Genetics and Workplace Issues

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Attention to genetic issues in the workplace is a relatively recent occurrence (Schulte, 1987; Office of Technology Assessment [OTA], 1990). Historically, genetic factors have not been considered to any extent in occupational safety and health research, practice, regulation, or litigation. This was, in part, due to the overwhelming and relatively discernible effects of exposure to occupational hazards and to the absences of technology that could assess genetic factors. Various changes have led to increased attention to genetic factors in the workplace. These factors include development of the technology and science related to the human genome, improved control of some of the most egregious chemical and physical hazards (high doses) in the workplace (increasing the likelihood that gene-environment interactions may have an impact), and the rapidly increasing costs of health care, which fosters an environment for consideration of genetics as causal factors of occupational diseases.

The scientific and technological developments from the various genome projects have provided the opportunity for investigators to study the genetic components of disease more easily and in greater depth. Us-

ing polymerase chain reaction amplification and DNA microarray technologies, researchers can obtain minute amounts of DNA and analyze them for a vast number of genes. Scientists are now beginning to be able to explore the genetic components of disease in general and of environmental and occupational disease in particular (Christiani et al., 2001). The increasing control of exposure to most occupational chemical and physical hazards has increased the likelihood that differential personal factors, such as genetics, may play more of a role in disease causation. One reason for that could be that enzyme systems involved in activation or detoxification of chemicals may have been saturated when exposures were high but may be still active at lower exposures (Vineis, 1992). Polymorphism in the genes that code for these enzymes may influence a person's risk for disease, once exposed.

Increased health care costs serve as the backdrop against which many workplace issues currently occur (Council on Ethical and Judicial Affairs, 1991). Moreover, a small percentage of workers may account for the majority of health care costs of an employer (Light, 1992). Thus, there may be motivation for the employers to consider genetic risk factors along with other risk factors in job actions such as hiring, placement, and termination. It may be, however, that the largest impact of genetics in the workplace will not be from work-related diseases but rather from non-work-related diseases that an employer will have to pay for in insurance premiums or in self-insurance costs or from employee absence or reduced productivity. In addition, employers may be motivated to look for genetic or other non-work-related risk factors in legal disputes over claims of work-relatedness of disease (Poulter, 2001).

Regardless of the reason for increased attention to genetics in the workplace, the underlying fact is that all diseases have a genetic component. That is, that etiology (the reason for disease), mechanism, pathogenesis, treatment, and prognosis are all influenced by the action of somatic (nonhereditary cells) or germ (hereditary) cell genes (Khoury, 2003). It is now increasingly common practice to identify genetic components of disease in general medical research and practice (Crooke, 1996; Grody, 2003). It has long been known that there is a range of variability in human response to occupational hazards, particularly chemical hazards. Genetic factors contribute to the variability and consequently may be useful to consider in research and in control of hazards (Neumann and Kimmel, 1998). Growing knowledge about the role of genetic factors promises the

development of sensitive, early-warning indicators of exposure or risk and the identification of characteristics on which to base workplace interventions (Perera, 2000; Christiani et al., 2001). For the most part, these advances are yet to be realized. In fact, although genetic information about disease is inherently important, it is yet to be demonstrated whether it will mean much in investigating genetic factors to improve the ultimate understanding and control of occupational disease.

In this chapter, genetics related to the workplace will be considered in three categories of use: research, practice, and regulation or litigation (Table 9.1). To further explore these categories, I will consider them with respect to inherited genetic factors and acquired genetic effects—a common classification scheme for genetic risks. Inherited genetic effects pertain to somatic and germ cell DNA transmitted through mitosis or meiosis, respectively. These are the processes of cell division that involve the formation of either new body cells (mitosis) or new reproductive cells in the gonads (meiosis). Acquired genetic effects involve modification of genetic material over time and can include genetic damage or genetic expression resulting from workplace or environmental exposures. When measured in a biological specimen, either type of information can be considered a genetic biomarker (Ashford et al., 1990).

The line between inherited genetic factors and acquired genetic damage and effects can be blurry in some areas, particularly those related to gene expression status, such as observed by the technologies of transcrip-

