

Some implications of genetic biomarkers in occupational epidemiology and practice

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This paper addresses the use of genetic biomarkers in occupational epidemiology and some of the scientific, ethical, and social implications for epidemiologists and practitioners to consider, including issues involving individual risk estimation, the communication of epidemiologic results, and the translation of epidemiologic data into clinical or occupational health practice. Three scenarios from the occupational setting illustrate some of these issues and implications. The scenarios involve glutathione-S-transferase theta 1 (GSTT1) and hematopoietic cancer in hospital workers, human leukocyte antigen coding for glutamic acid in the 69th position (HLA DPB1^{E69}) and chronic beryllium disease in beryllium workers, and peripheral myelin protein 22 (PMP22) deletion and carpal tunnel syndrome in railroad track workers. Epidemiologic research involving genetic biomarkers requires the application of genetic tests and can be considered on a continuum between basic sciences and clinical and occupational and public health practice for which questions of test relevance, validity, and utility become important.

Key terms epidemiology, ethics, genetics, genetic testing, genomics, molecular epidemiology, polymorphisms.

The field of epidemiology has a rich history of using biological samples and measurements in its research. For example, antibody titers were the hallmarks in the growth of infectious disease epidemiology (1), blood lipids have been used as markers of exposure and risk in cardiovascular disease epidemiology (2), proteins were mechanistic markers in reproductive epidemiology (3), and blood lead levels were exposure and disease surrogates in occupational and environmental epidemiology (4). Therefore, it is a logical next step to incorporate molecular and genetic measures into epidemiology. This incorporation has been referred to by the nomenclature, "molecular epidemiology," (5, 6) (and earlier, genetic epidemiology) (7), and it pertains to understanding disease and risk factors at the molecular and genetic level. More recently, in 1998, the term "human genome epidemiology" was used to denote an evolving field of inquiry that uses systematic applications of epidemiologic methods to assess the impact of human genetic variation on health and disease (8). Epidemiologic research, be it genetic, molecular, or human genome, is the link between basic laboratory investigations and medical and public health applications (figure 1). Even when

epidemiologic research involving genetic biomarkers is conducted to provide insight on mechanism or population distribution, it requires the development and application of genetic tests. While a continuum is depicted for this process, in actuality, there are numerous iterative processes between the laboratory and the field that actually drive progress along the continuum.

Epidemiologists are beginning to have a complete set of tools with which to assess both environmental and genetic factors in common diseases. The power of the

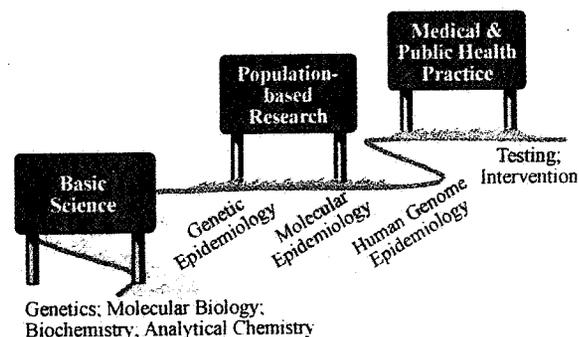


Figure 1. Continuum from basic science to medical and public health practice.

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technologies to make molecular and genetic measurements is alluring, and some people are misled by thinking that making such measurements automatically results in a better understanding, but it is not always the case. Moreover, the lure of the technology may lead to narrow explorations that do not represent the most judicious use of scarce public health resources (9, 10).

