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Ethical Issues in the Use of Genetic Markers in Occupational Epidemiologic Research

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Abstract

This review was conducted to characterize the nature of contemporary occupational epidemiological research involving genetic markers, consider how genetic information is unique with regards to its social applications and examine some of the ethical dilemmas that may arise over the course of studies. We have reviewed the literature and the lessons from our experience on conducting occupational epidemiologic research involving genetic markers. This review describes how occupational epidemiologic studies differ from other epidemiologic study on issues of participation, confidentiality and the history of including genetic markers. Of most concern in occupational studies are genes which have multiple alleles and are sometimes referred to as "metabolic polymorphisms." They generally do not confer risk on their own but only in combination with a specific exposure. There is a need for clear policy and guidelines for the conduct of occupational epidemiological studies using genetic material. This policy should address all the steps in study design, implementation, interpretation and communication of results.

Advances in molecular genetics and human genome research have provided new tools to assess exposure-disease relationships. Recent findings suggest that inherited, genetic, differences in host metabolic capacity contribute to response variability following exposure to exogenous agents.[1] Such findings are particularly relevant to exogenous exposures to the workplace. A more complete assessment of occupational risks can be undertaken when genetic factors are considered along with environmental factors.[2]

However, investigators need to be aware that interpretations that reduce the cause of complex multifactorial diseases etiologies, such as cancer, to relatively simplistic genetic answers are misleading. Genetic factors with a strong effect on the risk of occupational disease are usually rare. For most genes, their effect on risk is modest, complex and fairly uncertain.[3] Rather than having a singular role, genetic markers should be considered as another set of tools that can used in support of occupational disease prevention.

Before a particular genetic marker can be utilized reliably, the relevance of the marker to disease etiology must be resolved. Occupational epidemiologic research involving genetic markers and human-participants can serve to provide this resolution. However, such studies can result in epidemiological research becoming intertwined with range of ethical, social and legal controversies. The purpose of this paper is to characterize the nature of contemporary occupational epidemiological research involving genetic markers, consider how genetic information is unique with regards to its social applications and examine some of the ethical dilemmas that may arise over the course of studies.

Distinguishing Features of Occupational Epidemiologic Studies

Several factors distinguish occupational epidemiologic studies from other epidemiologic studies. The potential study participants are in defined organizations and locales and therefore procedures to safeguard confidentiality may need to be more stringent than for general population studies. Participation in the study, and the meaning, handling, and impact of results can be intertwined with power and hierarchical relationships of the workplace. For example, there has been strong labor opposition to genetic testing in the workplace, for fear that it will result in discriminatory hiring practices and reduced efforts to minimize exposure to toxic substances. Current employees may fear that genetic screening will reveal a risk factor to the employer and induce job loss or reassignment.[4]

Historically, genetic factors rarely have been considered in studies of occupational health risks for a variety of reasons.[5] These range from the overwhelming effect of occupational exposures as compared to genetic influences for some diseases, to concerns that emphasis on genes will be to the detriment of efforts to control the environment. In many classic occupational studies, the exposures were substantial, the outcome under study was mortality, and there was neither access to biological specimens nor relevant genetic tests. The rapid increase in understanding of molecular mechanisms of cancer over the past decade, along with the identification of genetic factors related to cancer risk, have resulted in increased opportunity to incorporate genetic factors in epidemiological studies of occupational cancer etiology. Although there are notable examples, fewer opportunities have arisen for other nonmalignant occupational diseases.

Role of Genetic Factors

Despite the strong causal associations that have been detected in many occupational studies, there remains a differential distribution of diseases among workers that cannot be accounted for by differences in exposures, work practices, or life-style. Genetic factors are likely to be responsible for some of this distribution.[6-9] In the early history of occupational epidemiology, individual genetic risk factors generally were accounted for only by controlling for race or sex. Today, as many occupational exposures are being controlled to lower levels, the importance of genetic factors as sources of variability in risk estimates is increasing. This is not to imply that occupational etiologies will be replaced with genetic etiologies, but rather that genetic factors, which might influence exposure-disease associations, should be included as relevant variables in study design and analysis.[5]

Susceptibility Genes

Molecular genetic technologies offer a range of capabilities for research. For example, it is now possible to compare directly DNA sequences of case participants and control participants for genes potentially involved in disease etiology. These techniques also enable identification of "susceptibility" genes or, at least phenotypic expressions that may differentiate populations according to risks. A genetic marker of susceptibility is a host factor that enhances some step in the progression between exposure and disease such that the downstream step is more likely to occur. The term *genetic marker* is used here in reference to susceptibility genes.