TABLE 9.1
Uses of Genetic Information in the Workplace

Use	Type of genetic information	
	Inherited genetic factors	Acquired genetic effects
Research	Gene-environment interactions Mechanistic insight Population characterization Predictive value	Effects of exposure Linkage to disease Early warning Mechanistic insight
Practice	Disease diagnosis Preventive services Genetic screening Risk management	Genetic monitoring Intervention evaluation Risk profiling Risk management
Regulation or litigation	Risk assessment Workers' compensation Tort litigation Standard-setting	Risk assessment and management Premarket testing Workers' compensation cases Tort litigation Standard-setting

tomics, proteomics, toxicogenomics, and metabolomics (the study of metabolic response to environmental exposures, drugs, and diseases). Gene expression is a series of biochemical steps resulting in the production of a specific protein by a specific gene. It is also part of the underpinning of metabolomics. The term "inherited genetic factors" indicates knowledge about the structure and function of the gene and how that gene compares with similar ones in other species. Often this knowledge can be used for the genetic characterization of cell lines or disease tissue leading to molecular classification of the disease (Golub et al., 1999; Nuwaysir et al., 1999; Hanash, 2003). The products of genes (the transcriptomes, proteomes, and metabolomes) involve not only the gene but also the exogenous (environmental) and endogenous (internal) stressors that up- or down-regulate the gene as it responds. For heuristic purposes, these are included in the broad category of "acquired genetic effects." In many cases, these effects are purely adaptive or homeostatic and are not pathological. In other words, a gene may code for a protein (enzyme) that will respond to an environmental stress. The response may be a normal adaptation and not indicative of disease. In short, the distinction between "inherited genetic factors" and "acquired genetic factors" is that the former is what a person is born with and the latter is what occurs during life.

The definition of genetic information includes not only the results of genetic tests but also a variety of elements in a medical record. The medical record of a worker can include family history, history of disease with known strong genetic etiologies, and results of physical examinations and common laboratory tests. This type of information is often routinely reported by workers on job applications, health questionnaires for jobs, insurance applications, and workers' compensation forms. Such information could be used discriminatorily and should be treated like other sensitive medical information (Rothstein, 1999).

Inherited Genetic Factors

Research

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 exposure, work practice, or lifestyle. Genetic factors are likely to be responsible for

some of this distribution (Neumann and Kimmel, 1998). It is clearly accepted that practically no disease is determined solely by either genes or environment. In the early history of occupational epidemiology, genetic influences were considered only with respect to confounding by race and 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, rather that genetic factors, which might confound exposure-disease associations, are being included as relevant variables in study designs and analyses.

Five major methodological approaches have been commonly used in the use of occupational disease involving genetic factors. These are (1) adjustment for confounding by race, ethnicity, and sex in epidemiologic studies; (2) case studies of occupational diseases in genetically susceptible workers; (3) cross-sectional studies of the prevalence of disease among genetically differentiated groups; (4) case control studies of the association of genetic characteristics and disease; and (5) family studies of disease aggregations (Schulte, 1987).

These approaches coupled with the scientific advances brought about by the sequencing of the human genome and by advances in molecular biology, such as the polymerase chain reaction and the use of restriction enzymes to identify gene variants, have begun to transform research questions and study designs and analytic approaches in occupational health (Shostak, 2003). This transformation focuses more on studies of gene-environment interactions, which aim to describe how genetic and environmental occupational factors jointly influence the risk of developing disease (Kelada et al., 2003; Hunter, 2005). The study of gene-environment interactions (1) allows for better estimates of population-attributable risk of genetic and occupational factors, (2) strengthens associations between occupational risk factors and disease, (3) provides insight into mechanisms of action, and (4) provides new opportunities for intervention and prevention (Hunter, 2005).

In addition to the approaches mentioned earlier, new analytic and methodological techniques are being used. These include case-only designs, genome-wide association studies, Mendelian randomization, and neural networks (Vineis et al., 2004; Hunter and Kraft, 2007). Case-only designs use only a sample of people with a particular disease. This approach allows for testing whether there is interaction, the coparticipation

of two or more factors, in the same causal mechanism leading to disease. That the case-only approach allows for assessing the interaction of genetic and environmental factors in only a series of cases, but with no comparison group (Vineis et al., 2004). Genome-wide association studies are case-control studies involving entire or major parts (e.g., 500,000 polymorphisms) of a genome (Hunter and Kraft, 2007). Mendelian randomization (the use of genotype-disease associations to make inferences about environmental causes of disease) involves exploiting the random assignment of genes as a means of reducing confounding in exposure-disease associations (Khoury et al., 2005). Neural networks (an approach to modeling complex relationships) may allow for the identification of multiple genetic risk factors (gene-gene interactions) in relatively small sample sizes (Ritchie et al., 2003).

New high-throughput technologies, such as DNA and gene microarrays, and automated work stations capable of extracting, amplifying, hybridizing, and detecting DNA sequences will present a number of benefits and issues in studying genetic and environmental variables (Christiani et al., 2001). The benefits include the ability to study large numbers of genes, practically the entire human genome, in one study or experiment and to have access to data banks containing further information on genomic DNA. The primary attendant issue with this technology includes heightened difficulties in analyzing and interpreting such large amounts of data (Ermolaeva et al., 1998).

