals may have a right not to know certain information that might be very sensitive and troubling to them. Increasingly, molecular epidemiologists may also be dealing with epigenetic data, which may be far more complex and difficult to interpret than biomarker data currently under investigation (60–62).

The communication of the results of biologic tests (particularly genetic tests) in molecular epidemiologic studies is still a difficult area. While generally the literature identifies adherence to the principles of autonomy (beneficence, respect for persons, reciprocity, and justice), the actual ways to do that are still subject to interpretation and opinion. It is clear that the approach taken concerning communicating results should be made explicit in the informed consent process. However, there are differing opinions on whether, or to what extent, test results should be communicated to study participants. On one extreme, some argue for full disclosure of genetic information, while others argue for balance of benefit and harm and that disclosure should be limited to certain situations. US federal regulations regarding biomedical research have been characterized as not providing clear guidance on this matter (52).

Timeliness of communication of results is also important to consider. This particularly becomes an issue when results indicate an action that could reduce exposure or risk, or affect timely treatment. As discussed above, situations exist where additional support to participants may be warranted. Evaluating the impact of notifying research participants of results may not need to be a routine matter, but since the consequences of notification cannot always be anticipated, it may be useful to provide the opportunity for participants to obtain more information or provide feedback about the results (6).

Avoiding inappropriate actions based on study results

Molecular epidemiologic investigators must concern themselves with how study results are incorporated into epidemiologic knowledge and public health practice. In some sense, the results of molecular epidemiologic studies of biomarkers of susceptibility are particularly at risk of being misunderstood or abused (6,45,52,55,56,63–65). For example, many common low penetrance gene variants, some of which require specific environmental exposures to increase risk of disease, do not provide unambiguous information. Yet various groups in society may start using such genotype information as if it represented diagnoses rather than risk factors (66). The consequences of such misinterpretation and application of biomarker results can include discrimination, labelling and stigmatization of subjects. Moreover, the deleterious effects of the inappropriate application of results can extend to family members, communities, ethnic groups, and other social groups as well. Unfortunately, there is a paucity of research about the negative repercussions of molecular epidemiologic research findings on participants, family members, communities and society. There is the widely expressed concern that genetic biomarkers can be used in ways that are discriminating and unjust, but there is little published evidence (22,45,67). Similarly, this concern has also been voiced with epigenetic data (68).

To facilitate the appropriate use of study results as much as possible, investigators should assure their quality. Methodological considerations in study design bear directly on the kind and strength of the inferences that can be drawn (e.g. increasing generalizability of study results through sample selection, and achieving appropriate statistical power with large enough sample sizes). This in turn affects what evidence can be provided from any particular study and what prevention or interventions can be envisioned. Inappropriate actions can thus inadvertently occur when interventions (or lack thereof) are based on results from a study that used biased or inappropriate methods. Some aspects of the research process provide investigators greater control over ensuring the appropriate application of findings; namely by strengthening the study's internal and external validity (such as in regards to study design and selection of research participants). Other dimensions are less in the control of investigators, such as public perception, media coverage, and the application of the results in the policy arena. The importance of the availability of all relevant evidence becomes apparent here as well (69). Timely publication of negative results is also crucial, for they contribute to the evidence on a particular biomarker and help to define the uncertainty accompanying a particular finding.

Molecular epidemiology holds promise for our ability to identify changes earlier in the natural history of a disease that may be amenable to intervention, leading to prevention of clinical disease or a better prognosis. This contribution is not without potential ethical issues. Premature marketing or use of tests is one problematic area that results from an inappropriate assessment of whether biomarkers or molecular tests have been validated for the specific use intended (25,26,70,71).