Molecular and genetic measurements are tools for use in epidemiologic studies and should be considered along with other tools, such as questionnaires, job-exposure matrices, record review, and phenotypic data, and not as ends in themselves. Ultimately, the tools of epidemiology need to be used to improve public health. In addition to their use in research and in the elucidation of mechanisms, studies that have found an association between biological measurements or markers and disease or risk have implications. These include how the findings should be treated in emergent research or will be applied or used in various nonresearch settings, such as in the development of protection strategies or in the screening or testing of individuals. A broad range of implications of genetic testing has been extensively described in the literature (11–22) and, generally, will not be repeated in this discussion. They address issues of respect for persons, confidentiality, privacy, equity, fairness, discrimination, autonomy, nonmaleficence, and self-determination. While many epidemiologists work with sensitive and private information, molecular and genetic epidemiologists may appear to be different because their tasks often involve applying genetic tests (validated or unvalidated) to research participants. This application creates genetic information about persons or groups that did not exist earlier (11). However, many argue that genetic information is fundamentally similar to other health information (23). In this paper, the occupational setting is examined because it provides useful opportunities to focus on other scientific, ethical, and social implications, such as those pertaining to the interpretation, communication, and use of epidemiologic findings involving genetic markers.

There is a framework for understanding biological measurements and markers that has been promoted by the United States (US) National Research Council (NRC) (24) and others (25–27). It represents a way to conceive of biological markers in terms of the following three categories: exposure, effect (disease), and susceptibility. These are linked in a continuum of events from exposure to disease. The category of susceptibility markers has been expanded in the last 15 years by molecular biological techniques and genomic research. Historically, epidemiologists, with the exception of genetic epidemiologists, have rarely considered inherited factors directly in studies.

Molecular epidemiology expands the use of genetic biomarkers in epidemiologic research as independent

and dependent variables. Molecular epidemiology is a heuristic term that broadens the focus of epidemiology to consider inherited and acquired risk factors, as well as environmental ones. The inherited or genetic factors can be of various types. The following two broad categories of genes have been widely considered: (i) rare single genes of high penetrance, such as the gene for Huntington's disease, and (ii) common genes of low penetrance. These latter categories include genes, often with polymorphic alleles that code for phase I and II metabolic enzymes and also genes for DNA (deoxyribonucleic acid) repair, cell cycle functioning, and various single nucleotide polymorphisms (27). Single gene conditions are responsible for about 5% of human diseases. The other 95% of diseases not normally considered "genetic" is due to the complex intervention of multiple genes and the environment. "Environment" is broadly conceived to include infectious, chemical, nutritional, and social factors. For these diseases, genes for which population variation is common may be involved and, in addition to the aforementioned polymorphisms, it will be important to study genes that code for blood groups, immunologic factors, antigens, and many other genes with population variation [<http://www.cdc.gov/genomics/info/reports/policy/editorial.htm> (November, 2001)].

At this time, there are various interpretive, communicative, and translational issues that epidemiologists and others face as when conducting, or as a result of, research involving genes (13, 22, 28). Three case scenarios from occupational settings will illustrate some of these issues. For the most part, they pertain to the problem of obtaining individual risk information from epidemiologic data, communicating epidemiologic results, and translating epidemiologic data to the practice of medicine and public health.

Ethylene oxide and glutathione-S-transferase theta 1

The first scenario involves hospital workers exposed to ethylene oxide (EtO), classified by the International Association for Research on Cancer (IARC) as a human carcinogen (29). EtO is used to sterilize hospital equipment and materials. A study was conducted to assess the relationship between the glutathione-S-transferase theta 1 (GSTT1) null variant (a gene that will detoxify the active form of EtO) and hydroxyethyl valine (HEV) hemoglobin adducts, surrogates for DNA adducts and, hence, cancer risk (30). The study showed a twofold higher risk of HEV adducts in exposed workers with the GSTT1 null genotype than in those with the wild type (at least one copy of the gene). The researchers were faced with the question of what to tell the study participants who were found to have the GSTT1 null genotype during the research. Three issues merit consideration.