The underlying rationale of most research involving genetic and occupational risk factors is determining the extent to which the genetic factors may modify the exposure-effect relationship. That is, will the risk of disease attributable to an occupational exposure be decreased, unchanged, or increased among individuals with a particular genetic characteristic (Le Marchand and Wilkens, 2008)? For the most part, this may be because the gene in question codes for an enzyme or receptor involved in the activation, metabolism, or detoxification of the occupational exposure. This genetic factor is generally not a risk for disease without the exposure. In contrast, some genes may be risk factors for the same disease that the occupational exposure is and, thus, the two may be additive (Vineis et al., 2004). In addition, there may be variation in genetically coded repair capabilities in people for mutations or damages.

Ultimately, the focus of occupational genetic research should be conditioned by criteria for the importance of the research to answer questions with workplace relevance. As Millikan (2002) noted: "If epidemi-

ologists 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 opportunities to prevent disease" (p. 477).

For research on the role of genetics in occupational disease to be useful and informative, the validity of the genetic information needs to be assessed or confirmed. Validity can pertain to the assay used to evaluate genetic polymorphisms and also to the population characteristics that influence the prevalence and distribution of a polymorphism. Only when the underlying validity questions have been assessed can a genetic assay be used effectively to study occupational exposure-disease associations. Genetic research that focuses on one or a few genes may be overly simplistic (Staley, 2003). There are many genes that might affect risk in the event of an exposure. Ultimately, the research needed regarding genes or gene expression will need to take a systems biology approach (Toyoshiba et al., 2004). Such an approach requires much investment and experimentation. However, with the emergence of technologies that enable collection of comprehensive genomic data sets it may be possible obtain system level understanding (Kitano, 2002; Hunter and Kraft, 2007).

Also on the horizon is the possibility of research on the genetic basis of behavior and on psychological characteristics and their role in workplace injuries and accidents. This is a highly controversial area, even more than research on physiological effects of genetic factors (Bouchard and McGue, 2003; Hobert, 2003). Understanding the behavior of workers and employers is an important part of identifying occupational safety and health risk factors, but applying behavioral genetics to that factor will raise many ethical, legal, and social issues (Nuffield Council on Bioethics, 2002). Moreover, focusing on behavior of workers fails to account for the responsibilities of employers to provide safe and healthy workplaces.

Rights of Participants in Research

How workers are recruited into occupational genetic studies can involve serious ethical and social issues (Schulte and Sweeney, 1995). These issues hinge on what potential subjects are told about the study and whether they can truly give informed consent. If subjects are deceived or coerced in to participating in a study or are given false expectations (e.g., "We can tell if you are sick or well") with respect to the value of the study to the participant, ethical principles are violated. For

example, a researcher could coerce a potential subject directly (e.g., "You may lose your job if you don't participate") or by implication. Communicating false expectations or using pressure is patently dishonest and unethical. It is unlikely that such deception or coercion would be overt; rather, it would be more subtle and difficult to detect.

A broad spectrum of opinion exists about what obtaining informed consent entails and when it is achieved (Clayton et al., 1995; Samuels, 1996; Hunter and Caporaso, 1997; Schulte, Hunter, and Rothman, 1997). Some believe that for genetic data (biomarkers) for which the meaning is not known at the time of the study, a subject or worker in an occupational study cannot give truly informed consent (Samuels, 1996). This implies a much higher standard of interpretation for genetic biomarker information than for other information routinely obtained by questionnaires, environmental monitoring, or record linkage. Until there is determination of predictive value and course in the natural history, such genetic biomarkers are clearly only research variables with no clinical meaning, and participants should be made aware of this. The extent to which a biomarker has been validated (i.e., quantitatively linked to risk of disease at the group or individual level) should be clearly described to potential research participants.

With regard to informing participants of risks, general practice has been to identify only medical risks; however, it has been argued that truly informed consent should include reference to nonmedical risks that might affect participants. For example, a person might need to be informed that the mere acknowledgment on an employment or insurance application that the subject had a biological or "genetic test" in a research study may result in risk of denial of employment or insurance, although this may be less of an issue with the passing of the Genetic Information Nondiscrimination Act of 2008. Participants in occupational genetic studies consent to provide the specimens and corollary demographic and risk factor information and, hence, cooperate in the specified research. The participant generally does not consent or imply consent to distribution of the data in a way that identifies him or her individually to any other parties, such as employers, unions, insurers, and so on (Schulte et al., 1997).