Inappropriate action also includes the lack of action, such as where there is some evidence from molecular epidemiologic research that indicates the need for preventive measures, and none are taken. There is increasing concern that public health practice has failed to take action on preliminary findings on the basis of uncertainty in the evidence. Delays in recognizing risks from past exposures, and acting on the findings, such as for cigarette smoking and exposure to asbestos and benzene, are failures that were not only scientific but ethical, since they resulted in preventable harm to exposed populations (72). One explanation offered for such delay is the absence of adequate proof or evidence of the certainty of a causal relationship. Such a position reflects an unwillingness to accept what may appear to be a preponderance of evidence as a trigger for public health actions even if there are some uncertainties (73).

The precautionary principle, a contemporary re-definition of Bradford Hill's case for action, provides a common sense rule for doing good by preventing harm to public health from delay: when in doubt about the presence of a hazard, there should be no doubt about its prevention or removal (70). It shifts the burden of proof from showing presence of risk to showing absence of risk and aims to do good by preventing harm, subsuming the upstream strategies of the Driving Forces Pressure Stress Exposure Effect Action (DPSEEA) model and downstream strategies from molecular epidemiology for detection and prevention of risk (74). It has emerged because of ethical concerns about delays in detection of risks to human health and the environment, and serves to emphasize epidemiology's classic role for early detection and prevention. At the same time, such precautionary strategies can have significant unintended consequences that also must be considered (71,75). Further, the translation of epidemiologic findings into public health policy generally involves multiple parties with various vested interests. The arena is complex: the role in this arena of those who carry out molecular epidemiologic research is not altogether clear, and there is a concern that the perception of an investigator's ability to carry out objective research could potentially be compromised through advocacy.

In keeping with the wider field of epidemiology, it is important that molecular epidemiology strive towards disease detection and prevention in populations. A concern has been expressed that when a public health problem is reduced to the level of the individual, such as with molecular biomarkers, then so too shall the intervention lie at the individual level (76). In some instances, this may be perfectly appropriate, yet in others, it may lead to the non-individual level factors (such as ecological chemical exposures) that gave rise to the public health problem in the first place and allow it to persist unabated (77). Inappropriate action could result from appropriate research. While there is no clear path to follow to those studies that will be beneficial and to avoid those that will not, considering why and how a particular research question is being asked, and what truly is the best manner in which to answer it, may aid molecular epidemiology in a balancing act between a high-risk approach and population-wide applicability of findings.

The results of molecular epidemiologic research may be used to support regulation or litigation. For regulatory agencies, there is a need to balance the risk of premature use of inadequately validated data with the harm from unduly delaying the use of relevant data from overly cautious policies (12). Critical in assessing the validity of molecular epidemiologic research for regulation or litigation will be whether the studies are of sufficient size and methodologic quality, and whether the findings have been replicated or corroborated. However, the ability of molecular epidemiologic research to provide evidence of toxicant-induced injuries, long before any clinical symptoms emerge, could profoundly affect how regulation is conceived to protect the public from environmental risks (78).

Sharing the benefits of molecular epidemiologic research: Public health ethics

In addition to the scientific benefits of sharing genomic and molecular epidemiologic data, there are also social and ethical issues. Fourteen stakeholder groups (many of which are outside the scientific community) have been identified who have at least eight different perspectives on the question of donor privacy and scientific efficiency (16). The researchers conclude that, at present, society lacks the sophisticated ethical or

policy framework to simultaneously weigh multiple perspectives and interests. More broadly, the benefits of molecular epidemiologic research involving genes may not be equally shared among poorer people in developed countries or among developing countries (21,79–81). The responsibilities of molecular epidemiologists to share the benefits of their research are generally viewed as limited. With that said, there is a need for molecular epidemiologists to consider broader questions, such as under what general conditions genome-based knowledge in molecular epidemiology could be further used in public health.