First, this is a manifestation of the problem that epidemiologic information pertains to the group and not to any particular person. Thus there is a need to extrapolate and make assumptions about individual risks. Second, when the risk factors were modeled, the variability (R^2) HEV adducts for GSTT1 null genotype was 4% compared with 28% for smoking (which contains ethylene) and 30% for workplace exposure to EtO (30). Thus the genetic factor, while statistically significant, may not play an important role in risks from EtO exposure because it explained a relatively small proportion of the adduct variability. Third, while we were apparently the first to find the link between GSTT1 and hydroxyethyl hemoglobin adducts in EtO-exposed workers, our research was a small transitional study. Consequently, although there was laboratory support from *in vitro* studies (31, 32), without epidemiologic corroboration, our results were tentative. Thus we informed participants of what we knew, namely, "The absence of the gene may be related to a person's risk of cancer if exposed to EtO, but this is not certain." At the time this study was being conducted, there was relatively little or no guidance available specifically for population-based or occupational studies of low-penetrance gene variants. Subsequently, a Centers for Disease Control and Prevention (CDC) multidisciplinary group (33) using expert opinion, as well as Federal regulations, the National Bioethics Advisory Commission's report on research involving human biological materials (34), and the relevant literature suggested that participants not be told of information that has no direct clinical relevance. However, occupational studies differ from population-based studies in the sampling frame used and the types of intervention available. In occupational settings "clinical relevance" could be defined as whether participants could take reasonable preventive or medical action based on the results. In the workplace, these reasonable actions could include various engineering, administrative, or behavioral controls (35). Nonetheless, although the findings of this epidemiologic study were not deemed to be clinically relevant, we had informed participants of the results as part of a prior informed consent agreement.

Beryllium disease and human leukocyte antigen coding for glutamic acid in the 69th position

The second scenario involves beryllium manufacturing workers and the association of human leukocyte antigen coding for glutamic acid in the 69th position (HLA DPB1^{E69}) (referred to as Glu-69) polymorphism with chronic beryllium disease. Chronic beryllium disease is a debilitating fibrotic lung disease that can be life threatening. Richeldi et al (36) have reported an 85-fold (95% CI 10.9–3578.0) risk of chronic beryllium disease for

workers with an HLA-DPB1 coding for glutamic acid (Glu-69) in the 69th position. Subsequent studies confirmed this relationship (37–39); however, the risk ratios were lower. The question in this scenario is whether prospective employees in a beryllium manufacturing plant should be screened for Glu 69 variant prior to employment. First, the answer depends on the predictive value of the screening test. Despite a high odds ratio of susceptibility to chronic beryllium disease, the positive predictive value ranged from 8% to 14% for a genetic trait prevalence of 33–59% where the odds ratio odds ratio was taken as 35. Using a smaller odds ratio of 3, the positive predictive value was calculated to be 7–9% (39). The test has a poor predictive value. Second, there are other variants on chromosome 6 for which risks of chronic beryllium disease are suspected. Thus not having the Glu 69 variant is not complete assurance of lower risk. In addition, there is no curative treatment for chronic beryllium disease. It has occurred even in relatively well-controlled work areas. With this in mind the employer thought it important to provide information on Glu 69 to prospective employees and to establish a voluntary and anonymous testing program for employees at a university. In addition to genetic testing, genetic counseling was also provided by the university. The prospective employee received the individual results. The employer was provided only aggregate data. This example may illustrate how best to use genetic information, namely, provide it to a person at risk to make his or her own decision. But it may be a slippery slope from this use to the use in mandatory pre-employment placement. At issue is whether society in general, and employers in particular, will use genetic information in job placement. The American with Disabilities Act (1990) requires that placement decisions involving genetic information be job-related and consistent with business necessity. These are defined as whether the employee's ability to perform essential job function will be impaired by a medical condition or an employee will be a direct threat to others due to a medical condition.

Less clear is the extent to which the employer has to demonstrate the link between a genetic characteristic and a medical condition. Does genetic information differ from other risk factor information already in use? This issue has been referred to as "genetic exceptionalism" (40). It has been argued that genetic information is unique because it allows for the prediction of future health, it pertains to family members as well as the index person, and it can be the focus of discrimination and prejudice. Researchers, employers, and insurers already have access to genetic information in medical records, which are in the direct form of family histories and which can be inferred from such information as early age onset (41, 42).