Interpreting and Communicating the Results of Occupational Genetic Research: A Case Study

Critical in research are issues in interpretation and communication of results. These issues are illustrated by a case study of an occupational

genetic investigation involving hospital workers exposed to ethylene oxide, which is used to sterilize hospital equipment and materials and has been classified as a human carcinogen by the International Agency for Research on Cancer (1994). 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 ethylene oxide) and hydroxethyl valine (HEV) hemoglobin adducts, surrogates for DNA adducts and, hence, cancer risks (Yong et al., 2001). 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 regarding interpreting and communicating results in this study merit consideration. First, making a decision about what to tell particpants 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) of HEV adducts for workers with the *GSTT1* null genotype was 4 percent compared with 28 percent for smoking (tobacco smoke contains ethylene) and 30 percent for workplace exposure to ethylene oxide exposure. Thus, the genetic factor, while statistically significant, may not play an important role in risks for ethylene oxide exposure because it explained a relatively small proportion of the adduct variability. Third, while this study was apparently the first to find the link between *GSTT1* and HEV hemoglobin adducts in ethylene oxide-exposed workers, it was a small transitional study. The results of many initial or transitional studies of gene-environment interactions have not been replicated due to the use of small sample size or samples of convenience with little control for bias (Bogardus, Concato, and Feinstein, 1999). Consequently, although there was laboratory support from in vitro studies (Fost et al., 1991, 1995) without epidemiologic corroboration linking exposure and disease, the results were tentative.

Thus, investigators informed participants of what they knew; namely, "The absence of the gene may be related to a person's risk of cancer if exposed to ethylene oxide, but this is not certain." At the time this study was being conducted, there was relatively little or no guidance regard-

ing informed consent available specifically for population-based or occupational studies of low-penetrance gene variants like *GSTT1*. Subsequently, a Centers for Disease Control and Prevention multidisciplinary group (Beskow et al., 2001) using expert opinion, as well as federal regulation, the National Bioethics Advisory Commission's report on research involving human biological materials (National Bioethics Advisory Commission [NBAC], 1999), 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 implementation of various engineering, administrative, or behavioral controls (Weeks, Levy, and Wagner, 1991). Nonetheless, although the findings of this epidemiologic study were not deemed to be clinically relevant, the investigators had informed participants of the results as part of a prior informed consent agreement. While informing the participants of these results was appropriate, the larger issue is that in population studies of low penetrant genes, informing participants of results should be based on clinical relevance.

Practice

Prevention and Diagnosis

Genetic tests have been shown to be useful for various nonoccupational diseases in diagnosing disease, assessing individual risk, and providing preventive services (Burke et al., 2002; Grody, 2003). Thus these tests are becoming a part of general medical practice. The extent to which they will permeate practice related to the workplace and workers is not known, nor is whether such approaches will be useful for preventing or controlling occupational disease. If genetic tests are to be useful in occupational health, a process of evidence-based integration of data will be needed to develop of guidelines for disease prevention and health services, similar to that which has been suggested for general clinical and public health practice (Centers for Disease Control and Prevention, 2007).

In the future, the practice of occupational medicine may occur against the backdrop of individualized or personal medicine. At the least this

inquiries and tests prior to extending a conditional job offer. At other times, use of genetic information must be "job-related" and consistent with "business necessity." These two criteria are defined by the Equal Employment Opportunity Commission to mean that an employer has a reasonable belief based on objective evidence that (1) an employee's ability to perform essential job functions will be impaired by a medical condition or (2) an employee will pose a direct threat to other employees or customers because of a medical condition (U.S. Equal Employment Opportunity Commission [EEOC], 2000).

One way of obtaining genetic information is through screening, which examines the genetic makeup of employees or job applicants for certain inherited traits. The actual use of genetic assays or tests of workers in job offering or placement is believed to be rare, but the available data to assess such activity are weak. According to a 1999 survey of the American Management Association, 6.7 percent of companies tested and used genetic information to hire applicants, 7.3 percent to reassign employees, and 1.7 percent to dismiss or retain employees (AMA, 1999; Schill, 2000). The accuracy or generalizability of this survey has not assessed, and it is not clear to what extent these statistics are actually representative of the true use of genetic information.

Genetic screening has been assessed by the European Group on Ethics in Science and New Technologies (EGE; 2003), which concluded that the use of genetic screening in the context of the medical examination, as well as the disclosure of results of previous genetic tests, is not ethically acceptable. Furthermore, EGE found that, to date, there is no proven evidence that the existing genetic screening tests have relevance or reliability in the context of employment. Generally, genetic screening tests still have uncertain predictive value (EGE, 2003).

Genetic screening could focus on occupational-related and nonoccupational-related disease or susceptibility. There is no Occupational Safety and Health Act standard that requires genetic testing for occupational susceptibility. Such testing has been described as running contrary to the spirit and intent of the act, which requires a safe and healthy workplace for all workers (see Schill, 2000). Nonetheless, genetic information is increasingly used in understanding and diagnosing of disease. Some proponents of genetic screening argue that, in a competitive business environment, employers should have the opportunity to use technical innovations, such as genetic screening, to select employees, or may, in fact,

have the responsibility to use it (Seltzer, 1998; French, 2002). Genetic factors are already indirectly considered in job decisions to the extent that they affect abilities, skills, and knowledge. Ostensibly, organizations would use genetic screening to avoid placing hypersusceptible workers in hazardous jobs (OTA, 1990). With these potential benefits, some have argued that companies may have an obligation to screen (Seltzer, 1998).