There are two general types of phenotypic expressions that are associated with susceptibility to disease. The first are single genes that are strongly associated with rare diseases, for example, the HLAB27 gene and ankylosing spondylitis, or the gene for hereditary diseases like Ataxia telangiectasia. In contrast, and more relevant to the occupational environment, are genes that code for enzymes involved in the metabolism of occupational toxicants or carcinogens. These genes have multiple alleles and are sometimes called "metabolic polymorphisms." They (each allele) occur by definition in more than 1% of the population. They generally do not confer risk on their own but only in combination with a specific exposure. An example is CYP2D6 and benzo-a-pyrene (B(a)P) exposure (discussed below).

Characterization of Studies: Validation or Utilization

The extent to which genetic markers can be applied towards occupational disease prevention will depend on future research. Contemporary occupational epidemiology research involving genetic information can be viewed as either validation or utilization (as independent or dependent variables or for occupational medicine practice studies) of genetic susceptibility markers.[10] The first is where there is research to validate whether a genetic assay result is a biomarker of susceptibility. The latter involves use of genetic markers in epidemiologic studies as variables to answer a question about something other than the markers or to use them to screen populations such as at pre-placement. For example, a validation study might determine that individuals with a particular CYP2D6 polymorphism have a higher risk of lung cancer associated with B(a)P exposure than those without. In contrast, if several well-designed studies document that CYP2D6 is a valid effect modifier for the B(a)P -lung cancer relationship, then the marker can be utilized to stratify populations and possibly to screen individuals.

Uncertain Meaning of Molecular Marker

Even if CYP2D6 is validated as a marker of risk associated with B(a) P exposure, the risk will still only be a probabilistic statement. Having B(a)P exposure and the high risk CYP2D6 polymorphism is not a 100% determinant of disease. In fact, for most diseases, at least, for most cancers, assessment of a single polymorphic genotype cannot be expected to be sufficient for evaluating individual susceptibility to environmental agents. There is a need to establish a broad risk profile involving multiple genes for each individual.[1] There is a small, but growing literature on the combined effects of metabolic genes on susceptibility to cancer. For example, Hayashi et al.,[11] described a 5.8-fold relative risk (95% CI 2.3–13.3) for all lung cancer types and 9.1-fold relative risk (95% CI 3.4–24.4) for squamous cell carcinoma of the lung, in Japanese individuals who were homozygous for the CYPIAI Val allele and concurrently lacked the GSTM1 gene.[1,11]

Uncertain Relevance of Molecular Marker

As data emerge on the combined effects of metabolic genes on disease susceptibility, three issues become apparent. First, almost everyone probably has some metabolic polymorphism that is associated with increased risk of cancer. In a subset of workers with potential exposure to the putative toxic substrate there will be a fairly large number with the polymorphism(s) in question. Second, the polymorphism may be related to a disease only if other unknown polymorphic genes are involved. Third, the assays used to classify people with the polymorphism need rigorous testing, before they can be acted upon.[13] For example, it must be demonstrated that a specific metabolic phenotype is a risk factor for cancer and further, that the available tests accurately classify the participants as to phenotype. If there is a poor correspondence between phenotype and genotype or a larger intra-individual variability in phenotype, misclassification may result.

Further research should serve to elucidate both the meaning and relevance of genetic markers thus enabling improvements in occupational disease prevention. For example, the inability of current risk assessment procedures to explicitly account for interindividual variation may result in a significant understatement of risk, especially for higher risk subgroups.[7] Many scientists working in the field believe that inclusion of genetic factors along with refinements in exposure assessment will serve to better explain variation in the distribution of diseases among workers, thus allowing improved risk estimates for higher risk subgroups.[8] The challenge becomes one of sufficiently validating biomarkers, so they may become useful in disease prevention programs.

Ethical Concerns in the Use of Genetic Research

Uncertainty over the meaning and relevance of a single metabolic gene, or combinations of genes is a source of ethical controversy. If there were certainty that a particular genetic characteristic had an exact risk, then the basis

might exist for a deliberative societal response. Genetic information derived from biological specimens adds an element of "individual results" to epidemiologic studies. Further, genetic markers may be predictive of health-related outcomes such as the likelihood of illness or early death. Information concerning future morbidity and mortality has a range of social applications. The potential for adverse social application of genetic information leaves groups -- whose members are asked to participate in studies with genetic markers -- feeling compelled to take extremely defensive positions. The distinguishing features of occupational studies, mentioned previously, amplify such concerns.