The arguments for genetic exceptionalism all have counter examples that show that other types of medical and sensitive information have the same attributes as genetic information. Press & Burke have argued that the more appropriate question is not whether genetic information is exceptional but, instead, how it fits in the progression of biomedicine that has increasingly moved from bringing people into the medical system at the onset of symptoms to bringing them in as part of a prevention and early detection paradigm in which information on risk factors, including genetic information, triggers monitoring or intervention (<http://www.tech-res-intl.com/ELSI/agenda.asp>). However, when genetic information in the workplace is under consideration, there is a need to be aware that genetic screening is not viewed by all as involving neutral technologies (43, 44). Rather, it must be considered in the context of the power relations of a workplace and includes critical issues involving control, use, and consequences of risk information. There is a growing debate about genetic testing information in the scientific and lay literature that is fueled by the growing number of genetic discoveries and attempts to apply them. This situation is illustrated in the next scenario.

Carpal tunnel syndrome and peripheral myelin protein-22

The third scenario involves railroad track workers who filed injury reports or compensation claims for carpal tunnel syndrome (CTS) due to repetitive stress in their work (45). Without their knowledge and consent the employer tested them for chromosome 17 deletion, involving a protein, peripheral myelin protein-22 (PMP22). This is a test, not for carpal tunnel syndrome, but for "hereditary neuropathy with liability to pressure palsies", which may have a manifestation that includes carpal tunnel syndrome (46). The issue here is that, beyond the ethical and legal aspects at the time of use, there was an inadequate knowledge base (most particularly an absence of epidemiologic data) on which to make a decision to incorporate such a test (47). There is extensive information on the work-relatedness of carpal tunnel syndrome and less information on the role of hereditary factors (48–50). For the most part, the role of hereditary factors for carpal tunnel syndrome was assessed in family studies (51) but, on a population basis, the PMP22 deletions are rare. It is not likely that there would be any people in the group of 20 railroad workers tested that had this deletion. This is an example of inappropriate and premature testing, that is, testing for a genotype that has not been validated at the population level; specifically, the predictive value, absolute, relative and attributable risks had not been assessed. Second, unresolved is the question of whether society

should use genetic testing for a susceptibility genotype to apportion causation. This question raises the issue of whether immutable traits beyond a worker's control should be factored into a claim of work relatedness of a disease. Indeed in some jurisdictions (various states such as Iowa, Wisconsin, New York, and New Hampshire) consensual genetic testing is allowed in compensation cases. In the United States, most worker compensation statutes permit medical testing, including genetic testing, to ascertain the medical condition of the claimant and the potential work-relatedness of the claim. However, various US organizations do not generally condone genetic testing without informed consent (52 and American College of Occupational and Environmental Medicine. Genetic screening in the workplace. position statement. Approved October 24, 1994. Last updated: April 1997. <http://www.jserranomd.medem.com/>).

Emerging genetic tests

Although the tests in each of the three scenarios were not necessarily developed for clinical use, they, in fact, may at times in the research process have clinical attributes, if findings are reported to participants for the purpose of taking preventive actions or because they are potentially indicative of a health condition. Genetic research on etiology and mechanisms of disease often contributes to the evidence-base that will help establish the validity and utility of genetic tests. Hence each of the three scenarios addresses tests that may be considered at various places on the continuum from development in basic research to application in a clinical setting. For GSTT1, research on the genotype–outcome association was the focus. With HLA Glu 69, the application of a new test with low positive predictive value but some potential utility was at issue, and, for PMP22, the issue was a lack of knowledge base and premature and inappropriate application of a test.