Genetic screening information may be useful to inform potential employees of job risks, if that information is not available to employers in individually identifiable form. This was illustrated in a pilot screening program in a company where beryllium was machined. The employer developed the program for prospective employees because of concern for the debilitating lung condition, chronic beryllium disease, in workers with beryllium exposure. Research had shown that in addition to beryllium exposure, a certain genetic characteristic, *HLA-DPB*^{E69} was also a risk factor. Moreover, beryllium sensitization could occur regardless of dose and had occurred even in relatively well-controlled areas. The employer established the screening program so that job applicants could receive their individual results. The predictive value of the screening test was poor, and a negative test was not an assurance for lack of risk because other variants on chromosome 6, which were not tested for, also were risk factors (Weston, 2002). There are no published data on the results of the program or the issues that arose. The program was stopped after a few years. While, in principle, it seems useful that prospective employees would benefit from information about potential risks, the attendant problems are without impact. In such a test there would be many false positive findings, and many people would make employment decisions based on flawed information. Second, it is a slippery slope from voluntary anonymous screening to mandated screening of individually identifiable applicants by prospective employers. In this case with the test for *HLA-DPB*^{E69} many workers not at increased risk would be discriminated against. In contrast, if the test had a high (>90%) predictive value an employer may have an argument for the right to use it in employee selections.

The occupational safety and health community has identified a hierarchy of controls for preventing occupational disease and injuries (Halperin and Frazier, 1985). Genetic screening is not part of the hierarchy of control. It involves evaluating employees prior to employment. There is, however, a history of medical evaluation as part of job place-

ment decision making. The addition of genetic screening to the process of job placement has the potential to reverse the emphasis in the hierarchy of controls from changing the environment to changing (excluding) the workers (Schulte and Halperin, 1987).

Various authoritative and scholarly groups have identified criteria for the use of genetic screening tests (Van Damme et al., 1995; American College of Occupational and Environmental Medicine [ACOEM], 1994; ACOEM, 1995; NBAC, 1999). In addition to the ADA requirements that tests be job-related and consistent with business practice, as well as other civil rights stipulations in legislation, there are the issues of the validity and utility of the tests as well as ethical, legal, and social safeguards. In short, an adequate evidence base is needed before the use of a genetic screening test in the unique case such testing might be useful. Until such a base is established, the test would not be ready for use in a worker population. In 1994, the American College of Occupational and Environmental Medicine concluded in that "until extensively validated by researchers, tests should be considered a form of human investigation." This means that until validated, the test is useful only in research and not in practice.

Although currently no genetic tests have been validated for assessing the increased risk of susceptibility to workplace hazards, it is anticipated that such tests will eventually become available. Whether these tests would be socially approved is still in question. The Genetic Nondiscrimination Act of 2008 will prohibit discrimination with respect to employment and health insurance.

Regulation and Litigation

One of the first workplace areas where genetic information has been used is workers' compensation. There is no legal prohibition against including any medical or genetic tests in the independent medical examination that is routine in workers' compensation cases (Rothenberg et al., 1997). In addition, informed consent for such testing is not required. By extension, genetic information may also be used as proof of causation in toxic injury litigation. However, analysis of the role of genetic factors in multiple cause cases requires statistical and mechanistic data about how the combination of genetic and toxic risks causes disease (Poulter, 2001).

The use of genetic information in a workers' compensation matter is illustrated by a case involving railroad track workers who filed compensation claims, under the Federal Railway Act (that does not have a no-fault-based compensation system), for carpal tunnel syndrome due to repetitive motion stress in their track work. Without their knowledge or consent, the employer tested them for a deletion in chromosome 17, involving a protein, peripheral myelin protein-22 (*PMP22*). This is not a test for carpal tunnel syndrome, but for "hereditary neuropathy with liability to pressure palsies," which may have a manifestation that includes carpal tunnel syndrome. 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 (Schulte, 2004). Although there is extensive information on the work-relatedness of carpal tunnel syndrome, there is less information on the role of hereditary factors. For the most part, the role of hereditary factors for carpal tunnel syndrome was assessed in family studies, however, on a population basis, the *PMP22* deletions are rare. It would therefore be unlikely that there would be any individuals 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 had not been validated at the population level. Specifically, the predictive value, absolute, relative, and attributable risks had not been assessed. Also of relevance to work-related cases, the question of whether society should use genetic testing for susceptibility genotypes to apportion causation is unresolved. In fact, under the Federal Railway Act, non–work-related causes may be considered in compensation cases. 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. 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 workers' compensation statutes permit medical testing, including genetic testing, to ascertain the medical condition of the claimant and the potential work-relatedness of the claim (Schulte, 2004). However, many U.S. organizations do not generally condone genetic testing without informed consent (ACOEM, 1994).