To illustrate a social application of genetic information, consider a case where a polymorphism appears related to a disease, but other unknown polymorphic genes are involved -- a marker requiring validation. From an epidemiological standpoint, disease "causation," resulting from the inherited marker, has not been established. But in the context of insurance law, causation is irrelevant: a statistical link alone can be used to construct a statistically accurate risk classification. If this risk classification is predictive of an insured's expected loss, then by denying coverage to an affected individual the insurer is engaging in the socially sanctioned practice of "fair discrimination".[14] While an in-depth discussion of insurance law beyond the scope of this article, it is important to recognize that genetic information has potential social application regardless of its validity in epidemiologic studies.

The example of risk classification in insurance is intended to illustrate how information demands vary according to particular societal activities. Validating genetic markers for use in disease prevention programs requires a level of rigor unique to epidemiological investigation. Many societal activities are not bound by the same rigor. This difference in information demands enables the intertwining of epidemiological research with other social activities. As a consequence, associations can be construed as truths until proven otherwise. Consider the case of a mutation in the gene that codes for monoamine oxidase (MAOA). Affected individuals lack MAOA which to researchers suggested a relation between the mutation and "abnormal behavior." Researchers reported being approached by lawyers hoping genetic testing might exculpate clients on death row.[16]

Implications for Future Research

Concerns over the applications of research findings and research ethics are not new. Professions, institutions and governments have developed guidelines, declarations and professional codes to promote ethical accountability. The four principles, upon which much health-related ethical analysis is conducted, are respect for autonomy, beneficence (doing good), nonmaleficence (doing no harm), and social justice. Some existing guidelines address vulnerable and dependent groups, but they do not directly address issues related to biomarkers.[17] To a greater degree than professional codes, the law requires professionals to be aware of and responsive to the concerns of research participants and the public at large. Although norms of beneficence and justice are implicated, preserving respect for individual dignity and autonomy is the primary goal of legal consent rules.[18]

The notion of responsiveness is a useful one. Researchers have an obligation to be responsive to ethical concerns relating to biomarker studies. Responsiveness implies that researchers have formally evaluated and accounted for the ethical dimensions of a proposed study. The Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC) offers a framework for ethical evaluation of studies involving biomarkers of susceptibility.[19] The SGOMSEC framework is particularly useful because it centers on research ethics as opposed to clinical practice.

The SGOMSEC framework identifies ethical issues needing to be addressed but does not prescribe definitive answers. Ethical evaluation is inherently value laden and therefore involves some degree of subjectivity. Researchers or institutions may make different decisions when presented with the same circumstances. The following sections

explore examples of issues that arise in occupational epidemiological research. The intent is to make more explicit some existing controversies and dilemmas. This exploration is prompted by the supposition that, if investigators are to be responsive to research concerns, there is a need for ongoing dialogue concerning applied ethics.

Protocol Development

In addition to the deontological (duty-based) requirement for scientists to be honest, objective and unbiased,[17,19] the ethical issues in protocol development arise from whether or not a study involving genetic markers should be done in the first place. The ethical issues pertain to the judicious use of scarce resources and the diversion of preventive efforts. The conflict is between a focus on molecular genetic mechanisms at the expense of research on preventive or control efforts. Clearly, both activities have their values. However, with limited budgets, it may be more appropriate to use research funds to effect the greatest health benefit. Principles of beneficence and nonmaleficence may be violated by mechanistic preoccupations that divert resources from more direct efforts at prevention or risk management. Further, the aforementioned example of "fair discrimination" in insurance illustrates how individual harm may result from research findings being applied in a social context. Beneficence may be best served by biomarker research in cases where exposures are comparatively high, the disease pathway has been elucidated, and the disease is prevalent among a group of workers. In such cases, a refined understanding of specific genetic factors that affect individual susceptibility may serve to prevent disease among those at greatest risk. However, there is justification for conducting hypothesis generating or mechanism elucidating studies if the worker population has recognized exposures and demographic characteristics and ultimately the research is expected to contribute to prevention efforts.

Recruiting Workers

There are two principle scenarios for obtaining biological specimens from worker participants. One is where specimens have been previously collected and banked; the study in question involves a previously unanticipated assay on the stored specimens. The other scenario involves specimens collected for the first time as part of the study.