A model process for evaluating data on emerging genetic tests has been developed by the US Task Force on Genetic Testing (53) and more recently by a collaborative group sponsored by the US Centers for Disease Control and Prevention (CDC) (<http://www.cdc.gov/genomics/info/perspectives/files/testACCE.htm>) (54). This group, the ACCE core group, takes its name from the four components of evaluation—analytical validity, clinical validity, clinical utility, and ethical, legal, and social implications and safeguards. The effort builds on a methodology described by Wald & Cuckle (55) for evaluating screening and diagnostic tests. The ACCE process includes collecting, evaluating, interpreting, and reporting data about DNA (and related) testing for disorders with a genetic component in a format that allows policy makers access to up-to-date and reliable information for decision making. The ACCE model contains

a list of 44 targeted questions aimed at a comprehensive review of a candidate test (54). The questions for analytic validity focus on the ability of the test to measure the genotype of interest accurately and reliably. For clinical validity, the focus is on the ability of the genetic test to detect or predict the associated disorder (phenotype). The questions on clinical utility address the elements that need to be considered when the risks and benefits associated with the introduction of the genetic test into routine clinical practice are evaluated. Finally, the questions pertaining to the ethical, legal, and social implications address safeguards and untoward effects or impediments (eg, stigmatization, discrimination, privacy, informed consent, ownership of biologic materials, results reporting, and protections in place) (54).

Of the tests in the three scenarios described in this paper, none meet all the ACCE criteria for clinical use. (See table 1.) Of course, clinical use was not the intention in the study involving GSTT1; it was a research variable in a cross-sectional study. The test for Glu 69 meets the broader definition of clinical use involving the prevention of disease. Glu 69 was used in voluntary preemployment screening, and the results were provided to applicants to help them make employment decisions. PMP22 was used in workers' compensation evaluation in part to establish the differential diagnosis and in part to apportion causality. This was not a clinical use in any sense of the meaning. All three tests had some degree of analytical validity, but only the Glu 69 had published information on clinical validity, albeit, that information indicated poor positive predictive value. The ethical, legal, and social issues were not completely known with the use of any of them; however, the effort involving GSTT1 and Glu 69, included the kinds of

safeguards widely recommended for ethical, legal and social implications (34, 59). Nonetheless, prior to regular use, a broader assessment of the social impact of such tests should be conducted.

Population-based research involving low-penetrance gene variants

Until recently there was little or no available guidance for addressing the ethical, legal, and social issues involved in population-based studies of low-penetrance gene variants. The guidance that does exist generally pertains to single genes of high penetrance that are investigated in family studies. The risks and benefits of population-based research involving low-penetrance gene variants can differ from those associated with the family-based research that has been the hallmark of genetic epidemiology (59). "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 [p 2316]" (33).

The issues of risks and benefits in epidemiologic research involving genetics are elucidated in the process of obtaining informed consent from study participants. The CDC formed a multidisciplinary working group to develop an informed consent approach needed for integrating genetic variation in population-based research (33). Although the recommendations are not policy-related, they provide a useful outline of the content, language, and considerations for an informed consent document. Much of

Table 1. Characteristics of the genetic tests or their application described in the text. (GSTT1 = glutathione S-transferase theta 1, HLA DPB1^{E69} = human leukocyte antigen coding for glutamic acid in the 69th position, PMP22 = peripheral myelin protein 22, IRB = institutional review board)

Genetic test	Disease	Purpose of test	Analytic validity ^a	Clinical validity ^a	Clinical utility ^a	Ethical, legal, social safeguards ^a
GSTT1	Hematopoietic and lymphatic cancers ^b	Research	Test had prior use; analytical characteristics were assessed ^c	Not applicable: gene-environment interaction study	Not applicable	Protocol approved by IRB
HLA DPB1 ^{E69}	Chronic beryllium disease	Preemployment screening	Test had prior use; analytical characteristics were assessed ^d	Low positive predictive value ^e	Intervention available; applicant's decision to work	Individual test results went only to applicants; counseling provided; IRB review
PMP22	Carpal tunnel syndrome ^f	Assessment of work-relatedness of a workers' compensation claim	No published data ^g	No published data ^h	Not applicable	No informed consent ^{a, h}

^a Criteria for clinical use from ACCE and Burke et al (54).

^b The study assessed whether GSTT1 was an effect modifier in the association between occupational exposure to ethylene oxide and the formation of hemoglobin N-2-hydroxyethyl valine (HEV) adducts. HEV adducts are believed to be surrogate risk factors for cancer.