There are no examples in occupational safety and health regulations where genetic information is required. Numerous state laws, laws in de-

velopment, and Federal Executive Order No. 13145 in 2000 (Clinton, 2000) have called for safeguards or prohibitions from such use (Rothenberg et al., 1997). In 1995, the Equal Employment Opportunity Commission updated the Compliance Manual for the Americans with Disabilities Act (ADA) to define "disability" to apply to those who are subject to discrimination on the basis of genetic information. However, the worker must be able to prove that the employer regards them as "disabled." This interpretation has not been tested in court (Rothenberg et al., 1997), but recent judicial decisions may call into question the Equal Employment Opportunity Commission's interpretation. (See Rothstein in this book.)

Genetic advances push at the historic boundaries of the Occupational Safety and Health Act of 1970. The act mandates standards and rules to assure "that to the extent feasible employees will not suffer material impairment of health or functional capacity." This raises the question of whether workers who could be defined by certain genetic polymorphisms as "hypersusceptible" should have special protections. The implementation of these protections raises a host of questions and issues regarding privacy, discrimination, and responsibility (Bergeson, 2003).

One component of the regulatory process is the practice of risk assessment, the quantitative identification of risks at given levels of exposure. Risk assessment is one of the activities related to regulation and litigation that may use genetic information (Neumann and Kimmel, 1998). Risk assessment involves the evaluation of exposure and response data to identify levels of risk and safety where limits can be set. The use of genetic data may help to better understand the risks of various levels of exposure. Genetic susceptibility information has been used in risk-assessment models to determine the impact of the role of metabolic polymorphisms on risk estimates (Bois, Krowech, and Zeise, 1995; El-Masri, Bell, and Portier, 1999). To gauge the impact of genetic markers on risk assessment, El-Masri, Bell, and Portier (1999) conducted a simulation study of cancer risk estimates for exposure to dichloromethane. The risk estimates from statistical models were 23 percent to 30 percent higher when an effect-modifying polymorphism (*GSTT1*) was not included. Susceptibility biomarkers may reflect variation in exposure, kinetics, and effects and are, therefore, important to consider in risk assessments. Mechanism-based modeling has the potential to decrease uncertainties across and within species and exposure scenarios and to quantify pathways and complex relationships within gene networks.

The establishment of a recommended level of exposure with some margin of safety is an important aspect of quantitative risk assessment. In the occupational field, the historic approach involved the use of uncertainty factors to account for cross-species and interindividual variability. More recently, the benchmark has been the 1 in 1,000 level of risk described by the Supreme Court in the *Industrial Union Department, AFL-CIO v. American Petroleum Institute* 448 US 607 (1980), which is commonly known as the *Benzene* decision. Genetic factors could be used to address uncertainties and provide more precise risk assessments and identify specific subgroups with different risks.

Acquired Genetic Effects

Research

There is an extensive scientific literature assessing the impact of environmental hazards on genetic material (Albertini et al., 2000; Albertini, 2001a; Jones et al., 2002; Bonassi et al., 2004; Hagmar et al., 2004). For the most part, this has involved assessment of cytogenetic effects (e.g., effects on chromosomes), changes in various reporter genes (e.g., glycophorin–A [GPA] and hypoxanthine phosphorsibosyltransferase [HPRT]), and mutations and the formation of DNA and protein adducts following exposure to electrophilic chemicals or ionizing radiation (Schulte and DeBord, 2000; Albertini, 2001b). In addition gene function can be altered by more than just changes in DNA sequences. A wide variety of illnesses, behaviors, and other health indicators have some level of evidence linking them with epigenetic mechanisms. These are any process that alters gene activity without changing the DNA sequence (Southerland and Costa, 2003; Weinhold, 2006). The objectives of much of this research were to determine whether genetic damage did occur and whether it could lead to harmful health effects. The forerunners of this type of research included studies of the Japanese atomic bomb survivors.

More recent studies of workers exposed to various genotoxic chemicals have demonstrated that high frequencies of chromosomal aberrations indicated increase risk of cancer in groups of healthy people (Bonassi et al., 2004; Hagmar et al., 2004). The newer DNA and expression technologies, including toxicogenomics, transcriptomics, proteomics, and metabolomics are means to assess acquired genetic effects (Christiani et al., 2001; Waters, Olden, and Tennant, 2003; Toyoshiba et al., 2004; Wang et al., 2005). These

approaches allow for the assessment of the expression of many thousands of genes before and after exposure. Implicit in these approaches is the assumption that effects of xenobiotics can be detected in expression of genes. The ability to analyze and interpret the vast amounts of data that arises from the studies will be critical in using this technology. Such interpretation is quite difficult because many factors affect gene expression, and adaptive or homeostatic responses need to be distinguished from pathologic ones.