With banked specimens, workers have already agreed to participate in a specific study and had consented for specimen collection for at least one proposed assay. The ethical issues will revolve around what participants agreed to with regard to subsequent assays on specimens. Agreement may range from no consent for new assays to 'carte blanche' acceptance of any assay and communicating of test and study results that range from no communication to communicate only when results are clinically relevant.

The question of whether participants will have to be recontacted to provide consent for a new study can depend on the extent to which specimens are anonymous and the nature of their first consent. Clayton et al.[20] suggested that anonymous specimens could be treated differently from identified specimens, but questioned whether there could be truly anonymous specimens. This may be because linkage to identifying records can be reconstructed unless records are destroyed; or, it may mean that since DNA is a personal identifier, anonymous samples of DNA is an oxymoron.

If the consent form was not explicit in identifying specific assays, the ethical issues become more nebulous. For example, a consent form in a cancer study may indicate "other genetic tests for metabolic polymorphisms will be conducted as they are developed" or it may say, "these specimens may be used in other studies." The former quotation may be considered an ethically acceptable basis to proceed with a study of CYP2D6 genotype and the latter less so, especially because genetic tests are often more sensitive than other assays. Hunter and Caporaso [21] have advocated that consent efforts note the distinction between "mutations that have high known risk of disease" and "genetic

polymorphisms that involve common alleles that are neither necessary nor sufficient for the development of disease, many of which are risk factors only in combination with particular environmental exposures or lifestyle factors". They suggest that the level of consent required should be proportional to the degree of risk involved and thus less stringent consent procedures may be appropriate for low-risk susceptibility genotypes than for high risk genotypes. This position is in contrast with that of the Ethical, Legal and Social Implications (ELSI) Working Group of the National Center for Human Genome Research which, while noting the distinction, indicated that most DNA testing entails enough risk to participants to require very explicit informed consent.[20] The ELSI statement did recognize that some research is low risk and eligible for some degree of waiver of the informed consent process, but it did not indicate the criteria for this.

There is an ethical tension between autonomy and nonmaleficence: self determination versus doing no harm. With uncertain information such as that which would arise in a validation or transitional case-control study that assesses the relationship between B(a)P and lung cancer in people with various CYP2D6 polymorphisms, what can be the autonomy a participant might realize? It may be that despite the uncertainty of the information, workers may choose to want to know it, and act on it, in the event that it is true. Or, workers may want to guard against someone collecting data on them and putting them in a position of having to indicate that they had genetic tests conducted. The issue of nonmaleficence pertains to the investigator who can do harm intentionally by misusing the data, or most likely, inadvertently, by failing to secure it or by putting the research participants in the aforementioned position of having to indicate genetic tests were conducted on them.

For specimens obtained in a new study (as compared to one with previously banked specimens) there is the problem of degree of uncertainty about what the research participants are agreeing to, and the extent to which they agree to future uses of their specimens. In both new and banked specimens collected in studies of workers, there is the belief that truly informed consent is unable to be achieved for genetic tests because workers are not truly informed or truly free to withhold consent.[22] For the former condition, workers are rarely told that confidentiality can never be guaranteed in the face of court-ordered discovery or public health needs, or that economic or social harm is likely to result if genetic information is available to insurers, employers, family members, or the media. With regard to consent, there is belief that a coercive economic or employment environment, or a misperception of what is being consented to, will lead to the supply of a signature when it might not otherwise be provided (23). Additionally, consent for specimen banking may have transgenerational implications, especially for high penetrance genes. What a parent agrees to may affect the progeny, or intragenerational siblings. For example, in the context of BRCA1 testing, Ashkenazi women have expressed fear over the effect testing might have on the well-being of their families and their larger community.[23] One concern being that Ashkenazi women may be permanently disadvantaged as a group if their genetic disposition is perceived to render them likely to manifest health problems.