Beyond the need for molecular epidemiologists to address the rights of individuals is the need to consider broader questions, such as clarifying the general conditions under which molecular epidemiological research findings will contribute to public health in a wide-ranging way. Population-based data on genome-disease and genome-environment interactions are the primary point for assessing the added value of genome-based information for all health interventions in different health care settings. This includes the integration of genome-based information into existing population-based surveillance systems, and the use of large-scale biobanks to quantify disease incidence in various populations and subpopulations, as well as to understand their natural histories of disease through risk factors including genome-environment interactions (15). Making such potential benefits of molecular epidemiology manifest requires paying particular attention to the public health-specific ethical, legal and social implications of such research (15,77,82).

Whole-genome research

A core element of molecular epidemiologic research is the ability to utilize whole-genome and related "omic" technologies (see Chapters 6 and 7), because of the considerable cost and effort directed at conducting large studies. The area of whole-genome research is in its formative stage. The initial recommendations have been formulated to protect the confidentiality of participants and, at the same time, make the data available to researchers who propose projects and adhere to strict guidelines for protection of the data sets and participants. To this end, the US National Institutes of Health (NIH) has made available GWAS data to researchers through a registered access process using the database of genotypes and phenotypes (dbGaP) resource of the National Center for Biotechnology Information (NCBI) (83). The procedure requires institutional support for a faculty member (from a university, organization, or commercial entity) to access GWAS genotype data under agreed-upon conditions (Table 2.1). Sign-off by the sponsoring institution must guarantee the security and validity of the proposed analyses according to the precepts of the Trans-NIH GWAS Sharing Policy along with subsequent updates (84). The policy addresses issues of data sharing and availability of data sets. Moreover, guidelines have been proposed for issues of informed consent prospectively, and review of older studies for use in GWAS studies. This includes explicit assent from the overseeing

Table 2.1. Requirements for conducting genome-wide association studies

The NIH GWAS certificate expects that a Principal Investigator (PI) and their institution certify the following:
The data submission is consistent with all applicable laws and regulations, as well as institutional policies;
The appropriate research uses of the data and the uses that are explicitly excluded by the informed consent documents are delineated;
The identities of research participants will not be disclosed to the NIH GWAS data repository;
An IRB and/or Privacy Board, as applicable, has reviewed and verified that: • The submission of data to the NIH GWAS repository and subsequent sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained; • The investigator's plan for de-identifying data sets is consistent with the standards outlined in the policy; • It has considered the risks to individuals, their families, and groups or populations associated with data submitted to the NIH GWAS data repository; and • The genotype and phenotype data to be submitted were collected in a manner consistent with 45 C.F.R Part 46.
After publication, a full GWAS data set, stripped of all identifiers and with limited covariate data (e.g. case-control status, study or geographic entity, age group, sex, and broad racial and ethnic groups), is transferred to a Data Access Committee (DAC), according to the trans-NIH GWAS data posting policy of January 25, 2008 (84). All investigators, regardless of whether or not they are PIs on the GWAS or external to the project, who desire access to the individual level genotype data with limited covariate data can obtain access by submitting a secured application proposal to a certified DAC. Access to the data through the DAC requires the use of an ERA number, registration with the NIH, support of an investigator's institution (signing official), IT security program including use of a controlled-access and secure site, and a Data Use Certificate and modified SF-424 form. Proposal application forms are completed and sent to the DAC, which is composed of NIH officials who make the final decision regarding access to the data.

IRB that the conduct and availability of the GWAS study are consistent with the informed consent signed by the participants. NIH and other large funding organizations, such as the Wellcome Trust in the United Kingdom, have mandated that funded GWAS studies be made available through the above described registered access process.

Conclusion

Relevance and rigor of molecular epidemiologic research is essential for enlightened public health policy and practice. Such research cannot be used effectively as the basis of public health policy if it lacks respect for people or contains flawed science. Moreover, if there is to be robust participation in research, participants must be motivated and assured that the research is conducted within a strong ethical framework (5,28). Consideration of the ethical issues in molecular epidemiological research should lead to maintaining the relevance and rigor of the discipline and ensure that the contributions it makes will be of great value.

Disclaimer: The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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