An investigation of workers exposed to welding fumes is illustrative of the type of studies that use microarray expression technologies. The study compared exposed workers (pre- and postexposure) compared with nonexposed controls. The investigators found that genes with altered response clustered in biological processes related to oxidative stress, intracellular signal transduction, cell cycle, and programmed cell death (Wang et al., 2005). A similar type of study of automobile emissions inspectors and waste-incineration workers involved 1,152 genes. The expression profiles showed that the expression of genes and proteins involved in oxidative stress was up-regulated in both groups of workers compared with controls. Additionally, proteomic analysis revealed that several proteins such as transthyretin, sarcolectin, and haptoglobin were highly up- or down-regulated, and the investigators concluded that these could serve as biological markers in future research (Kim et al., 2004). Thus, patterns of genes can be detected that may reflect specific exposures.

If a microarray pattern can be validated as a biomarker of effect, it may be used as an independent or dependent variable in etiologic or intervention research, and as evidence of harm in workers' compensation or tort litigation. These patterns could also be used in standards as biological exposure indices.

The acquisition of effects on the genome also involves change in gene expression that does not involve DNA. This is known as "epigenetics" (Southerland and Costa, 2003; Weinhold, 2006). A broad spectrum of diseases and environmental exposures has some evidence that links them with epigenetics. However, there is need for more mechanistic research before epigenetics can be used widely in population studies, practice, or regulation (Wade and Archer, 2006; Weinhold, 2006).

Practice

Ascertaining acquired genetic damage information in occupational safety and health practice would generally occur in the form of genetic

monitoring. This is the periodic examination of employees to evaluate modification of their genetic material (e.g., chromosomal damage or evidence of increased occurrence of molecular mutations) that might have occurred during the course of employment and exposure to workplace substances (OTA, 1990). In principle, genetic monitoring is similar to other types of health effects or exposure monitoring that is conducted in the workplace (for example, monitoring for lead in blood; Van Damme et al., 1995). However, the fact that genetic monitoring involves somatic genetic effects often leads to its being considered as a somewhat different form of monitoring. In fact, genetic monitoring is generally no different from other forms of biological monitoring and should have the following criteria met before use: an acceptable level of sensitivity and specificity; the acceptance by the population being monitored; an established linkage to exposure or disease; protections for privacy and confidentially; notification to participants of results; and a plan for addressing abnormal results. At present, the results of genetic monitoring can only be interpreted on a group level; they have not been validated as individual risk predictors (Van Damme et al., 1995). If high-throughput expression technologies become candidates for use in genetic monitoring, the issues of standardization, validation, and interpretability will have to be overcome because these will be much greater than with a single test.

Medical removal is a critical workplace issue that is related to any type of medical monitoring, including genetic monitoring. Medical removal is moving the worker to another job location where the exposure is lower or absent. It has been argued that medical removal should be accompanied with continued pay at the rate before the removal (Ashford et al., 1990). Medical removal is not meant to replace exposure controls through engineering means.

Regulation and Litigation

Currently, no U.S. regulations require genetic monitoring of workers. In part, this is because questions arise about whether genetic monitoring indicates just exposure or a potential health problem or compensable injury (Schulte and DeBord, 2000). No genetic monitoring test has been fully validated to assess an individual's risk (Van Damme et al., 1995).

The various expression array technologies also can be applied to human or animal cell cultures that have been exposed to xenobiotics

(Waters et al., 2003; Toyoshiba et al., 2004; Wang et al., 2005). This approach could be used to screen chemicals prior to introduction into commerce.

The gene expression technologies have been viewed as potentially providing useful data for risk assessment (Simmons and Portier, 2002). However, there are numerous questions, as summarized by Freeman, regarding the use, by regulating agencies, of data from microarray experiments (Freeman, 2004). These include

- How does a regulator deal with risk-assessment data that scientists are often unable to interpret—data that some companies are anxious to submit and others to withhold?
- How does this same regulator evaluate information that is produced without a universally recognized standard for laboratory protocols or data formats?
- Should companies submit all information voluntarily without knowing whether regulators will be able to understand it, whether they will use it, and if they do, exactly how?
- What if data that cannot be interpreted now are later shown to indicate toxicity, perhaps at a low level that could not be detected in animal testing? The critical issue in using genomics data is that, if and when such data are interpretable with respect to population risks, what will be the regulatory focuses if sensitive subgroups are identified? Will controls be required to protect these groups? Or will risk-management strategies, such as communications, be applied (Freeman, 2004)?

In the short-term, transcriptomics and proteomics will probably be of most value for the hazard identification aspect of risk assessment (Faustman and Omenn, 1996; Morgan et al., 2002). However, if gene expression technology is to enter the mainstream of the risk-assessment process, protocols for assays to confirm selected biochemical responses will need to be developed as regulatory requirements (Morgan et al., 2002).