^c See Weincke et al (56) and Pemble et al (57).

^d See Sorrentino et al (58) and Weston et al (39).

^e See Weston et al (39).

^f Although the test is marketed as a test for carpal tunnel syndrome, it is actually a test for "hereditary neuropathy with liability to pressure palsies" which sometimes manifest with carpal tunnel syndrome. The sensitivity, specificity, and predictive value have not been found in published literature.

^g United States District Court (45).

^h Informed consent was apparently not obtained and is not required in a workers' compensation medical examination.

the language in these consent materials addresses the distinction between genetic research expected to reveal clinically relevant information about individual participants and genetic research that does not. Population-based research involving genetics will not be expected to identify clinically relevant information. Beskow et al (33) 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 may be difficult to define; therefore, they recommended that "when the risks identified are both valid and associated with proven intervention for risk reduction, disclosure may be appropriate [p 2320]" (33).

Challenges from high-output technologies

The issues illustrated in the three scenarios described earlier raise implications that occupational epidemiologists and practitioners may not be well informed about. In each of these scenarios, only one gene was the focus. These issues may be exacerbated by genomics and related technologies involving hundreds and thousands of genes and gene products that can be assessed simultaneously in a single experiment or analysis. The potential for this technology is large, but the technology is not necessarily ready for use in widespread epidemiologic research. Genomics not only refers to the technologies involved in genome sequencing, but also to "exploratory science", in which large resources of information are generated on biological molecules without necessarily knowing which pieces of information and correlations will be the most important. Related technologies that look at message (transcriptomics), toxic effects (toxicogenomics), and protein (proteomics) may all be referred to as "high output" technologies. These will present epidemiologists with great amounts of data that will require standardizing, sorting, reduction, and interpretation. Hence epidemiologists will also have to collaborate with specialists in bioinformatics and medical informatics (60–64).

From high output to high throughput

High output technologies have the potential to lead to greater insight about mechanisms (61). They may provide ways to screen new chemicals for commerce and possibly to identify high-risk groups or persons for preventive or therapeutic intervention. The identification of high risks in a subgroup of a population with a particular genetic characteristic or pattern is useful from an etiologic perspective and could be useful to target intervention in various subgroups at increased risk. However, as high-output technologies are used by epidemiologists in populations, the issue will not be high output (that is, a large number of genetic variables per person)

but, instead, how many samples can be analyzed in a reasonable length of time and at reasonable cost (high throughput). The application of high-output technologies to large populations will require extensive transition work for optimizing the technology. There will be a need to understand how patterns on a particular array vary with existing diseases, population distributions, and other biological, cultural, or social factors. Conducting these transitional studies will require the leadership of epidemiologists.

Both the single gene and the high-output technologies raise the question of whether using these technologies in epidemiologic studies to identify high-risk groups in the population at large or search for low penetrant gene variants will be a good use of scarce resources. On the one hand, there is a series of views indicating that marginal effects of common allelic variants account for a substantial proportion of population risk (65, 66). Hence according to this line of thinking, it is sensible to extend the search for risk factors into the human genomes to uncover high-risk persons hidden within exposure categories. With these new definitions of high-risk categories, it would be possible to better define who may benefit from intervention. However, the opposing view is that most known risk factors for chronic diseases have modest risk levels (67). Most people in the high-risk category will remain healthy, while some people in the low-risk category will develop diseases. Most of the cases of chronic disease arise from the mass of the population with risk factor values close to the average (68). Most cases do not arise from the high-risk tail of the risk factor distribution (67). The attributable risk of a susceptibility conferring genotype generally only reaches levels above 25% when the relative risk is above 5 and the frequency of the genotype is 10% or greater (69). Thus far, most studies of genetic polymorphisms have failed to uncover groups of people with relative risks greater than 3. There is also a debate over whether combining multiple genotypes will increase the predictive value of tests that involve them. In addition to identifying high-risk individuals, genetic biomarkers can lead to a more robust understanding of occupational and environmental determinants of disease relevant to whole populations, and not simply to genetically susceptible subpopulations (70, 71).