Assurance of privacy of participants and confidentiality of specimens and data

Genetic material (DNA) has the potential to be the source of information that can potentially be harmful to research participants or their families because of discriminatory practices or unwarranted actions.[24] The likelihood that this potential will be realized is not known and may be smaller than current public or IRB opinion indicates. This is because there is a misconception that biologic specimens are closer to truth than questionnaire data, exposure assessments, or information obtained from record reviews.[25] Nonetheless, we are in an era where DNA and genetic related information is likely to be misused. Many have identified a reductionist tendency in the biological sciences that is exemplified by focus on gene structure and identification of single genes or mutations as the cause of complex diseases with multifactorial etiologies or social problems.[3, 26-28] In such an era, it is not unrealistic for workers

presently to refuse participation in research when historically they have participated. Moreover, much of the genetic research in the workplace environment appears to be motivated by public health concerns aimed at providing only mechanistic insight. The results may nonetheless be used inappropriately to discriminate or deny compensation. DNA analysis results, used for improper or nefarious purposes, can put workers at risk of various types of discrimination. Thus, not only access to results of assays, but also access to DNA for other types of testing, needs to have safeguards for workers.

Additionally, as noted earlier, since study populations usually are in defined locales and organizations, assurance of confidentiality is difficult. Publication of results on small groups of workers with assorted covariates and descriptors can lead to the inadvertent identification of participants.

Communicating test and study results

Researchers trying to find relationships between exposures and diseases in workers often argue that informing participants about such studies should be minimal and confined to clinically relevant results. Worker participants seeking decisional autonomy and the ability to protect themselves from misuse of their information may want fully "informed" consent and disclosure. IRB's, in the face of uncertainty about meaning of specific genetic markers, may lean toward maximum consent before validation studies may be conducted. This could mean consent must be obtained in advance of every analysis, and individual debriefing must be administered about each identifiable finding. Employers, seeing preliminary information about potentially at risk workers, may respond by screening out such workers. Employers may perceive screening as a means of reducing liability. The ethical issues in occupational epidemiologic research do not directly pertain to screening workers for employment and job placement purposes; rather, they involve recruiting workers into studies, keeping information confidential, and communicating test and study results. However, as will be discussed later, use of genetic markers to screen workers should not be ignored.

Biologic test results pertain to individuals, while epidemiologic study results pertain to groups. Taken together, it may be possible, qualitatively if not quantitatively, to fashion an individual risk function.[29] Sorting this out in communication to study participants is difficult. In the face of uncertainty about disease, such as might be the case in transitional or validation studies, some researchers and institutions strongly believe that no communication is better than an uncertain one(s). In part, it is the tension between autonomy and nonmaleficence that is at issue. A recent international workshop on susceptibility biomarkers concluded that in studies to establish the sensitivity, specificity, and predictive value of new test participants should not have access to individual results until a clear interpretation is available and that participants should be advised of this at the time informed consent is obtained.[30]

Even when it is believed that autonomy is the driving force, it is difficult to determine what to tell study participants. For example, consider a study we are conducting of hospital workers exposed to ethylene oxide. The current part of the study involves whether workers with a particular polymorphism in GST theta (deletion of GSTT1) are likely to have more DNA or hemoglobin adducts or cytogenetic changes than individuals with the functional allele. However, the informed consent and results notification need to address the risk of cancer from EtO exposure in people with this polymorphism, even if it is not the specific focus of the study. How should this risk be portrayed?

The risk associated with the null form of GST theta might be conceptualized as follows: Even if a prior study showed a 2-fold risk of developing leukemia among individuals with the null form of the gene who are exposed to EtO, and no risk among individuals with the functional form of the gene, a particular individual exposed to EtO with the null form of the gene would not necessarily have a twofold risk of developing leukemia. Factors that may be at play in determining susceptibility to a particular carcinogen are the level of exposure, activity of metabolic enzymes that

convert the substance to the active carcinogen (based both on genetic factors and concomitant exposure to enzyme inducers), variations in activity of competing metabolic pathways (for some substances) and of enzymes that detoxify the active form of the carcinogen, as well as constitutional and environmental factors which might influence DNA repair (and probably a number of other factors). The researcher might conclude that the presence of the null form of GST theta need not be of substantial concern to study participants, since an individual with this single trait might have a leukemia risk either higher or lower than similarly-exposed co-workers if all possible factors were accounted for.

It is difficult to explain in a notification letter that the overall risk associated with a genetic factor in the study does not necessarily apply to an individual. We tried to explain this concept in the draft letter notifying study participants of their GST result by saying: "The absence of this gene may be related to a person's risk of cancer if exposed to EtO, but this is not certain. This study will not answer questions directly about what chemical exposures can trigger cancer. However, the study will address how the absence of the gene influences how the body processes EtO." The underlying issues are: how does population or overall risk relate to individual risk, and how can we communicate information about population risk without creating undue concern (especially for genetic factors over which there is no control). The communication of complex genetic information is always likely to be a challenge for investigators.