Development and Use of Occupational Genetic Biomarker Information

There is a continuum of stages between the discovery and use of genetic biomarker information in public health in general and in occupational safety and health, particularly (Figure 9.1). This continuum is multidirectional. While discoveries of genetic biomarkers in the labora-

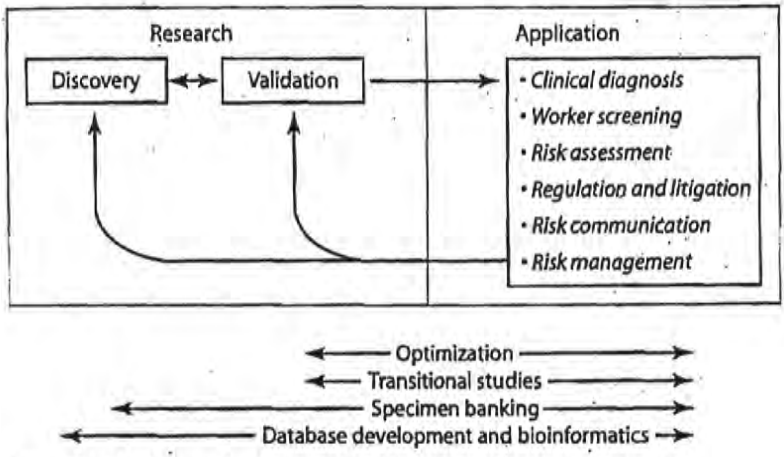

Figure 9.1. Continuum for the development and use of occupational genetic biomarkers

tory are driving factors, there is also an impetus for research provided by problems that arise in applications of genetic information. However, for genetic biomarkers to be successfully developed there is a critical need for laboratory and population validation. Laboratory validation pertains to characteristics of the marker and the assay. Population validation pertains to its prevalence and distribution in the population and in the predictive value of the marker. The developmental process for a validated useful biomarker may entail various studies to optimize the use of the assay and to assess its characteristics in various populations. These have been referred to as transitional studies (Schulte et al., 1997; Albertini, 2001). Knowledge of the relationship between exposure, genetic susceptibility, and disease is still limited, and further epidemiologic research aiming to clarify these relationships is needed (Van Damme and Casteleyn, 2003). Collection of biologic specimens (DNA) is usually costly; consequently, much of the specimen is often saved in biological specimen banks (or biobanks) following the initial study for other uses. Additionally, the results of analyses of DNA samples are often saved in human genetic databases. The establishment of human specimen banks and genetic databases raises complex questions about their ethical, legal, and social implications (Arnason, Nordal, and Arnason, 2004). Of particular relevance to the workplace setting is determining who will have access to the information and specimens, and for what purpose.

Ultimately, genetics should be integrated into public and occupational health. It should not be treated as exceptional but should be handled like other sensitive medical information and used as other disciplinary tools are used—when needed (Schulte, 2004; Khoury et al., 2005). Until that integration occurs, there may be a need for specific safeguards that address the real and perceived power of genetic information.

Safeguards against Improper Use of Genetic Information

The power of genetic information, both inherited factors and acquired indications of effects, must be carefully considered before use in the workplace (Ashford et al., 1990). Uncertainty over the meaning and relevance of a single metabolic gene or combinations of genes can be the basis of ethical controversy (Lemmons, 1992; Van Damme et al., 1995; Schulte et al., 1999; Grody, 2003; Holtzman, 2003). 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 epidemiological studies. However, until genetic markers are validated as individual risk predictors, their use should be restricted.

Van Damme et al. (1995) concluded that the availability of a genetic test should neither automatically enhance the assumption of its usefulness nor allow its application in the absence of clear objectives and without evaluation of its relevance and consequences in a particular context. There is no federal legislation that explicitly and completely protects against genetic discrimination in the workplace or in individual insurance coverage.

Information on acquired genetic effects is less controversial and may be more useful in monitoring exposed workers. While such approaches may have issues that need to be considered, they do not have the same degree of concern as that is involved with inherited genetic factors.

Occupational safety and health researchers, practitioners, and policy specialists should consider the wide range of deleterious effects of using genetic information without proper safeguards (Rothstein, 2000; Burke et al., 2002; McCunney, 2002; Holtzman, 2003; Brandt-Rauf and Brandt-Rauf, 2004). These safeguards include protecting the autonomy of workers in making decisions about their genetic information and providing for the confidentiality and security of genetic information. To a large extent, the passage of the Genetic Information Nondiscrimination Act will

provide some protection against using genetic information in employment and insurance decisions. Meanwhile genetic knowledge will continue to pervade medical science and public health, and judicious use should result in practical advances for workers.

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GENOMICS AND ENVIRONMENTAL REGULATION

SCIENCE, ETHICS, AND LAW

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