The impact of genomics research can be viewed in different ways. One perspective is that the sequencing of the human genome is the greatest opportunity for epidemiology since John Snow discovered the Broad Street Pump (65). How to use the massive data sets from high-output technologies is the question. Some suggest a "discovery science" and an informed effort to look for associations or correlations on which to focus further research (72). Others are more disparaging of the effort. As Weiss & Terwilliger (73) noted, some ask if the mas-

sive scaling-up of genetic epidemiology studies provides new information on the genetic components of health and disease when a major justification is that nothing else has worked so far. They further observed that no one can deny that disease pathways have been identified in genetic epidemiology and, therefore, contributed to biological knowledge. However, so far, it is lifestyle changes that have made the most impact on the incidence of chronic disease (73). Nonetheless, the use of genetic biomarkers to improve the design and analysis of studies of occupational and environmental determinants of disease may be one way to address the limitations of observational epidemiology that have been described in recent years (74, 75). It is possible to exploit the random assignment of genes as a means of reducing confounding in exposure disease associations through the application of "Mendelian randomization" principles (70). According to Mendel's second law, the random assortment of alleles at the time of gamete formation results in a random association between loci in a population and is independent of occupational and environmental factors which, in theory, will lead to a similar distribution of unlinked genetic loci in persons with and without disease (76). However, there are various caveats to this approach. Attention must be paid to study size, differences in patterns of linkage disequilibrium, knowledge of candidate gene function, and impact of population stratification (76). Study designs that assess genotypes unrelated to potential confounding factors may lead to a clear assessment of exposure-disease associations (70, 77).

Ultimately, these contentions do not reduce to a question of whether to support genomics research. Such research will inevitably proceed. The question is what role will epidemiologists play? As Millikan cautions, if epidemiologists only direct their efforts toward a comprehensive search for the genetic underpinnings of every discrete health outcome and ignore environmental exposures and attributable risks, they will miss the opportunity to prevent disease (63). Nonetheless, epidemiologists can provide a population perspective to genomics research that is clearly lacking. But, in the larger scheme, epidemiologists need to contribute to the development of a conceptual framework that incorporates genomics into occupational and public health (63).

Concluding remarks

Ultimately, the use of genetic biomarkers in occupational epidemiologic studies holds some potential for elucidating underlying mechanisms and contributing to occupational and public health. Clearly, learning about gene variants can provide insight into pathways relevant to disease etiology, which may indicate certain exposures as potentially important in causing disease (77-80). Hence genetic markers form another important set

of tools for epidemiologists to consider and use when needed. The implications, such as those described in this paper, of using these tools inappropriately should also be considered and guarded against by epidemiologists.

Epidemiologists may have two orientations with regard to genomics and related research, one toward occupational and public health and the other toward clinical care. In either orientation, the population prevalence, variability, validity, and other characteristics of genetic markers will need to be investigated. For clinical uses, the epidemiologist will be called upon to contribute to the assessment of the analytical and clinical validity and clinical utility. For occupational public health use, in addition to validity and utility issues, epidemiologists will be challenged to take both a macro- and micro-view of health problems and integrate information from both levels to identify risk factors, causes, and interventions. At the micro-level, not only will genetic markers and genomics be important, but also, and eventually more so, proteomics may be an important complementary discipline (81-82). Epidemiologists will be called upon to identify and characterize population distributions and variations of protein patterns and relate them to genotypes, clinical phenotypes, and environmental conditions.

When much of the world faces rampant occupational and environmental hazards, the current emphasis on genetics may seem to lack relevance. Moreover, epidemiologists may find that understanding the role of some genetic factors in disease does not contribute extensively to strategies for the prevention, intervention, and, ultimately, reduction of morbidity and mortality (83). But that is exactly the challenge epidemiologists and practitioners face, namely, to identify and apply genetic information in the study of human disease in instances in which it will make a difference to public health (63, 83).

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