There has been little research on the impact of individual results resulting from medical investigations on the worker participants notified. In general, not much is known about what lay persons understand about genotyping, genetics research and the role of alleles as probabilistic moderating variables in the etiology of disease. The experience of genetic counselors offers some insight into the impacts of notification in the context of reproductive planning. This experience suggest that counselees have difficulty interpreting probabilistic statements of risk. Counselees tend to shift focus from risk to outcome and the subsequent burden that results. Knowledge about being at risk and the potential impact of what might occur can contribute psychologic stress.[31-32] In blood pressure screening programs, the labeling individuals as "at-risk" has resulted adverse physical and psychological health in participants.[32] Workers who have had an accidental high exposure, who themselves have been diagnosed with cancer, or who have close family members with the disease, may have heightened sensitivity to even the suggestion that they are at increased risk. These examples illustrate the tension that may exist between the principles between autonomy and nonmaleficence. Ethical evaluation may serve to inform researcher how to best balance this tension.

On the horizon far more complicated questions may emerge as investigators attempt to inform subjects of multiple genetic marker studies such as those that might be conducted with high throughput DNA chips -- technology that can screen for multiple polymorphisms in a single assay. Those results may not only yield multiple findings, but findings that integrate markers of exposure, susceptibility and preclinical conditions in one set of outputs. These data may lead to entirely new ways of defining, classifying, diagnosing and treating disease.

Finally, it may not be appropriate to discuss research-related issues for genetic markers without considering how they will be used once they are validated. Researchers have responsibilities in this regard from a number of perspectives. First, in the current climate, there is economic pressure to use (market) genetic tests before they are completely validated. It is imperative that researchers assess whether the appropriate validation studies (including determination of the predictive value) have been conducted.[30] This would also include assessing the underlying prevalence of the marker. Second, the application of genetic tests for preemployment screening needs to have protections from discrimination and stigmatization, including stipulations of confidentiality. Currently, in the United States and in the European Community, legislation is being drafted to address use of genetic testing in workers. While these issues are not in the disciplinary purview of occupational epidemiologists, they need to be aware of them so as not to be naive about the ethical implications of their work. Third, in the limited instances where genetic tests may be justified for

employment or job placement screening, the effectiveness of this practice as well as adverse consequences must be carefully monitored and evaluated.[30,34-35] These evaluations may require expertise from a range of disciplines, and therefore, ongoing dialogue concerning applied ethics is essential.

Conclusions

There is a need for a clear policy guidelines for the conduct of occupational epidemiological studies using genetic material. Such policy should address issues of recruiting, informed consent, confidentiality, privacy, communication of test and study results, and follow up. The policy should also distinguish single disease genes from metabolic genes, and newly initiated studies from those using banked specimens.

References

1. Hirvonen A. Combinations of susceptible genotypes and individual responses to toxicants. *Env Health Persp*. 1997;105(Supp.4):755–758.
2. Hattis D. Human interindividual variability in susceptibility to toxic effects: from annoying detail to a central determinant of risk. *Toxicology*. 1996;111:5–14.
3. Weiss KM. Introduction. In: Chadwick, Derek Cardew, Gail eds. *Variation in the human genome*. New York: John Wiley & Sons; 1996:1–5.
4. Ashford N. Monitoring the worker and the community for chemical exposure and disease: legal and ethical considerations in the US. *Clin Chem*. 1994;40/7:1426–1437.
5. Schulte P. Simultaneous assessment of genetic and occupational risk factors. *J Occup Med*. 1987;29:884–891.
6. Calebrese E. Ecogenetics: Genetic variation in susceptibility to environmental agents. New York: John Wiley and Sons; 1984.
7. Omenn GS. Predictive identification of hyper susceptible individuals. *J Occup Med*. 1982;24:369–374.
8. Brain J, Beck B, Warren A, Shaikh A (eds). Variations in susceptibility to inhaled particles. Baltimore: John Hopkins University Press; 1988.
9. Grandjean P (ed). Ecogenetics: Genetic predisposition to the toxic effects of chemicals. Published on behalf of the World Health Organization Regional Office for Europe: London: Chapman & Hall; 1991.
10. Schulte, P, Hunter D, Rothman N. Ethical and social issues in the use of biomarkers in epidemiological research. *IARC Scientific Publications*. 1997;55(142):313–318.
11. Hayashi S, Watanabe J, Nakachi K, Kawajiri K. Genetic linkage of lung cancer- associated Msp I polymorphisms with amino acid replacement in the hemo binding region of the human cytochrome P450/AI gene. *J Biochem*. 1991;110:407–411.
12. Schulte P. Biomarkers in Epidemiology: Scientific Issues and Ethical Implications. *Environ Health Perspect*. 1992;98:143–147.
13. Perera F, Mayer J, Santella M, et al. Biological markers in risk assessment for environmental carcinogens. *Env Health Persp*. 1991;90:247–254.
14. Hayes R. Biomarkers in Occupational Cancer Epidemiology: Considerations in study design. *Env Health Persp*. 1992;98:149–154.
15. Gaulding J. Race, sex and genetic discrimination in insurance: what's fair? *Cornell Law Review*. September, 1995;80:1646.
16. Mann C. Behavioral genetics in transition. *Science*. 1994;264:1686–1689.

17. Soskolne C. Ethical, social, and legal issues surrounding studies of susceptible populations and individuals. *Env Health Persp*. 1997;105 (Suppl 4): 837–841.
18. Shultz M. Legal and ethical considerations in securing consent to epidemiological research in the US. In: Coughlin S, Beauchamp T.(eds.). Ethics and epidemiology. Oxford University Press; 1996: 97–127.
19. Barrett J, Vainio H, Peakall D, Goldstein (eds.). 12th meeting of the scientific group on methodologies for the safety evaluation of chemical: susceptibility to environmental hazards. *Env Health Persp*. 1997;105(4):699–737.
20. Clayton E, Steinberg K, Khoury M, et al. Informed consent on stored tissue samples. *JAMA*. 1995;274:1786–1792.
21. Hunter D, Caporaso N. Informed consent in epidemiologic studies involving genetic markers. *Epidemiology*. 1997;8:596–599.
22. Samuels S. A moral history of the evolution of a caste of workers. *Env Health Persp*. 1996;104(Suppl. 5):991–998.
23. Wiesner G. Clinical implications of BRCA 1 genetic testing for Ashikenazi-Jewish Women. Workshop on the BRCA1 breast cancer gene in the Jewish population. *Journal of Law-Medicine*. 7 Health Matrix 3, Winter 1997.
24. Bondy M, Mastromarino C. Ethical issues of genetic testing and their implications in epidemiologic studies. *Ann Epidemiol*. 1997;7:363–366.
25. Schulte P, Haring Sweeney M. Ethical considerations, confidentiality issues, rights of human subjects and uses of monitoring data in research and regulation. *Environ Health Perspect*. 1995;103(Suppl 3):69–74.
26. Strachan T, Abitol M, Davidson D, Beckmann JS. A new dimension for the human genome project: towards comprehensive expression maps. *Nature Genetics*. 1997;16:126–32.
27. Strohman R. The coming Kuhnian revolution in biology. *Nature Biotechnology*. 1997;15:194–200.
28. Pearce N. Traditional epidemiology, modern epidemiology, and public health. *Amer J of Public Health*. 1996;86:678–683.
29. Truett J, Cornfield J, Kannel W. A multivariate analysis of coronary heart disease in Framingham. *J. Chron Dis*. 1967;20:511–524.
30. Vineis P, Schulte P. Scientific and ethical aspects of genetic screening of workers for cancer risk: the case of the n-acetyltransferase phenotype. *J Clin Epidemiol*. 1995;48:189–197.
31. Lippman-Hand A, Fraser C. Genetic counseling -- The postcounseling period: 1 parents' perception of Uncertainty *Am. J Med Gen*. 1979;4:51–71.
32. Capron A, Lappé M, Murry R, Powledge T, Twiss S, Bergsma D (eds). Genetic counseling: facts values and norms. New York: Alan R. Liss Inc.; 1979,183–185.
33. Lefebvre C, Hursey K, Carleton R. Labeling of participants in high blood pressure screening programs, *Arch Intern Med*. 1988;148:1993–1997.
34. Schulte P, Halperin W. Genetic screening and monitoring of workers. In: Recent Avenues in Occupational Health, Vol. 3, M. Harrington (ed), Edinburgh: Churchill Livingstone; 1987,135–154.
35. Eng C, Vijg J. Genetic testing: the problems and the promise. *Nature Biotech*. 1997;15:422–426.